Module 2.7.1

Summary of Biopharmaceutic Studies and Associated Analytical Methods

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ABBREVIATIONS

API	Active pharmaceutical ingredient
AUC	Area under concentration-time curve
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
AUC28d or AUC28d	Area under the concentration-time curve from zero (pre-dose) to 28 days (4 weeks)
AUC0-wk12	Area under the concentration-time curve from zero (pre-dose) to Week 12
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
BMI	Body mass index
C24	Plasma concentration 24 h after dosing
CAB	Cabotegravir (GSK1265744)
CI	Confidence interval
CL/F	Apparent clearance following oral and LA dosing
Cmax	Maximum observed plasma concentration
[redacted]	[redacted]
CSR	Clinical study report
CTAB	Cetyltrimethylammonium bromide
CV%	Coefficient of variance
%CVw	Within subject coefficient of variation
[redacted]	[redacted]
Cwk12	Plasma concentration observed at week 12 after dosing
[redacted]	[redacted]
DMPK	Drug Metabolism and Pharmacokinetics
FTIH	First time in humans
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
h or hr	Hour(s)
HCl	Hydrochloric acid
HLQ	Higher limit of quantification
HPLC-MS/MS	High performance liquid chromatography tandem mass spectrometric method
ICH	International Conference on Harmonisation
IM	Intramuscular
IV	Intravenous
K_2-EDTA	Ethylenediaminetetraacetic acid
L	Liter
LA	Long-acting injectable, extended release suspension for injection, or prolonged release suspension for injection
LAP	Long-acting parenteral
LC-MS/MS	Liquid chromatography tandem mass spectrometric method
LLQ	Lower limit of quantification
mg	milligram

mL	Milliliter
NA	Not applicable
ND	Not determined
ng	Nanogram
[redacted]	[redacted]
nm	Nanometer
PBS	Phosphate buffered saline
pg	Picogram
PK	Pharmacokinetic
Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
QC	Quality control
RBA	Relative bioavailability
RPV	Rilpivirine (TMC278)
RPV LA	Rilpivirine long-acting
SC	Subcutaneous
SDS	Sodium dodecyl sulfate
t1/2 or t1/2term	Terminal phase elimination half-life
tmax	Time of occurrence of Cmax
µg	Microgram
µL	Microliter
µm	Micrometer
UV	Ultraviolet
Vz/F	Apparent volume of distribution
w/v	Weight/volume

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1. BACKGROUND AND OVERVIEW

CAB LA is intended to be co-administered with RPV LA as part of the CAB + RPV 2-drug regimen for the treatment of HIV-1 infection. This Application supports the registration of CAB (oral and LA) single agent and focuses on the CAB component of the 2-drug regimen.

1.1. Organization of Data

This document summarizes data from relevant biopharmaceutic studies, formulation development, and bioanalytical methods to form the basis of the biopharmaceutical evaluation of oral and injectable CAB in this submission.

1.2. Main Biopharmaceutical Conclusions

The bioanalytical methods used to measure concentrations of CAB in human plasma were selective, accurate, and reproducible.

1.2.1. CAB LA

- The proposed commercial formulation of CAB LA was used in Phase III studies.

1.2.2. Oral CAB

- The proposed commercial formulation of CAB 30 mg tablets was used in Phase III studies.
- CAB can be taken with or without food.

1.3. Formulation Development

1.3.1. Overview of Formulation Development of Injectable Suspension

CAB LA is a white to light pink, free-flowing suspension containing 200 mg/mL of CAB free acid. CAB LA 200 mg/mL consists of [redacted]. CAB LA formulations used in early clinical trials are described in m3.2.P.2.2_Cabotegravir Injectable Suspension, Section 1.2.1.1.

As part of the formulation [redacted] selection for Phase II clinical trials, a RBA study (LAI116815) was conducted to evaluate the effect of [redacted] on the PK performance of CAB LA with different [redacted] ([redacted] nm, [redacted] µm, and [redacted] µm, [redacted]). The [redacted] nm formulation was selected for Phase II clinical studies. Following successful Phase II clinical studies, this formulation was progressed into Phase III clinical studies and is the proposed commercial formulation, refer to m3.2.P.1_Cabotegravir Injectable Suspension.

Each sterile, single-use vial of CAB LA 200 mg/mL is intended to provide a dose of 400 mg/2 mL or 600 mg/3 mL (200 mg/mL) for IM administration.

Dosage formulations and strengths administered in clinical studies are provided in Appendix Table 1.

1.3.2. Overview of Oral Formulation Development

1.3.2.1. Oral CAB Suspension Formulation

During early clinical trials, an oral suspension of CAB sodium was administered. This was prepared extemporaneously in the clinic from bulk CAB sodium ( ) drug substance and a vehicle containing 0.01% SDS and 1.00% hypromellose in sterile water for injection.

1.3.2.2. Oral CAB Tablet Formulation

During the development of oral CAB, different formulations were investigated. Phase I and IIa clinical trials were conducted using oral CAB 5 mg. The use of CAB (free acid) in 2 capsule formulations was evaluated in study LAI116585, which confirmed that the free acid had lower bioavailability than the sodium salt when administered orally. Two additional tablet formulations containing CAB sodium equivalent to 10 mg or 30 mg of CAB as the free acid were developed to support Phase IIb clinical studies (Studies LAI116482 and 200056) to determine the appropriate therapeutic dose for Phase III clinical studies. The dose for Phase III clinical studies was confirmed as 31.62 mg of CAB sodium ( ), which is equivalent to 30 mg of CAB free acid. Complete statements of the components and quantitative composition of the oral CAB dosed in these studies are presented in m3.2.P.2.2_Cabotegravir Tablets, Section 1.2.2.

RBA study 1 (LAI117020) was conducted to evaluate the relative performance of formulations designed to improve on the Phase IIb formulation. An additional objective of the study was to evaluate the need for drug substance micronization from a bioavailability perspective. Two formulations with (mg) were developed and evaluated in this study and were shown to have decreased bioavailability when compared with the Phase IIb formulation, the reference formulation. Complete statements of the components and quantitative composition of the oral CAB dosed in this study are presented in m3.2.P.2.2_Cabotegravir Tablets, Section 3.6.1.

RBA study 2 (201741) evaluated the relative performance of tablets with a mg mg , . Study 201741 concluded that the formulations met the bioavailability criteria with exposures similar to the exposures of the reference formulation. However, the formulations containing did not meet the exposure criteria as compared with the reference formulation. Although both formulations met the bioavailability criteria, the mg formulation was considered as an advantage and it was selected as the Phase III formulation. Complete statements of the components and quantitative composition of the oral CAB dosed in this study are presented in m3.2.P.2.2_Cabotegravir Tablets, Section 3.6.1.

The formulation of oral CAB 30 mg remained unchanged during Phase III clinical studies, primary stability and is the proposed commercial formulation.

1.4. In Vitro Dissolution Data

1.4.1. CAB LA

Dissolution testing was not conducted during clinical studies, [redacted].

A suitable dissolution method was developed during development and to test the proposed commercial formulation. This method is provided in m3.2.P.5.2. Analytical Procedures_Dissolution by HPLC_Cabotegravir Injectable Suspension. The rationale for this method [redacted] are discussed in m3.2.P.5.3. Analytical Development_Cabotegravir Injectable Suspension.

A summary of in vitro dissolution studies is provided in Appendix Table 2. The RBA study (LAI116815) was conducted prior to the introduction of the dissolution method and hence no dissolution data are presented for this study in Appendix Table 2.

1.4.2. Oral CAB

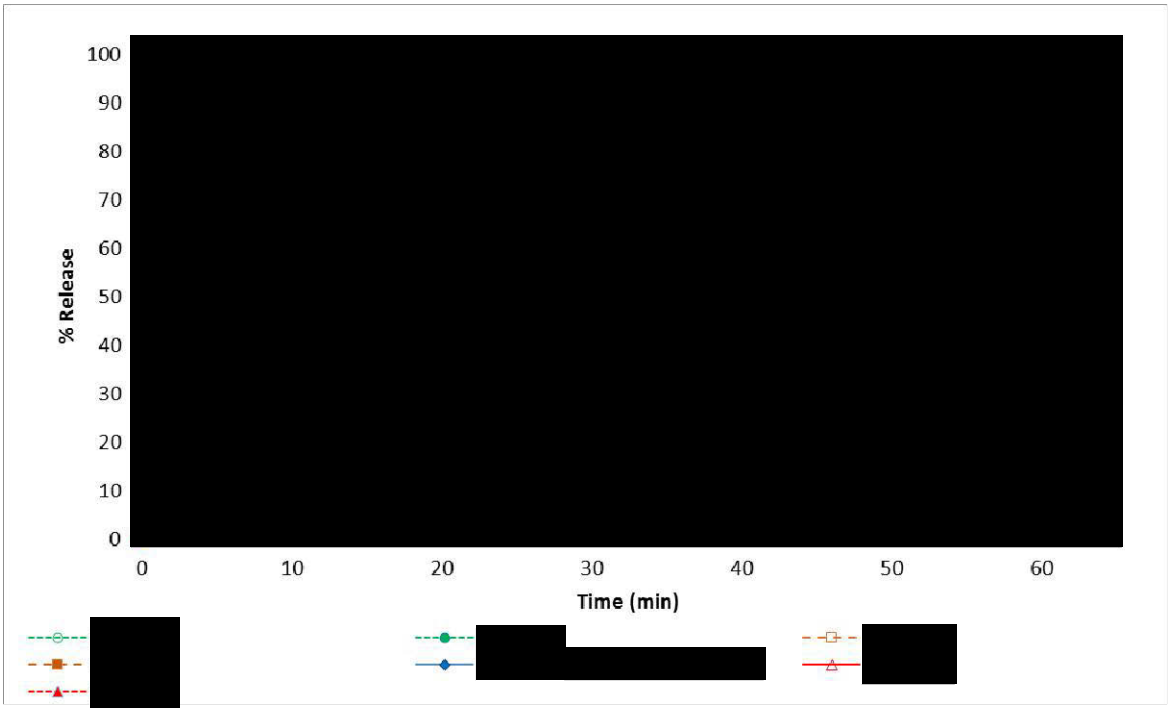
Phase-appropriate in vitro dissolution methodology was used for the testing of Phase I and Phase II formulations.

A suitable dissolution method was developed for testing of the Phase III and proposed commercial formulation. This method is provided in m3.2.P.5.2 Analytical Procedures_Identity and Dissolution by UV_Cabotegravir Tablets. The rational for this method and its discriminatory power are discussed in m3.2.P.5.3 Analytical Development_Cabotegravir Tablets.

In vitro dissolution testing was performed on all batches used in the RBA studies. A summary of the batches used are provided in Appendix Table 1 and the dissolution results are presented in Appendix Table 2.

Dissolution profiles for the formulations used in RBA Studies LAI117020 and 201741 are provided in Figure 1.

Figure 1 Dissolution of Formulations Evaluated in Relative Bioavailability Studies (LAI117020 and 201741) (0.01M HCl, 1000 mL, 60 rpm; Dissolution Procedure D)



1.5. Analytical Methods

1.5.1. Validation

Human plasma samples have been analyzed for CAB concentrations using a validated analytical method based on protein precipitation, followed by HPLC-MS/MS analysis. Across the program, the assay of CAB concentrations in plasma has had 1000-fold linear range with a LLQ of 10 ng/mL or 25 ng/mL and a HLQ of 10,000 ng/mL or 25,000 ng/mL [GSK Doc. # 2012N133238_00, GSK Doc. # RD2008/00249/00, and GSK Doc. # 2014N192374_01].

The bioanalytical method for the measurement of CAB (GSK1265744) concentrations in human plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([$^{13}C^{2}H_{2}{}^{15}N$]-GSK1265744, in 50/50, acetonitrile/water), followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The method was first validated over a range of 10 to 10,000 ng/mL by the Bioanalytical Sciences and Toxicokinetics Section of Platform Technology and Science DMPK, GSK, Research Triangle Park, North Carolina.

The human plasma assay for CAB was transferred to and independently validated over the concentration range of 10 to 10,000 ng/mL, then validated at a range of 25 to 25,000 ng/mL, to accommodate the higher concentrations of CAB observed at clinical doses by [redacted], to provide continuing support.

The human plasma assay for CAB was also transferred to and independently validated over the concentration range of 25 to 25,000 ng/mL by [redacted] - [redacted], [redacted], [redacted].

Unbound CAB concentrations were measured in human plasma ultra-filtrate: human plasma (90:10). The assay was validated with a calibration range in human plasma ultra-filtrate: human plasma (90:10) from 1 to 1000 ng/mL by [redacted], [redacted], [redacted]. The measurement of CAB concentrations in cerebrospinal fluid was validated over a range of 1 to 2500 ng/mL by [redacted], [redacted], [redacted].

The bioanalytical method for the determination of ethinyl estradiol and levonorgestrel in human plasma by HPLC-MS/MS was validated over a range of 150 to 10,000 pg/mL for levonorgestrel and 7.50 to 500 pg/mL for ethinyl estradiol by [redacted], [redacted], [redacted].

A summary of the validation data that supported application of the bioanalytical methods for each clinical study during the development of CAB is summarized in Appendix Table 3. All methods were validated to perform to the same, predefined acceptance criteria for precision and accuracy.

1.5.2. Summary of Within Study Quality Control Sample Analysis

QC samples were analyzed with each batch of study samples. Performance results of the bioanalytical methods used for each study were generated from bioanalytical runs meeting the same run acceptance criteria based upon the predefined requirements for QC performance that no more than one-third of the QC results and 50% from each QC concentration were to deviate from the nominal concentration by more than 15%.

The overall precision and accuracy of the CAB bioanalytical assays are shown in Appendix Table 4.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Tabular summaries for the CAB biopharmaceutical studies and PK parameters are provided in Appendix Table 5 and Appendix Table 6.

Narrative descriptions of the individual biopharmaceutical studies for CAB (oral and LA) formulations are provided in this section. In all studies, CAB PK parameters were determined using standard non-compartmental methods.

2.1. Absolute Bioavailability

Absolute bioavailability studies have not been conducted with CAB LA or CAB tablet formulations; CAB across the physiologic pH range of 1 to 7.4 cannot be formulated in a way suitable for IV administration given its [redacted] across the physiologic pH range.

2.2. Relative Bioavailability

CAB RBA for IM administration has been assessed for the LA formulation in 2 studies and for the tablet formulation in 4 studies.

2.2.1. LAI114433: PK of CAB LA 200 mg/mL (Impact of [redacted])

Study Title: An observer- and subject-blinded, randomized, placebo-controlled, single dose escalation study to investigate the safety, tolerability and pharmacokinetics of intramuscular and subcutaneous long acting GSK1265744 in healthy subjects

Location of Report: m5.3.3.1, LAI114433

Study Design and Methods: Amendment 3 of this first LA study in humans separately evaluated the impact of 2 different clinical study batch formulations of CAB LA and the impact of [redacted] ([redacted]) using the same clinical study batch formulation on CAB PK following sing e dose CAB LA IM administration.

[redacted], [redacted], [redacted] mg [redacted] mg [redacted].

[redacted], [redacted], [redacted] mg [redacted].

To assess the effect of formulation changes, CAB PK was compared following administration of CAB 400 mg IM from the first clinical batch (Cohort 3) vs. the second clinical batch (Cohort 8) (Table 1) (Refer to Appendix Table 1 for formulation details). To assess the effect of [redacted], CAB PK was measured following [redacted] ([redacted] mg, [redacted]) and [redacted] ([redacted] mg, [redacted]) (Table 1) (Refer to Appendix Table 1 for formulation details). Drug formulation from the second clinical batch was used for this evaluation.

All IM injections were administered intragluteally. Per study procedures, for Cohort 9, [redacted] were administered [redacted] ([redacted] mL) to the right side and [redacted] ([redacted] mL) to left side of the gluteus medius muscle for a total of [redacted] mL ([redacted] mg [redacted]) administered.

Serial PK sampling was evaluated in real-time and continued for each subject until concentrations were ≤0.100 μg/mL or withdrew consent.

For details of the study design refer to m2.7.2, Section 2.3.1.3. For details regarding the SC cohorts refer to GSK Doc. # 2013N159605_00.

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Table 1 Study Treatments in LAI114433

Treatment (IM Cohorts)	Drug	Dose/Form/Route/Frequency/Batch
Cohort 3	CAB	[redacted] mg/[redacted] mL/[redacted]
Cohort 8	CAB	[redacted] mg/[redacted] mL/[redacted]
Cohort 9	CAB	[redacted] mg/mL/[redacted]

Refer to Appendix Table 1 for formulation details.

Results: CAB plasma exposures were similar following [redacted] mg [redacted] injections regardless of clinical study batch administered. Using the same clinical study batch, [redacted] mg [redacted] injections resulted in a >2-fold increase in plasma CAB AUC(0-28d) and Cmax. [redacted] did not affect CAB AUC(0-inf) (Table 2).

Table 2 Summary of Impact on CAB LA PK Parameters Following Clinical Study Formulation Change from Batch 1 to Batch 2 and [redacted] (PK Parameter Population)

Parameter	GLS Mean		GLS Mean Ratio [90% CI]
	Test	Reference	Test: Reference
	IM 400mg [redacted][a] Batch 1 (Cohort 3) (N=6)	IM 400mg [redacted][b] Batch 2 (Cohort 8) (N=8)	IM 400mg [redacted] Batch 1 (Cohort 3) vs. Batch 2 (Cohort 8) (N=14)
AUC(0-inf) (μg.h/mL)	2802	2557	1.10 [0.76, 1.58]
AUC(0-28d) (μg.h/mL)	278	299	0.93 [0.60, 1.44]
Cmax (μg/mL)	0.741	0.665	1.11 [0.67, 1.86]
	Test	Reference	Test: Reference
	IM 400mg [redacted][a] Batch 1 (Cohort 3) and Batch 2 (Cohort 8) (N=14)	IM 400mg [redacted][b] ([redacted]) Cohort 9 (N=8)	IM 400mg [redacted] Batch 1 (Cohort 3) and Batch 2 (Cohort 8) vs. IM 400mg [redacted] ([redacted]) (Cohort 9) (N=22)
AUC(0-inf) (μg.h/mL)	2652	2687	1.01 [0.73, 1.41]
AUC(0-28d) (μg.h/mL)	290	644	2.22 [1.53, 3.23]
Cmax (μg/mL)	0.70	1.41	2.03 [1.37, 3.00]

Data Source: GSK Doc. # 2013N159605_00 Table 11.7

a. IM 400 mg [redacted] = CAB LA 400 mg IM single dose of Batch 1 (Cohort 3) and CAB LA 400 mg IM single dose of Batch 2 (Cohort 8).

b. IM 400 mg [redacted] ([redacted]) = CAB LA IM 400 mg ([redacted] mg [redacted]) (Cohort 9).

Refer to Appendix Table 1 for formulation details.

Conclusions:

- The clinical study batch formulations of CAB LA used in this study were not the primary determinants of variability on CAB PK.
- A 2-fold higher AUC and Cmax following [redacted] compared with [redacted], with no difference in the ratio for AUCinf, indicated that [redacted] increased the rate but not the extent of absorption.
- CAB apparent terminal half-lives following LA administration ranged from 25 to 54 days, reflecting rate-limiting absorption rather than the terminal phase elimination t1/2 of ~40 h observed following oral administration.

2.2.2. LAI116815: PK of CAB LA 200 mg/mL (Impact of [redacted])

Study Title: A single-center, randomized, open-label, study to assess the relative bioavailability of new formulations of GSK1265744 LAP in healthy adult subjects

Location of Report: m5.3.1.1, LAI116815

Study Design and Methods: This was a single-center, randomized, open-label, 3 parallel treatment arm study in healthy adult subjects to assess the RBA of CAB LA 400 mg IM using [redacted] (Table 3). Refer to Appendix Table 1 for formulation details.

Table 3 Study Treatments in LAI116815

Treatment	CAB LA 400 mg Single IM dose
Treatment A	[redacted] nm [redacted], reference
Treatment B	[redacted] µm [redacted]
Treatment C	[redacted] µm [redacted]

Refer to Appendix Table 1 for formulation details.

Results: For CAB LA formulations using a [redacted], the overall AUC(0-wk12) was 13% higher following [redacted] µm and 29% lower following [redacted] µm administration relative to the [redacted] nm reference formulation (Table 4).

Table 4 Summary of CAB LA PK Treatment Comparisons (PK Parameter Population)

Parameters	GLS Mean			GLS Mean Ratio [90% CI]		
	Reference	Test	Test			
	[redacted] nm (N=13)	[redacted] µm (N=12)	[redacted] µm (N=13)	[redacted] µm [redacted] nm (N=25)	[redacted] µm [redacted] nm (N=26)	[redacted] nm [redacted] nm (Cohorts 3 & 8) (N=14)
AUC(0-inf) (µg.h/mL)	2664[a]	2717[a]	2313[b]	1.02 [0.79, 1.32]	0.87 [0.66, 1.14]	ND
AUC(0-wk12) (µg.h/mL)	1266[c]	1453[d]	893[c]	1.13 [0.721, 1.78]	0.71 [0.46, 1.09]	1.33 [0.86, 2.05]
Cmax (µg/mL)	0.91[c]	1.27	0.7[c]	1.39 [0.79, 2.43]	0.76 [0.44, 1.32]	1.31 [0.76, 2.26]

Data Source: GSK Doc. # 2014N208332_00 Table 3.10

[redacted] nm: [redacted] nm [redacted] ([redacted]); [redacted] µm: [redacted] µm [redacted] ([redacted]); [redacted] µm: [redacted] µm [redacted] ([redacted]); [redacted] nm [redacted].

a. n = 5
b. n = 4
c. n = 13
d. n = 11

Refer to Appendix Table 1 for formulation details.

Plasma exposures of CAB from the [redacted] nm formulation made from [redacted] API were higher (33% AUC[0-wk12]) than those observed in the previous Study LAI114433 utilizing synthetic [redacted] API. Given the limitations of cross-study comparisons and a slight difference of formulation compositions, the [redacted] nm formulations made from [redacted] and [redacted] drug [redacted] were considered generally comparable.

Conclusions:

- CAB AUC(0-wk12) was similar between the [redacted] µm and [redacted] nm formulations. The [redacted] µm formulation resulted in reduced (~29%) exposure over 12 weeks relative to the [redacted] nm formulation.
- The [redacted] nm ([redacted]) [redacted] formulation of [redacted] was selected for further clinical development of CAB LA.

2.2.3. ITZ111682: PK of CAB 10 mg Oral Suspension vs. 10 mg (2 x 5 mg) Sodium Salt, [redacted] Formulation

Study title: A single dose, randomized study to assess the relative bioavailability of two formulations and food effect on GSK1265744 in healthy male and female subjects

Location of Report: m5.3.1.1, ITZ111682

Study Design and Methods: ITZlll682 was an open-label, single dose, randomized, single-period, parallel study in healthy subjects to assess the RBA of CAB 10 mg administered as either an oral suspension (Treatment A), 2 x 5 mg tablets fasted (Treatment B), or 2 x 5 mg tablets fed (Treatment C) and was the first RBA study of oral CAB. This study was conducted using a parallel rather than cross-over design. Refer to Appendix Table 1 for formulation details.

Food effect: The effect of food on CAB PK is presented in Section 2.3.3.

Subjects were randomized to 1 of 3 treatments. Subjects in Treatment C were fed a moderate fat meal prior to dosing. CAB was administered as described in Table 5.

Table 5 Treatments and Doses in ITZ111682

Treatment	CAB Dose
A	10 mg oral suspension, reference
B	Two 5 mg tablets, fasted
C	Two 5 mg tablets, fed (moderate fat/calorie meal)

Refer to Appendix Table 1 for formulation details.

Results: Under fasted conditions, the CAB 10 mg (2 x 5 mg) tablet formulation delivered 28% lower geometric mean plasma AUC(0-inf) and 41% lower Cmax than the suspension formulation (Table 6). Plasma CAB concentrations were quantifiable within 0.5 h of dosing of both formulations; however, median tmax was increased from 1 h for the suspension formulation to 2.5 h for the tablet formulation.

Table 6 Summary of Plasma CAB PK Parameters and Treatment Comparisons to Assess Relative Bioavailability Following Single Dose Oral Tablet Administration (PK Parameter Population)

Parameter	GLS Mean		GLS Mean Ratio [90% CI]	%CVw
	10 mg Oral Suspension Fasted (Reference) (Treatment A) N=15	10 mg (2x 5 mg) Oral Tablet Fasted (Treatment B) N=15	Tablet/Suspension (Treatment B/ Treatment A) N=15	
AUC(0-t) (μg.h/mL)	60.1	42.8	0.71 [0.61, 0.83]	25.7
AUC(0-inf) (μg.h/mL)	62.4	44.7	0.72 [0.61, 0.84]	26.7
Cmax (μg/mL)	1.93	1.13	0.59 [0.53, 0.66]	17.7

Data Source: GSK Doc. # RM2008/00637/00 Table 11.4
Treatment A = CAB 10 mg oral suspension, fasted, reference
Treatment B = CAB two 5 mg tablets, fasted
Refer to Appendix Table 1 for formulation details.

Conclusions:

- The tablet formulation showed a reduced rate and extent of absorption of CAB compared with the oral suspension formulation.
- Following administration of the tablet formulation under fasted conditions, CAB AUC(0-inf) and Cmax were lower compared with the oral suspension formulation.
- Median tmax was delayed from 1 h following the oral suspension formulation to 2.5 h following tablets.
- The tablet formulation was selected for administration in HIV infected subjects in ITZ111451 Cohort C, adjusting the dose to overcome reduced bioavailability of tablets relative to the suspension formulation.

2.2.4. LAI116585: PK of CAB 30 mg Sodium Salt, [redacted] mg [redacted], [redacted] Formulation (Impact of Free Acid Capsule Formulation and [redacted] vs. [redacted] API)

Study Title: A single-center, randomized, open-label, crossover study to assess the relative bioavailability of new formulations of GSK1265744 in healthy adult subjects.

Location of Report: m5.3.1.1, LAI116585

Study Design and Methods: This was a single-center, randomized, open-label, balanced, 3-way crossover study in healthy adult subjects to assess the RBA of 2 new free acid oral formulations of CAB 30 mg compared with the current CAB 30 mg sodium salt formulation and was the second RBA study of oral CAB. The new free acid formulations differ in [redacted]; one being [redacted], and the other [redacted]. Approximately 18 subjects were randomized to receive a single dose of the current reference sodium salt formulation, the CAB 30 mg free acid [redacted] formulation, and the free acid [redacted] formulation (Table 7). All treatments were administered as a single 30-mg dose of CAB under fasting conditions and treatment periods were separated by a 14-day washout. Refer to Appendix Table 1 for formulation details.

Table 7 Study Treatments in LAI116585

Treatment	Drug	Dose/Form/Route/Frequency
A	GSK1265744B sodium (Na) salt tablet as reference formulation	30 mg/Tablet/Oral/Single Dose
B	CAB free acid [redacted] formulation	30 mg/Capsule/Oral/Single Dose
C	CAB free acid [redacted] formulation	30 mg/Capsule/Oral Single Dose

Refer to Appendix Table 1 for formulation details.

Results: Plasma exposures of CAB following free acid [redacted] formulation and [redacted] formulation administration were lower than those following administration of the sodium salt tablet formulation (Table 8).

The ratios of GLS means of plasma CAB AUC and Cmax from the free acid [redacted] formulation administration were approximately 12% and 19% lower than those following administration of the sodium salt tablet formulation.

The ratios of GLS means of plasma CAB AUC and Cmax from the free acid [redacted] formulation administration were approximately 48% and 54% lower than those following administration of the sodium salt tablet formulation.

Table 8 Summary of Plasma CAB PK Parameters and Treatment Comparisons to Assess Relative Bioavailability Following Single-Dose Tablet Administration (PK Summary Population)

Parameter	GLS Mean			GLS Mean Ratio [90% CI]		%CVw
	Sodium Salt Tablet Reference (A) N=18	[redacted] Free Acid Capsule (B) N=18	[redacted] Free Acid Capsule (C) N=18	[redacted] Free Acid vs. Sodium Salt Tablet (B/A)	[redacted] Free Acid vs. Sodium Salt Tablet (C/A)	
AUC(0-t) (μg.h/mL)	163	142	82.9	0.87 [0.77, 0.98]	0.51 [0.45, 0.57]	21.4
AUC(0-inf) (μg.h/mL)	174	152	89.4	0.88 [0.78, 0.99]	0.52 [0.46, 0.58]	21.6
Cmax (μg/mL)	4.24	3.43	1.96	0.81 [0.72, 0.91]	0.46 [0.41, 0.52]	20.7

Data Source: GSK Doc. # 2012N152984_00 Table 3.6
Treatment A = GSK1265744B sodium (Na) salt as reference formulation
Treatment B = CAB free acid [redacted] formulation
Treatment C = CAB free acid [redacted] formulation
Refer to Appendix Table 1 for formulation details.

Conclusions:

- Following administration of the free acid [redacted] formulation, CAB AUC(0-inf) and Cmax were lower compared with the reference formulation (sodium salt tablet).
- Following administration of the free acid [redacted] formulation, CAB AUC(0-inf) and Cmax were lower compared with the reference formulation (sodium salt tablet).
- The sodium salt formulation was selected for administration in subsequent clinical studies.

2.2.5. LAI117020: PK of CAB 30 mg Sodium Salt, [redacted] mg [redacted] Formulation (Impact of [redacted] mg [redacted])

Study Title: A two part, single-center, randomized, open-label, crossover study to assess the relative bioavailability of new tablet formulations of GSK1265744 in healthy adult subjects

Location of Report: m5.3.1.1, LAI117020

Study Design and Methods: This was a single-center, randomized, 2-part, open-label, crossover study in healthy adult subjects to assess the oral bioavailability of 2 new CAB 30-mg tablet formulations relative to the reference CAB 30-mg sodium salt tablet formulation ([redacted] mg [redacted]) (Part A) administered in previous studies, and the effect of a moderate-fat meal on the bioavailability of the selected tablet formulation (Part B), and the third RBA study of oral CAB. Twenty-four subjects were randomized to Part A to receive the reference [redacted] mg [redacted] sodium salt formulation, the

[redacted] mg [redacted] formulation with [redacted], and the [redacted] mg [redacted] formulation [redacted] (Table 9). All treatments were administered as a single 30-mg dose of CAB under fasting conditions and treatment periods were separated by a 14-day washout. Refer to Appendix Table 1 for formulation details.

Table 9 Study Design for LAI117020

Treatment	Part A N=24					Washout	Part B N = 15
A: Reference formulation fasted (reference)	Period 1	Wash-out At least 14 days	Period 2	Wash-out At least 14 days	Period 3	Up to 21 days	
B: Formulation 1 fasted							
C: Formulation 2 fasted							
Formulation 1 or 2 fed							Period 4

Treatment A = CAB 30 mg sodium salt formulation [redacted], [redacted] mg [redacted], (reference)
Treatment B = CAB 30 mg formulation [redacted], [redacted] mg [redacted], fasted
Treatment C = CAB 30 mg formulation [redacted], [redacted] mg [redacted], fasted
Refer to Appendix Table 1 for formulation details.

Results:

Part A

The reference treatment for fasted comparisons was the original [redacted] mg [redacted].

Plasma CAB exposure for both new test formulations was lower than for the reference formulation. In Part A, plasma CAB AUC(0-inf) and Cmax were 30% and 36% and lower, respectively, following the test [redacted] tablet (Treatment B) as compared with the reference tablet (Treatment A), and were 42% and 47% lower, respectively, following the test [redacted] tablet (Treatment C) as compared with the reference tablet (Treatment A) (Table 10).

Table 10 Summary of Plasma CAB PK Parameters and Treatment Comparisons Following Single-Dose Tablet Administration Under Fasted Conditions (PK Summary Part A Population)

Parameter	GLS Mean			GLS Mean Ratio [90% CI]		%CVw
	A: CAB 30 mg (Reference) (N=22)	B: [redacted] CAB 30 mg (N=22)	C: [redacted] CAB 30 mg (N=22)	[redacted] 30 mg vs. Reference (B:A) (N=22)	[redacted] 30 mg vs. Reference (C:A) (N=22)	
AUC(0-inf) (μg.h/mL)	141	99	82	0.70 [0.62, 0.79]	0.58 [0.52, 0.65]	23.3
Cmax (μg/mL)	3.72	2.38	1.98	0.64 [0.56, 0.73]	0.53 [0.47, 0.61]	25.6

Data Source: GSK Doc. # 2014N206383_00 Table 3.9
Treatment A = CAB 30 mg sodium salt formulation [redacted], [redacted] mg [redacted], fasted (reference)
Treatment B = CAB 30 mg formulation [redacted], [redacted] mg [redacted], fasted (test)
Treatment C = CAB 30 mg formulation [redacted], [redacted] mg [redacted], fasted (test)
Refer to Appendix Table 1 for formulation details.

Part B

The food effect part of the study is summarized in Section 2.3.2.

Conclusions:

- Following administration of the test [redacted] tablet (Treatment B), CAB AUC(0-inf) and Cmax were lower compared with the reference tablet (Treatment A).
- Following administration of the test [redacted] tablet (Treatment C), CAB AUC(0-inf) and Cmax were lower compared with the reference tablet (Treatment A).
- Neither of the [redacted] or [redacted] tablet formulations met the criteria for progression into Phase III and were not used in further studies.

2.2.6. 201741: PK of CAB 30 mg Sodium Salt, [redacted] mg [redacted], [redacted] Formulation (Impact of [redacted] mg [redacted] mg [redacted])

Study Title: Phase I, single-center, randomized, open-label, crossover study to assess the relative bioavailability of Phase III tablet formulation candidates in healthy adult subjects

Location of Report: m5.3.1.1, 201741

Study Design and Methods: This study was a single-center, randomized, open-label, 2-cohort, 3-way crossover study in healthy adult subjects to assess the oral bioavailability of 4 new CAB 30 mg tablet formulations relative to the reference CAB 30 mg sodium salt tablet ([redacted] mg [redacted] with [redacted]) used in Phase IIb studies and the fourth RBA study of oral CAB. Subjects in Cohort 1 (n=18) were randomized to receive the reference [redacted] mg [redacted] formulation with [redacted], the [redacted] mg [redacted] formulation with [redacted], and the [redacted] mg [redacted] formulation with [redacted]. Subjects in Cohort 2 (n=18) were randomized to receive the reference [redacted] mg [redacted] formulation with [redacted], the [redacted] mg [redacted] formulation with [redacted], and the [redacted] mg [redacted] formulation with [redacted] (Table 11). All treatments were administered as a single 30-mg dose of CAB under fasting conditions separated by a 14-day washout. Subjects were assigned to 1 of the 12 sequences in accordance with the randomization schedule generated by Clinical Statistics. Refer to Appendix Table 1 for formulation details.

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Table 11 Study Design for 201741

Cohort	Subjects		Treatment Periods					Follow-up
Cohort 1	N=18	30 day Screening period	Period 1	Wash-out At least 14 days	Period 2	Wash-out At least 14 days	Period 3	14 days after last dose
Cohort 2	N=18							

Cohort 1/Sequences 1-6
Treatment A: CAB 30 mg ( ) = CAB 30 mg reference formulation
Treatment B: CAB 30 mg ( ) = CAB 30 mg test formulation 3, , mg
Treatment C: CAB 30 mg ( ) = CAB 30 mg test formulation 4, , mg
Cohort 2/Sequences 7-12
Treatment A: CAB 30 mg ( ) = CAB 30 mg reference formulation
Treatment D: CAB 30 mg ( ) = CAB 30 mg test formulation 5, , mg
Treatment E: CAB 30 mg ( ) = CAB 30 mg test formulation 6, , mg
Refer to Appendix Table 1 for formulation details.

Results: CAB 30 mg oral tablets with new mg and either were compared with the reference 30 mg formulation with a mg. The mg formulation was bioequivalent to the reference formulation (Table 12). Exposures (AUC and Cmax) following the -mg formulation were reduced 9% relative to the reference formulation. Exposures following the mg and mg formulations were reduced 19 to 21% and 25%, respectively, relative to the reference formulation.

Table 12 Summary of Plasma CAB PK Parameters Following Single Dose Tablet Administration (PK Summary Population)

Parameter	GLS Mean			GLS Mean Ratio [90% CI]		
Cohort 1 (n=18)	**Test [redacted] (B) (N=18)**	**Test [redacted] (C) (N=18)**	**Reference [redacted] (A) (N=18)**	**Test: Reference (B:A) (N=18)**	**Test: Reference (C:A) (N=18)**	**%CVw**
AUC(0-t) (μg.h/mL)	128	101	124	1.04 [0.93, 1.15]	0.81 [0.74, 0.90]	18.4
AUC(0-inf) (μg.h/mL)	135	106	131	1.03 [0.93, 1.15]	0.81 [0.73, 0.90]	18.5
Cmax (μg/mL)	3.43	2.65	3.35	1.03 [0.92, 1.15]	0.79 [0.71, 0.88]	19.9
Cohort 2 (n=18)	**Test [redacted] (D)**	**Test [redacted] (E)**	**Reference [redacted] (A)**	**Test: Reference (D:A)**	**Test: Reference (E:A)**	**%CVw**
AUC(0-t) (μg.h/mL)	123	101	135	0.91 [0.8, 1.04]	0.75 [0.66, 0.86]	24.1
AUC(0-inf) (μg.h/mL)	129	106	142	0.91 [0.79, 1.04]	0.75 [0.65, 0.86]	24.2
Cmax (μg/mL)	3.15	2.60	3.48	0.91 [0.78, 1.05]	0.75 [0.64, 0.87]	26.6

Data Source: GSK Doc. # 2015N248022_00 Table 3.6
Treatment A: CAB 30 mg ([redacted]) = CAB 30 mg reference formulation
Treatment B: CAB 30 mg ([redacted]) = CAB 30 mg test formulation 3, [redacted] mg [redacted]
Treatment C: CAB 30 mg ([redacted]) = CAB 30 mg test formulation 4, [redacted] mg [redacted]
Treatment D: CAB 30 mg ([redacted]) = CAB 30 mg test formulation 5, [redacted] mg [redacted]
Treatment E: CAB 30 mg ([redacted]) = CAB 30 mg test formulation 6, [redacted] mg [redacted]
Refer to Appendix Table 1 for formulation details.

Conclusions:

- Following administration of the [redacted]-mg [redacted] formulation with [redacted], CAB AUC(0-inf) and Cmax were bioequivalent to the reference formulation ([redacted] mg [redacted] with [redacted]).
- Since a [redacted] tablet is desirable for ease of administration, the tablet formulation with [redacted] mg, with [redacted] was selected for progression into Phase III studies.

2.2.7. CAB Bioequivalence

Bioequivalence studies for either oral CAB or CAB LA have not been conducted as the proposed commercial formulations were used in the pivotal Phase III clinical studies. The proposed commercial formulation of oral CAB is a 30 mg sodium salt tablet, [redacted] mg [redacted]. The proposed commercial formulation of CAB LA is a 200 mg/mL CAB free acid, extended-release injectable suspension.

2.3. Effect of Food on Bioavailability of CAB

CAB LA will be administered by IM injection, therefore studies to assess the effect of food on CAB LA absorption are not relevant.

Three studies have evaluated the effect of food on the bioavailability of CAB following administration of tablet formulations.

2.3.1. 205696: PK of CAB 30 mg Sodium Salt, [redacted] mg [redacted], [redacted], Phase III Formulation (Impact of High-fat Meal)

Study title: A Phase I study evaluating the effect of a high fat meal on the pharmacokinetics of cabotegravir in healthy adult volunteers

Location of Report: m5.3.3.1, 205696

Study Design and Methods: This study was a single-center, randomized, open-label, 2-way crossover study in healthy adult subjects to assess the effect of a high-fat meal on the single dose PK of CAB 30 mg tablet formulation used in Phase III studies (Refer to Appendix Table 1 for formulation details). Subjects were randomized to 1 of 2 treatment sequences (AB, BA) (Table 13).

Table 13 Study Design for 205696

Sequence	Subjects		Treatment Periods			Follow-up
	n	30-day Screening period	Period 1	Wash-out At least 14 days	Period 2	14 days after last dose
Sequence 1	12		A		B	
Sequence 2	12		B		A	

Treatment A: Single CAB 30 mg, [redacted] mg [redacted] oral tablet in a fasted state, with at least 10 h of fast, reference
Treatment B: Single CAB 30 mg, [redacted] mg [redacted] oral tablet administered following a high-fat meal (53% fat and 870 calories)
Refer to Appendix Table 1 for formulation details.

Results:

Table 14 Summary of Selected Plasma CAB PK Parameters Following Single Dose Administration with and without a High-fat Meal (PK Summary Population)

Treatment	AUC(0-inf) [a] (μg.h/mL)	Cmax [a] (μg/mL)	tmax [b] (h)	C24 [a] (μg/mL)	t1/2 [a] (h)	CL/F [a] (L/hr)	Vz/F [a] (L)
A (n=21)	143 [126, 162] (28)	3.33 [2.95, 3.77] (27)	3.0 (1.0-4.0)	1.62 [1.45, 1.81] (25)	40.6 [38.0, 43.5] (15)	0.210 [0.19, 0.24] (28)	12.3 [11.2, 13.6] (22)
B (n=21)	163 [144, 185] (29)	3.85 [3.46, 4.28] (24)	3.0 (1.0-8.0)	1.88 [1.69, 2.10] (24)	40.6 [37.8, 43.7] (16)	0.18 [0.16, 0.21] (29)	10.8 [9.8, 11.9] (21)

Data Source: GSK Doc. # 2016N298724_00 Table 3.3
Treatment A: Single CAB 30 mg, [redacted] mg [redacted] oral tablet in fasted state, with at least 10 h of fast, reference
Treatment B: Single CAB 30 mg, [redacted] mg [redacted] oral tablet following a high-fat meal
a. Geometric mean [95% CI] (CV%)
b. median (range)
Refer to Appendix Table 1 for formulation details

Plasma CAB AUC(0-inf), Cmax, and C24 were increased 14, 14, and 17%, respectively, following single-dose administration of 30 mg tablet with a high-fat meal when compared with fasted conditions (Table 15, Data Source: GSK Doc. # 2016N298724_00 Table 3.5). Median tmax was 3 h with and without food.

Table 15 Plasma CAB PK Treatment Comparison Following Single-Dose Tablet Administration with and without a High-fat Meal (PK Summary Population)

Plasma CAB PK Parameter	Ratio of GLS Means [90% CI] (%CVw)
	B: Fed vs A: Fasted N=21
AUC(0-t) (μg•h/mL)	1.14 [1.03, 1.27] (20.3)
AUC(0-inf) (μg•h/mL)	1.14 [1.02, 1.28] (20.5)
Cmax (μg/mL)	1.14 [1.03, 1.27] (20.0)

Data Source: GSK Doc. # 2016N298724_00 Table 3.5
Treatment A: Single CAB 30 mg, [redacted] mg [redacted] oral tablet in fasted state, with at least 10 h of fast, reference
Treatment B: Single CAB 30 mg, [redacted] mg [redacted] oral tablet following a high-fat meal
Refer to Appendix Table 1 for formulation details.

Conclusions:

- Following administration of a single CAB 30 mg tablet formulation (mg oral tablet) with a high-fat meal, CAB AUC(0-inf) and Cmax were increased compared with fasted conditions.
- CAB 30 mg tablet formulation can be administered with or without food and without regard to fat or caloric content of food.

2.3.2. LAI117020: PK of CAB 30 mg Sodium Salt, mg , Formulation (Impact of Moderate-fat Meal)

Study title: A two part, single-center, randomized, open-label, crossover study to assess the relative bioavailability of new tablet formulations of GSK1265744 in healthy adult subjects

Location of Report: m5.3.1.1, LAI117020

Study Design and Methods: See Section 2.2.5 for a summary of the methods.

Part B

Fifteen subjects (from Part A) continued into Part B for the food effect evaluation. CAB 30 mg, was selected for testing in the Fed condition in Part B (refer to Appendix Table 1 for formulation details). In the food effect part of the study, subjects received Treatment D (classified as Treatment B in Part A) as described in Table 16.

Table 16 Study Treatments in LAI117020

Treatment	CAB Dose
B (Reference) [Part A]	CAB 30 mg formulation , mg , fasted, reference
D (Test)	CAB 30 mg formulation , mg , fed (~30% fat and ~ 670 calories)

Refer to Appendix Table 1 for formulation details.

Results: The reference treatment for the fed comparison was the mg tablet administered in the fasted state to the same subset of subjects (n=15).

In an analysis of the 15 subjects who received the test formulation, both fasted (Treatment B) and with a moderate-fat meal (Treatment D), food slightly increased but did not have a significant impact on CAB AUC(0-inf) or Cmax (Table 17).

Table 17 Summary of Plasma CAB PK Parameters and Treatment Comparisons Following Single-Dose Tablet Administration with and without a Moderate-fat Meal (PK Summary Part B Population)

Parameter	GLS Mean		GLS Mean Ratio [90% CI]	%CVw
	B: [redacted] CAB 30 mg (Fasted) (Reference) (N=15 subset)	D: [redacted] CAB 30 mg (Fed) (N=15)	D:B [redacted] Fed vs. [redacted] Fasted (N=15 subset)	
AUC(0-inf) (μg.h/mL)	104	113	1.08 [0.98, 1.20]	15.7
Cmax (μg/mL)	2.50	2.71	1.08 [0.96, 1.22]	19.0

Data Source: GSK Doc. # 2014N206383_00 Table 3.10
Treatment B: CAB 30 mg formulation [redacted], [redacted] mg [redacted], fasted
Treatment D: CAB 30 mg formulation [redacted], [redacted] mg [redacted], fed
Refer to Appendix Table 1 for formulation details.

Conclusion:

- Following administration of the CAB 30 mg tablet formulation ([redacted] mg [redacted]) with a moderate-fat meal, CAB AUC(0-inf) and Cmax were increased slightly compared with fasted conditions ([redacted] mg [redacted]) but did not have a significant impact.
- CAB can be administered with or without food.

2.3.3. ITZ111682: PK of CAB 10 mg Oral Suspension vs. 10 mg (2 x 5 mg) Sodium Salt, [redacted] mg [redacted], [redacted] Formulation (Impact of Moderate-fat Meal)

Study title: A single dose, randomized study to assess the relative bioavailability of two formulations and food effect on GSK1265744 in healthy male and female subjects

Location of Report: m5.3.1.1, ITZ111682

Study Design and Methods: See Section 2.2.3 for a summary of the methods.

Subjects were randomized in a parallel design to 1 of 3 treatments listed in Table 18.

Table 18 Treatments and Doses in ITZ111682

Treatment	CAB Dose
A	10 mg oral suspension
B	Two 5-mg tablets, fasted, reference for food effect evaluation
C	Two 5-mg tablets, fed (moderate fat/calorie meal)

Refer to Appendix Table 1 for formulation details.

Results: A moderate-fat meal increased the geometric mean plasma CAB AUC(0-inf) and C24 following administration of the CAB 10 mg (2 x 5 mg) tablet formulation by 15% and had no impact on CAB Cmax (Table 19).

Median tmax was delayed from 2.5 h for tablets administered after an overnight fast to 4 h for tablets administered with food.

Table 19 Summary of Plasma CAB PK Parameters and Treatment Comparisons Following Single-Dose Tablet Administration (PK Parameter Population)

Plasma CAB PK Parameter	GLS Mean		GLS Mean Ratio [90% CI]	%CVw
	10 mg (2 x 5 mg) Oral Tablet Fasted (Reference) (Treatment B) N=15	10 mg (2 x 5 mg) Oral Tablet Fed (Treatment C) N=15	Fasted vs. Fed (Treatment C/ Treatment B) N=15	
AUC(0-t) (μg.h/mL)	42.8	49.4	1.15 [0.99, 1.35]	25.7
AUC(0-inf) (μg.h/mL)	44.7	51.6	1.15 [0.98, 1.36	26.7
Cmax (μg/mL)	1.13	1.2	1.04 [0.93, 1.16]	17.7

Data Source: GSK Doc. # RM2008/00637/00 Table 11.4
Treatment B = CAB two 5 mg tablets, fasted, reference for food effect evaluation
Treatment C = CAB two 5 mg tablets, fed
Refer to Appendix Table 1 for formulation details.

Conclusions:

- Following administration of a CAB 10 mg (2 x 5 mg) tablet formulation with a moderate-fat meal, CAB AUC(0-inf) increased by 15% compared with fasted conditions and had no impact on CAB Cmax.
- CAB can be administered with or without food.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. In vitro Dissolution and In vivo Bioavailability

3.1.1. CAB LA

CAB is practically insoluble below pH 9 and slightly soluble above pH 10 in aqueous media. The low solubility, in combination with IM administration, results in the required PK performance.

RBA Study LAI116815 investigated the effects of [redacted] of CAB on PK performance of CAB LA. CAB LA demonstrates an inverse relationship between [redacted] and [redacted]; as [redacted] increases, [redacted] decreases, see m3.2.P.2.2_Pharmaceutical Development_Cabotegravir Injectable Suspension and m3.2.P.5.6_Justification of Specification_Cabotegravir Injectable Suspension. The [redacted], discussed in m3.2.P.2.2_Cabotegravir Injectable Suspension, is therefore, expected to be more of a [redacted] than an indicator of [redacted].

3.1.2. Oral CAB

CAB sodium is considered a poorly soluble compound, demonstrating low solubility over the physiological pH range (pH 1 to 7.8). CAB was determined to have high passive membrane permeability (256 nm/s at pH 7.4). The absorptive membrane permeabilities were also high in the presence of FaSSIF at pH 7.4 and pH 5.5 (P7.4[abs] value of 1088 nm/s and a P5.5[abs] value of 1374 nm/s, respectively). Based on the low solubility of CAB sodium and the high passive permeability, CAB sodium is considered to be a BCS Class 2 compound.

In vitro dissolution testing (using the dissolution method described in m3.2.P.5.2_Analytical Procedures_Cabotegravir Tablets) of tablets manufactured using [redacted] and [redacted] drug substance and the in vivo performance demonstrates that the [redacted] has a significant impact on oral CAB [redacted]. [redacted].

3.2. Bioavailability

Absolute bioavailability studies have not been conducted with CAB LA or CAB tablet formulations; CAB across the physiologic pH range of 1 to 7.4 cannot be formulated in a way suitable for IV administration given its low solubility across the physiologic pH range.

3.2.1. CAB LA

Phase I and Phase II studies utilized CAB LA 200 mg/mL suspension for injection with [redacted] nm. LAI116815 evaluated the RBA of 2 new formulations of CAB LA 400 mg formulated with different [redacted] ([redacted] µm and [redacted] µm) compared

with the reference [redacted] nm [redacted] formulation (Table 20). Increased [redacted] prolonged the plasma half-life by 13% and 66% following the [redacted] µm and [redacted] µm formulations, respectively, relative to the [redacted] nm formulation. Given that the kinetics of CAB LA are absorption rate limited, the prolonged terminal phase t½ reflected slower absorption of the new formulations from the IM depot, rather than elimination. The 3 formulations resulted in a similar concentration 12 weeks post-injection. Although the [redacted] nm and [redacted] µm [redacted] products achieved similar exposures, wide variability was observed at earlier timepoints, and an ad hoc analysis suggested a higher exposure with the [redacted] nm product when adjusted for gender and BMI. Therefore, the [redacted] nm [redacted] was selected for Phase II studies as it was used in all previous clinical studies and, therefore, viewed as the option to most reliably provide adequate exposures.

Study LAI116815 also compared the RBA of CAB 400 mg LA ([redacted] nm [redacted]) manufactured via [redacted] to historical data from Cohorts 3 and 8 from LAI114433, for which [redacted] (Table 20). Given the limitations of cross-study comparisons, [redacted] were generally comparable with [redacted], having a higher AUC(0-wk12) but a lower Cwk12 compared with [redacted].

Table 20 Comparison of CAB LA PK Parameters following a 400 mg Single Dose Administration of the [redacted] nm, [redacted] µm, and [redacted] µm Formulations (LAI116815) (PK Parameter Population)

PK Parameters	GLS Mean Ratio [90% CI]		
	[redacted] µm vs. [redacted] nm	[redacted] µm vs. [redacted] nm	[redacted] nm vs. [redacted]
AUC(0-inf)	1.02 [0.79, 1.32]	0.87 [0.66, 1.14]	ND
AUC(0-wk4)	1.26 [0.71, 2.23]	0.78 [0.44, 1.36]	1.47 [0.85, 2.56]
AUC(0-wk12)	1.13 [0.72, 1.78]	0.71 [0.46, 1.09]	1.33 [0.86, 2.05]
Cmax	1.39 [0.79, 2.43]	0.76 [0.44, 1.32]	1.31 [0.76, 2.26]
Cwk4	1.03 [0.61, 1.75]	0.65 [0.39, 1.10]	1.62 [0.97, 2.69]
Cwk12	1.01 [0.67, 1.52]	0.97 [0.65, 1.44]	0.65 [0.44, 0.96]
CL/F	0.98 [0.76, 1.27]	1.15 [0.88, 1.51]	ND
t1/2	1.13 [0.79, 1.62]	1.66 [1.13, 2.42]	ND

Data Source: GSK Doc. # 2014N208332_00 Table 3.10

[redacted] nm = [redacted] nm [redacted] ([redacted]); [redacted] µm = [redacted] µm [redacted] ([redacted]); [redacted] µm = [redacted] µm [redacted] ([redacted]); [redacted] nm [redacted].

3.2.2. Oral CAB

Oral RBA of CAB has been evaluated in 4 single dose studies (Table 21). In ITZ111682, CAB 10 mg (2 x 5 mg tablets, fasted, test treatment) was compared to the sodium salt oral solution administered in the FTIH study (ITZ111451 Part A and Part B) (Table 21). Median CAB tmax was increased from 1 h following oral solution to 2.5 h following administration of the sodium salt tablet formulation (fasted). In clinical studies, oral CAB has been administered as a sodium salt formulation whereas CAB LA has been administered as a free acid formulation. LAI116585 evaluated the RBA of 2 new free acid oral formulations ([redacted] and [redacted]) of CAB 30 mg compared with the original CAB 30 mg sodium salt formulation (Table 21). Median tmax increased from 2 h following administration of the sodium salt to 3 h following administration of both free acid formulations. In LAI117020, CAB 30 mg [redacted] and [redacted] tablet formulations were compared with the original sodium salt tablet formulation. Median tmax increased from 2 h following the sodium salt to 3 h following administration of both test formulations. Neither test formulation was selected for further development.

In 201741, CAB 30 mg with [redacted] or [redacted] mg and either [redacted] or [redacted], were compared with the original 30 mg [redacted] formulation with a [redacted] mg. The [redacted] test formulation with a [redacted] mg was bioequivalent to the reference formulation (Table 21). Therefore, CAB 30 mg tablets using [redacted] with a [redacted] mg was selected for Phase III and future studies.

Table 21 Comparison of PK Parameters following Single Dose Administration of Various CAB Oral Formulations

Study	CAB Comparison Test:Reference	Plasma CAB PK Parameter Test:Reference GLS Mean Ratio [90% CI]			
		AUC(0-inf)	AUC(0-t)	Cmax	C24
ITZ111682 (n=15)	10 mg (2x 5 mg) Na Salt tablets fasted vs. Na Salt Solution	0.72 [0.61, 0.84]	0.71 [0.61, 0.83]	0.59 [0.53, 0.66]	0.75 [0.65, 0.85]
LAI116585 (n=18)	30 mg Free acid [redacted] vs. Na Salt tablets	0.88 [0.78, 0.99]	0.87 [0.77, 0.98]	0.81 [0.72, 0.91]	0.87 [0.77, 0.98]
	30 mg Free acid [redacted] vs. Na Salt tablets	0.52 [0.46, 0.58]	0.51 [0.45, 0.57]	0.46 [0.41, 0.52]	0.50 [0.44, 0.56]
LAI117020 (n=22)	30 mg [redacted] vs. Na Salt tablets	0.70 [0.62, 0.79]	0.69 [0.61, 0.78]	0.64 [0.56, 0.73]	0.71 [0.63, 0.80]
	30 mg [redacted] vs. Na Salt tablets	0.58 [0.52, 0.65]	0.58 [0.51, 0.65]	0.53 [0.47, 0.61]	0.57 [0.51, 0.65]
201741 (n=18)	30 mg [redacted] vs. [redacted] Na Salt tablets	1.03 [0.93, 1.15]	1.04 [0.93, 1.15]	1.03 [0.92, 1.15]	1.04 [0.94, 1.16]
	30 mg [redacted] vs. [redacted] Na Salt tablets	0.81 [0.73, 0.90]	0.81 [0.74, 0.90]	0.79 [0.71, 0.88]	0.82 [0.74, 0.92]
	30 mg [redacted] vs. [redacted] Na Salt tablets	0.91 [0.79, 1.04]	0.91 [0.80, 1.04]	0.91 [0.78, 1.05]	0.91 [0.76, 1.08]
	30 mg [redacted] vs. [redacted] Na Salt tablets	0.75 [0.65, 0.86]	0.75 [0.66, 0.86]	0.75 [0.64, 0.87]	0.68 [0.57, 0.81]

Data Source: GSK Doc. # RM2008/00637/00 Table 11.4; GSK Doc. # 2012N152984_00 Table 3.6; GSK Doc. # 2014N206383_00 Table 3.9; GSK Doc. # 2015N248022_00 Table 3.6

3.3. Dosing Relative to Food

The effect of food on CAB is modest and not dependent on calorie or fat content. Oral CAB can be taken without regard to meals.

Single oral dose administration of the Phase III CAB 30 mg tablet formulation ([redacted], [redacted] mg [redacted]) with a high-fat meal (53% fat, 870 calories) resulted in a 14 to 17% increase in plasma CAB PK parameters in Study 205696. Median tmax and variability in PK parameters were unaffected by administration following a high-fat meal.

The impact of a high fat meal on CAB PK using the proposed commercial formulation was consistent with prior RBA studies evaluating the impact of a moderate-fat meal on early prototype formulations and dose levels (Table 22). Food modestly increases the oral bioavailability of CAB; therefore, CAB can be taken without regard to meals or caloric-content.

The modest 14 to 17% increase in CAB exposure with a high-fat meal is not considered clinically significant based on the accumulated safety data in Phase IIb and III studies (see m5.3.5.3). In Phase IIb and III studies, oral CAB was recommended to be taken with a meal during co-administration with oral RPV because RPV should be taken with a meal to ensure optimal absorption.

Refer to Appendix Table 1 for formulation details.

Table 22 CAB PK Treatment Comparisons Following Single-Dose Administration with and without a High-fat or Moderate-fat Meal Across Studies

Study	Dose and Formulation	Fat Content	GLS Mean Ratio [90% CI] Fed:Fasted		
			AUC(0-inf)	Cmax	AUC(0-t)
205696 (n=21)	CAB 30 mg single dose [redacted] tablet	High	1.14 [1.02, 1.28]	1.14 [1.03, 1.27]	1.14 [1.03, 1.27]
LAI117020 (n=15)	CAB 30 mg single dose [redacted] tablet	Moderate	1.08 [0.98, 1.20]	1.08 [0.96, 1.22]	NR
ITZ111682 (n=15)	CAB 10 mg single dose [redacted] tablet	Moderate	1.15 [0.98, 1.36]	1.04 [0.93, 1.16]	1.15 [0.99, 1.35]

Data Source: GSK Doc. # 2016N298724_00 Table 3.5; GSK Doc. # 2014N206383_00 Table 3.10; GSK Doc. # RM2008/00637/00 Table 11.4
Refer to Appendix Table 1 for formulation details.

4. MAIN BIOPHARMACEUTICAL CONCLUSIONS

The bioanalytical methods used to measure concentrations of CAB in human plasma were selective, accurate, and reproducible.

4.1. CAB LA

- The proposed commercial formulation of CAB LA was used in Phase III studies.

4.2. Oral CAB

- The proposed commercial formulation of CAB 30 mg tablets was used in Phase III studies.
- CAB can be taken with or without food.

5. APPENDIX

Appendix Table 1 Summary of Drug Substance and Drug Product

Study Reference Number	Dosage Form	Formula Code[a, b]	Treatment or Cohort Number	Drug Product Batch Number	Input Drug Substance Batch Number
LAI114433	Injectable Suspension (200 mg/mL	1	Cohorts 1, 2, 3, 5, 6, and 7	[redacted]	[redacted] (Manufacturer's batch number: [redacted])
			Cohorts 4, 8, and 9	[redacted]	
LAI116815	Tablet, 30 mg	30/800M	Oral lead-in	[redacted]	[redacted]
	Injectable Suspension (200 mg/mL	2	Treatment A		(Manufacturer's batch number: [redacted])
		3	Treatment B		
		4	Treatment C		
201741	Tablet, 30 mg	30/800M	Treatment A (Cohorts 1 and 2)	[redacted]	(Manufacturer's batch number: [redacted])
		30/500M	Treatment B (Cohort 1)	[redacted]	[redacted]
		30/500U	Treatment C (Cohort 1)		
		30/650M	Treatment D (Cohort 2)		
		30/650U	Treatment E (Cohort 2)		
LAI117020	Tablet, 30 mg	30/800M	Treatment A	[redacted]	(Manufacturer's batch number: [redacted])
		30/200M	Treatment B	[redacted]	[redacted]
		30/200U	Treatment C		
LAI116585	Tablet, 30 mg	30/800M	Treatment A	[redacted]	[redacted]
	Capsule	30/200U[c]	Treatment B	[redacted]	(Manufacturer's batch number: [redacted])
		30/200M[c]	Treatment C	[redacted]	[redacted]

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study Reference Number	Dosage Form	Formula Code[a, b]	Treatment or Cohort Number	Drug Product Batch Number	Input Drug Substance Batch Number
ITZ111682	Powder for Reconstitution, 10 mg	10/M	Treatment A	[redacted][d] (Manufacturer's batch number: [redacted])	[redacted][d] (Manufacturer's batch number: [redacted])
	Tablet, 5 mg	5/109.1M	Treatments B and C	[redacted] (Bulk drug product batch number: [redacted])	[redacted]
205696	Tablet, 30 mg	30/500M	Treatments A and B	[redacted]	[redacted]
207966	Injectable Suspension, 200 mg/mL	2	Q8W and Q4W	[redacted]	[redacted]
	Tablet, 30 mg	30/500M		[redacted]	[redacted]

a. For parenteral formulations, the Formula Code given corresponded to that used in m.3.2.P.5.4 Batch Analyses. Formulations 2, 3 and 4 correspond to formulations A, B and C, respectively in Section 1.2.1.1 in m.3.2.P.2.2 Pharmaceutical Development_Drug Product_Cabotegravir Injectable Suspension.

b. For oral formulations, 'Formula Code' describes the formulation [redacted]; a [redacted].

c. Drug substance is CAB free acid.

d. For Powder for Reconstitution formulation used in Study ITZ111682, CAB sodium ([redacted]) was provided directly to the clinical study sites and extemporaneously prepared by a site pharmacist. No additional drug substance release data were generated for the extemporaneously prepared drug product. Batch analysis data for the batch of drug substance used in the study is presented m3.2.S.4.4 Batch Analyses_Cabotegravir Sodium.

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 2 Summary of in vitro Dissolution Studies

Study Reference Number	Dosage Form	Formula Code[a,b]	Batch Number[c]	Conditions USP App 2	No. of Dosage Units	Collection Times (min)[d] % Dissolved (Mean)
LAI114433	Injectable Suspension[e], 200 mg/mL	1	[redacted]	[redacted]	[redacted]	[redacted]
LAI116815	Tablet, 30 mg	[redacted]	[redacted]			
	Injectable Suspension[e], 200 mg/mL	2				
		3				
		4				
201741	Tablet, 30 mg	[redacted]				
LAI117020	Tablet, 30 mg					
LAI116585	Tablet, 30 mg	[redacted]	[redacted]			
	Capsule, 30 mg	[redacted]	[redacted]			
ITZ111682	Powder for Reconstitution[f], 10 mg	[redacted]	[redacted]			
	Tablet, 5 mg	[redacted]	[redacted][g]			
205696	Tablet, 30 mg	[redacted]	[redacted]			

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study Reference Number	Dosage Form	Formula Code[a,b]	Batch Number[c]	Conditions USP App 2	No. of Dosage Units	Collection Times (min)[d] % Dissolved (Mean)
207966	Injectable Suspension, 200 mg/mL	2	[redacted]	[redacted]		
	Tablet, 30 mg	30/500M	[redacted]			

a. For parenteral formulations, the Formula Code given corresponded to that used in m.3.2.P.5.4 Batch Analyses. Formulations 2, 3 and 4 correspond to formulations A, B and C, respectively in Section 1.2.1.1 in m.3.2.P.2.2 Pharmaceutical Development_Drug Product_Cabotegravir Injectable Suspension.

b. For oral formulations, 'Formula Code' describes the formulation [redacted].

c. Batch numbers for bulk product.

d. " – " = Timepoint not required in test method.

e. Studies LAI114433 and LAI116815 were conducted prior to the introduction of the dissolution method and hence no dissolution data are presented.

f. For Powder for Reconstitution formulation used in Study ITZ111682, CAB sodium ([redacted]) was provided directly to the clinical study sites and extemporaneously prepared by a site pharmacist. No additional drug substance release data were generated for the extemporaneously prepared drug product. Batch analysis data for the batch of drug substance used in the study is presented in m3.2.S.4.4 Batch Analyses_Cabotegravir Sodium.

g. Packaged drug product batch number: [redacted]

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 3 Bioanalytical Methods Summary

Validation Report	Clinical Studies Supported	Method Description and Performance	
Validation of a Method for the Determination of GSK1265744 in Human Plasma by HPLC with MS/MS Detection GSK Doc. #: 2012N133238_00 **Supplemental Report (Incorporation of long-term stability and interference checks)** GSK Doc. # 2014N193953_00 [redacted], [redacted], [redacted] USA	LAI115428 LAI116482 LAI116585 LAI116815 LAI117008	GSK1265744 is extracted from 50µL human plasma by protein precipitation using 50/50 (acetonitrile/water) containing [$^{13}C^{2}H_{2}{}^{15}N$]-GSK1265744 as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 ng/mL
		Validated Range	10.0 to 10000 ng/mL
		Within-run Precision (%CV)	≤13.9%
		Between-run Precision (%CV)	≤9.1%
		Accuracy (%Bias)	-4.3 ≤ bias ≤ 10.0%
		Stability in Human Plasma	5 freeze-thaw cycles at -10°C to -30°C and at -60°C to -80°C 140 days at -10°C to -30°C 284 days at -60°C to -80°C 271 days at -10°C to -30°C in the presence of Rilpivirine 267 days at -60°C to -80°C in the presence of Rilpivirine 24 h at ambient temperature
		Processed Sample Viability	164 h at 2°C to 8° C
Validation of a Method for the Determination of GSK1265744 in Human Plasma by HPLC with MS/MS Detection [redacted] Study 8298139	LAI117009 LAI117010 LAI117011 LAI117020 201120 201741 201479 201480	Cabotegravir (GSK1265744, CAB) was extracted from 25 µL of human plasma by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([$^{13}C^{2}H_{2}{}^{15}N$]-GSK1265744 in 50/50, acetonitrile/water), followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring.	
		LLQ	25.0 ng/mL
		Validated Range	25.0 to 25,000 ng/mL
		Within-run Precision (%CV)	≤6.8%

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
GSK Doc. # 2014N192374_01 **Supplemental Reports (Incorporation of long-term stability and interference checks)** 2015N236615_00 2015N263259_00 2016N306524_00 [redacted], [redacted], USA	201584 201585 200056 200056 sub study 205696 205712 207966	Between-run Precision (%CV)	≤9.1%
		Accuracy (%Bias)	-8.8% ≤ bias ≤8.0%
		Stability in Human Plasma	24 h at ambient temperature 24 h at ambient temperature in the presence of CAB-Glucuronide 5 cycles freeze-thaw cycles at -10 to -30°C 5 cycles freeze-thaw cycles at -60 to -80°C 5 cycles freeze-thaw cycles in the presence of CAB-Glucuronide at -10 to -30°C 5 cycles freeze-thaw cycles in the presence of CAB-Glucuronide at -60 to -80°C 998 days at -10 to -30°C 231 days at -10 to -30°C in the presence of CAB-Glucuronide 231 days at -60 to -80°C in the presence of CAB-Glucuronide
		Processed Extract Stability	145 h at 2 to 8°C 145 h at 2 to 8°C in the presence of CAB-Glucuronide
The Validation of a Method for the Determination of GSK1265744 in Human Plasma (10 to 10000 ng/mL) using HPLC-MS/MS GSK Doc. # RD2008/00249/00	LAI116181 LAI114433 ITZ111451 ITZ111682 ITZ111839 ITZ112929	GSK1265744 is extracted from 25 μL human plasma by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([$^{13}C^{2}H_{2}{}^{15}N$]-GSK1265744, in 50/50, acetonitrile/water). Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	10.0 ng/mL
		Validated Range	10.0 to 10000 ng/mL
		Within-run Precision (%CV)	≤12.6%
		Between-run Precision (%CV)	≤5.6%
		Accuracy (%Bias)	-9.1% ≤ bias ≤11.1%

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
Supplemental Report (Incorporation of long-term stability) GSK Doc. # 2014N208171_00 GlaxoSmithKline Five Moore Drive, Research Triangle Park, NC 27709 USA		Stability in Human Plasma	3 freeze-thaw cycles at -30° C 595 days at -30°C 24 h at ambient temperature
		Processed Extract Stability	5 days at ambient temperature
Validation of a Method for the Determination of Ethinyl Estradiol and Levonorgestrel in Human Plasma by HPLC with MS/MS Detection GSK Doc. # 2018N369172_00 [redacted], [redacted], USA	LAI117011	Ethinyl Estradiol and Levonorgestrel is extracted from 500 μL human plasma by liquid-liquid extraction followed by derivatization using acetonitrile/water containing Ethinyl Estradiol-D_4 and Norgestrel-D_6 as an internal standard. Extracts are analyzed by LC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring	
		LLQ	7.50 pg/mL for Ethinyl Estradiol 150 pg/mL for Levonorgestrel
		Validated Range	7.50 to 500 pg/mL for Ethinyl Estradiol 150 to 10,000 pg/mL for Levonorgestrel
		Within-run Precision (%CV)	≤6.5% Ethinyl Estradiol ≤6.7% Levonorgestrel
		Between-run Precision (%CV)	≤5.5% Ethinyl Estradiol ≤7.7% Levonorgestrel
		Accuracy (%Bias)	-7.9% ≤ bias ≤-1.0% Ethinyl Estradiol -5.0% ≤ bias ≤ 10.3% Ethinyl Estradiol
		Stability in Human Plasma	5 freeze-thaw cycles at -10°C to -30° C and at -60°C to -80° C 926 days at -10°C to -30° C Ethinyl Estradiol: at least 591 days at -60°C to -80° C Levonorgestrel: at least 926 days at -60°C to -80° C 24 h at ambient temperature
		Processed Sample Viability	120 h at 2°C to 8°C

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
Validation of a Method for the Determination of GSK1265744 in Human Plasma Ultrafiltrate: Human Plasma (90:10) by HPLC with MS/MS Detection GSK Doc. # 2015N230737_00 **Supplemental Report (Incorporation of long-term stability)** GSK Doc. # 2016N284755_00 [redacted], [redacted], [redacted] USA-	LAI116181 LAI114433 ITZ111839 ITZ112929 200056 sub study	GSK1265744 is extracted from 50 μL human plasma ultrafiltrate: human plasma (90:10) by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([$^{13}C^{2}H_{2}{}^{15}N$]-GSK1265744, in 50/50, acetonitrile/water). Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring	
		LLQ	1.00 ng/mL
		Validated Range	1.00 to 2500 ng/mL
		Within-run Precision (%CV)	≤7.2%
		Between-run Precision (%CV)	≤12.6%
		Accuracy (%Bias)	-14.8% ≤ bias ≤8.0% -6.3% ≤ bias ≤4.0%
		Stability in Human Plasma Ultrafiltrate: Human Plasma (90:10)	5 freeze-thaw cycles at -10°C to -30° C and at -60°C to -80° C 126 days at -10°C to -30° C and at -60°C to -80° C 24 h at ambient temperature
		Processed Extract Stability	118 h at 2°C to 8°C
Validation of a Method for the Determination of GSK1265744 in Human Cerebrospinal Fluid by HPLC with MS/MS Detection GSK Doc. # 2018N370858_00 [redacted],	200056 sub study	GSK1265744 is extracted from 25 μL cerebrospinal fluid (CSF) by dilution using 50/50 methanol/water) containing [$^{13}C^{2}H_{2}{}^{15}N$]-GSK1265744 as an internal standard. Extracts are analyzed by HPLC MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	1.0 ng/mL
		Validated Range	1.0 to 1000 ng/mL
		Within-run Precision (%CV)	≤9.1%
		Between-run Precision (%CV)	≤9.8%
		Accuracy (%Bias)	-4.5 ≤ bias ≤ 6.0%

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
[redacted], USA		Stability in CSF	4 freeze-thaw cycles at -10°C to -30°C and at -60°C to -80°C 258 days at -10°C to -30°C and at -60°C to -80°C 24 h at ambient temperature
		Processed Sample Stability	190 h at 2°C to 8°C
Quantification of Cabotegravir (GSK1265744) in Human K_2EDTA Plasma via Combined Liquid Chromatography-Tandem Mass Spectrometric (LC-MS/MS) Analysis GSK Doc. # 2019N405235_00 [redacted], USA	201103 (HPTN 077)	GSK1265744 is extracted from 25 μL of human plasma by protein precipitation using acetonitrile containing an isotopically labelled internal standard, ([$^{13}C^2H_2{}^{15}N$]-GSK1265744, in 50/50, acetonitrile/water). Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	25 ng/mL
		Validated Range	25 – 25000 ng/mL
		Within-run Precision (%CV)	≤ 19.77%
		Between-run Precision (%CV)	≤ 16.43%
		Accuracy (%Bias)	-7.00% ≤ bias ≤ 16.27%
		Stability in Human Plasma	198 days at -70°C
		Processed Sample Stability	3 days at 4°C

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 4 Between-run Accuracy and Precision of Quality Control (QC) Samples

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
LAI115428 (2012N144299_00)		**30**	**500**	**7500**		
	Overall Mean (ng/mL)	30.5	503	7390		
	S.D. (within-run means)	1.62	15.7	194		
	Precision (%CV)	5.3	3.1	2.6		
	Average Bias (%)	1.7	0.6	-1.5		
	n=	54	54	54		
LAI116482 (2012N153127_00)		**30**	**500**	**7500**		
	Overall Mean (ng/mL)	30.2	493	7320		
	S.D. (within-run means)	2.29	26.1	310		
	Precision (%CV)	7.6	5.3	4.2		
	Average Bias (%)	0.7	-1.4	-2.4		
	n=	82	82	82		
LAI116585 (2012N152369_00)		**30**	**500**	**7500**		
	Overall Mean (ng/mL)	32.2	532	7590		
	S.D. (within-run means)	1.10	21.0	199		
	Precision (%CV)	3.4	4.0	2.6		
	Average Bias (%)	7.3	6.4	1.2		
	n=	26	26	25		
LAI116815 (2013N164530_00)		**30**	**500**	**7500**		
	Overall Mean (ng/mL)	29.8	508	7400		
	S.D. (within-run means)	1.27	14.5	188		
	Precision (%CV)	4.3	2.9	2.5		
	Average Bias (%)	-0.7	1.6	-1.3		
	n=	24	24	24		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
LAI117008 (2013N171667_00)		**30**	**500**	**7500**		
	Overall Mean (ng/mL)	28.1	453	6970		
	S.D. (within-run means)	1.57	27.3	194		
	Precision (%CV)	5.6	6.0	2.8		
	Average Bias (%)	-6.3	-9.4	-7.1		
	n=	14	14	14		
LAI117009 (2014N200138_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	76.6	1280	18000		
	S.D. (within-run means)	5.64	70.3	967		
	Precision (%CV)	7.4	5.5	5.4		
	Average Bias (%)	2.1	6.7	-4.3		
	n=	20	20	20		
LAI117010 (2015N252398_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	75.7	1220	19000		
	S.D. (within-run means)	2.81	27.9	663		
	Precision (%CV)	3.7	2.3	3.5		
	Average Bias (%)	0.9	1.7	1.1		
	n=	14	14	14		
LAI117011 (2014N220153_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	81.7	1270	19200		
	S.D. (within-run means)	5.25	67.2	713		
	Precision (%CV)	6.4	5.3	3.7		
	Average Bias (%)	8.9	5.8	2.1		
	n=	8	8	8		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
LAI117020 (2014N202112_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	77.5	1250	18800		
	S.D. (within-run means)	8.54	98.6	1140		
	Precision (%CV)	11.0	7.9	6.1		
	Average Bias (%)	3.3	4.2	0.0		
	n=	44	44	44		
LAI116181 (2012N135068_00)		**30**	**800**	**8000**		
	Overall Mean (ng/mL)	31.3	847.8	8751.9		
	S.D. (within-run means)	1.2	20.2	261.5		
	Precision (%CV)	3.9	2.4	3.0		
	Average Bias (%)	4.3	6.0	9.4		
	n=	10	10	10		
LAI114433 (2013N161230_00)		**30**	**800**	**8000**		
	Overall Mean (ng/mL)	30.2	829.7	8391.2		
	S.D. (within-run means)	1.7	44.6	476.8		
	Precision (%CV)	5.7	5.4	5.7		
	Average Bias (%)	0.7	3.7	4.9		
	n=	80	80	80		
201120 (2014N213007_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	76.7	1210	18900		
	S.D. (within-run means)	5.38	40.9	672		
	Precision (%CV)	7.0	3.4	3.6		
	Average Bias (%)	2.3	0.8	0.5		
	n=	62	62	62		

2.7.1 Summary of Biopharmaceutic Studies
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Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
201741 (2015N235617_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	73.1	1160	18500		
	S.D. (within-run means)	10.3	198	2880		
	Precision (%CV)	14.1	17.1	15.6		
	Average Bias (%)	-2.5	-3.3	-1.6		
	n=	56	56	56		
201479 (2015N254802_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	81.2	1260	18500		
	S.D. (within-run means)	6.09	52.0	420		
	Precision (%CV)	7.5	4.1	2.3		
	Average Bias (%)	8.3	5.0	-1.6		
	n=	12	12	12		
201480 (2015N254804_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	79.9	1260	18700		
	S.D. (within-run means)	3.95	49.6	470		
	Precision (%CV)	4.9	3.9	2.5		
	Average Bias (%)	6.5	5.0	-0.5		
	n=	16	16	16		
205696 (2016N299628_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	79.9	1230	19300		
	S.D. (within-run means)	4.12	55.4	784		
	Precision (%CV)	5.2	4.5	4.1		
	Average Bias (%)	6.5	2.5	2.7		
	n=	20	20	20		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
205712 (2017N339493_00 *Statistics with outlier value **Statistics without outlier value		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	67.4^/73.6*	1230	18900		
	S.D. (within-run means)	22.3^/8.90*	47.0	1380		
	Precision (%CV)	33.1^/12.1*	3.8	7.3		
	Average Bias (%)	-10.1^/-1.9*	2.5	0.5		
	n=	11^/10*	12	12		
ITZ111451 (2018N384098_00)		**40**	**800**	**8000**		
	Overall Mean (ng/mL)	39.9	817.1	8104.6		
	S.D. (within-run means)	3.1	38.5	408.6		
	Precision (%CV)	7.8	4.7	5.0		
	Average Bias (%)	-0.3	2.1	1.3		
	n=	100	100	100		
ITZ111682 (2018N384190_00)		**40**	**800**	**8000**		
	Overall Mean (ng/mL)	38.8	769.7	7442.1		
	S.D. (within-run means)	3.7	58.8	627.8		
	Precision (%CV)	9.5	7.6	8.4		
	Average Bias (%)	-3.1	-3.8	-7.0		
	n=	30	30	30		
ITZ111839 (RD2009/01270/00)		**40**	**800**	**8000**		
	Overall Mean (ng/mL)	40.0	818.3	7971.1		
	S.D. (within-run means)	0.7	17.8	139.6		
	Precision (%CV)	1.8	2.2	1.8		
	Average Bias (%)	0.1	2.3	-0.4		
	n=	10	10	10		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
ITZ112929 (RD2009/01175/00)		**40**	**800**	**8000**		
	Overall Mean (ng/mL)	40.7	788.1	7731.7		
	S.D. (within-run means)	1.2	27.3	190.2		
	Precision (%CV)	3.1	3.5	2.5		
	Average Bias (%)	1.8	-1.5	-3.4		
	n=	10	10	10		
201479 (2015N254802_00) QC in Human Plasma: Human Plasma Ultrafiltrate (1:9, v:v)		**3**	**75**	**2000**		
	Overall Mean (ng/mL)	3.10	78.1	1960		
	S.D. (within-run means)	0.195	3.01	90.7		
	Precision (%CV)	6.3	3.9	4.6		
	Average Bias (%)	3.3	4.1	-2.0		
	n=	16	16	16		
201480 (2015N254804_00) QC in Human Plasma: Human Plasma Ultrafiltrate (1:9, v:v)		**3**	**75**	**2000**		
	Overall Mean (ng/mL)	3.02	77.3	1990		
	S.D. (within-run means)	0.244	3.33	165		
	Precision (%CV)	8.1	4.3	8.3		
	Average Bias (%)	0.7	3.1	-0.5		
	n=	30	30	30		
200056 sub study (2018N383277_00) QC in Human Plasma: Human Plasma Ultrafiltrate (1.9, v:v)		**3**	**75**	**2000**		
	Overall Mean (ng/mL)	3.19	79.9	1910		
	S.D. (within-run means)	0.206	3.19	32.0		
	Precision (%CV)	6.5	4.0	1.7		
	Average Bias (%)	6.3	6.5	-4.5		
	n=	10	10	10		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
200056 sub study (2018N383277_00) QC in Human CSF		**3**	**30**	**400**	**750**	
	Overall Mean (ng/mL)	3.16	31.5	422	766	
	S.D. (within-run means)	NA	NA	NA	NA	
	Precision (%CV)	NA	NA	NA	NA	
	Average Bias (%)	5.3	5.0	5.5	2.1	
	n=	2	2	2	2	
200056 (2018N383277_00) QC in Human Plasma		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	72.8	1050	17300		
	S.D. (within-run means)	NA	NA	NA		
	Precision (%CV)	NA	NA	NA		
	Average Bias (%)	-2.9	-12.5	-8.0		
	n=	2	2	2		
201584 (2017N319681_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	75.8	1220	18700		
	S.D. (within-run means)	5.31	101	1050		
	Precision (%CV)	7.0	8.3	5.6		
	Average Bias (%)	1.1	1.7	-0.5		
	n=	272	272	271		
201585 (2017N319687_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	76.0	1230	18600		
	S.D. (within-run means)	9.25	68.2	1020		
	Precision (%CV)	12.2	5.5	5.5		
	Average Bias (%)	1.3	2.5	-1.1		
	n=	222	222	222		

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**				
207966 (2018N369352_01)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	147^ / 75.7*	1240^ / 1200*	18500^ / 18600*		
	S.D. (within-run means)	1160^ / 6.4*	604^ / 57.2*	1830^ / 1470*		
	Precision (%CV)	789.1^ / 8.5*	48.7^ / 4.8*	9.9^ / 7.9*		
	Average Bias (%)	96.0^ / 0.9*	3.3^ / 0.0*	-1.6^ / -1.1*		
	n=	288^ / 286*	288^ / 287*	288^ / 287*		
201103 (2019N405235_00)		**75**	**1200**	**18800**		
	Overall Mean (ng/mL)	77.52	1206.14	18098.74		
	S.D. (within-run means)	5.91	104.03	1054.96		
	Precision (%CV)	7.63	8.62	5.83		
	Average Bias (%)	3.56	0.48	-3.60		
	n=	137	147	151		

^ Stats including all values
* Stats excluding likely Outliers

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 5 Tabular Listing of all Biopharmaceutic Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
201741	PK Relative Bioavailability	To evaluate the relative bioavailability of 4 new CAB 30 mg sodium salt tablet formulations ([redacted]) compared to a tablet of the current sodium salt formulation in the fasted state	R, OL, XO	Healthy subjects	37: 27/10 32.4 (19 – 57)	Cohort 1 Treatment A = CAB 30 mg current formulation, reference Treatment B = CAB 30 mg new formulation [redacted] mg [redacted] Treatment C = CAB 30 mg new formulation [redacted] mg [redacted] Cohort 2 Treatment A = CAB 30 mg current formulation, reference Treatment D = CAB 30 mg new formulation [redacted] mg [redacted] Treatment E = CAB	Complete; Full CSR	m5.3.1.1

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
						30 mg new formulation [redacted] mg [redacted]		
LAI117020	PK Relative Bioavailability	Part A: To evaluate the relative bioavailability of 2 new CAB 30 mg sodium salt tablet formulations compared to a tablet of the current sodium salt formulation in the fasted state. Part B: To evaluate the effect of a moderate-fat meal on the bioavailability of the selected tablet formulation	R, OL, XO	Healthy subjects	24: 14/10 41.8 (20 – 60)	Treatment A: 30 mg current formulation, fasted Treatment B: 30 mg formulation [redacted], fasted Treatment C: 30 mg formulation [redacted], fasted Treatment D = 744 30mg treatment B, fed (moderate-fat meal)	Complete; Full CSR	m5.3.1.1
LAI116585	PK Relative Bioavailability	To evaluate the relative bioavailability of 2 new GSK1265744 30 mg free acid capsule	R, OL, XO	Healthy subjects	18: 10/8 36.7 (21 – 60)	CAB 30 mg free acid capsule formulations CAB a tablet sodium salt formulation	Complete; Full CSR	m5.3.1.1

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
		formulations compared to a tablet of the current sodium salt formulation in the fasted state						
LAI114433	Relative Bioavailability	To investigate the safety, tolerability, and PK of CAB LA following single dose IM or SC administration in healthy subjects	PLC, R, DB	Healthy subjects	72: 39/33 35.1 (18-55)	Single dose CAB 100 mg IM CAB 100 mg SC CAB 200 mg IM CAB 200 mg SC CAB 400 mg IM CAB 400 mg SC CAB 800 mg IM	Complete; Full CSR	m5.3.3.1
LAI116815	Relative Bioavailability	To evaluate the RBA of two new formulations of CAB 400 mg LA given IM compared to the current formulation ([redacted] nm [redacted])	R, OL, PRL	Healthy subjects	43: 35/8; 34.8 (20-64)	Lead in (all treatments) CAB 30mg for 14 days Midazolam 3 mg probe x 2 doses (n=12) Treatment A: 400 mg [redacted] ([redacted] nm) Treatment B: 400 mg [redacted] ([redacted] μm) Treatment C: 400 mg [redacted] ([redacted] μm)	Complete; Full CSR	m5.3.1.1
ITZ111682	PK Relative Bioavailability Food Effect	To evaluate the single-dose relative bioavailability of CAB 10mg administered in	R, O, PRL	Healthy subjects	45: 36/9 33.2 (19 – 55)	CAB 10 mg oral solution, single dose, fasted CAB 10 mg (2x5 mg) tablet, single dose,	Complete; Full CSR	m5.3.1.1

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
		either oral solution fasted, two 5mg tablets fasted, or two 5mg tablets following a moderate-fat content meal.				fasted CAB 10 mg (2x5 mg) tablet, single dose, fed		
205696	PK Food Effect	To evaluate the effect of a high-fat meal on the PK of CAB following a single 30 mg dose using the Phase III formulation	R, OL, XO	Healthy subjects	24: 16/8 39.7 (23 – 66)	Treatment A: 30 mg Phase III tablet formulation, [redacted], [redacted] mg [redacted], fasted Treatment B: 30 mg Phase III tablet formulation, [redacted], [redacted] mg [redacted], fed	Complete; Full CSR	m5.3.3.1

Degree of Blinding
OL = Open label
SB = Single Blind
DB = Double Blind

Degree of Control
UC = Uncontrolled
PLC = Placebo control
AC = Active control

Treatment Assignment
R = Random
NR = Nonrandom

Treatment Sequence
PRL = Parallel
XO = Crossover
DR = Dose Rising

M = Male
F = Female
CAB = Cabotegravir
IM = Intramuscular
SC = Subcutaneous
PK = Pharmacokinetic
LA = Long-acting

Legend to Appendix Table 6 Summary Results of All Biopharmaceutic Studies

Protocol No.	The Study identifier.
Study Design:	Degree of blinding: O=open, SB=single blind, DB=double blind Degree of control: UC=uncontrolled, PLC=placebo, AC=active control Treatment assignment: R=random, NR=nonrandom Treatment sequence: XO=crossover, PRL=parallel, DR=Dose rising
Number of subjects (M/F):	Number of subjects/patients who received study medication; (number of males M/ females F)
Age Mean Range:	Provides the mean and range of ages in years
Treatment Details (Drug/Dose/Form/ Route/Frequency):	Study treatments are identified Dose (mg) of each treatment as specified in the protocol (od=once daily, bd=twice daily) Number of individual days receiving study medication
Cmax	Maximum observed plasma concentration.
tmax	Time to reach the maximum observed plasma concentration.
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
t½	Apparent terminal elimination half-life
Others	[Add As appropriate]

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Appendix Table 6 Summary Results of All Biopharmaceutic Studies

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean (Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)				Study Report Location
					Cmax (μg/mL)	tmax(h) Median (Range)	AUC0-inf (h.μg/mL)	t1/2 (h)	
201741	To evaluate the relative bioavailability of 4 new CAB 30 mg sodium salt tablet formulations ([redacted]) compared to a tablet of the current sodium salt formulation in the fasted state	R, O, XO	37: 27/10 32.4 (19 – 57) Healthy subjects	Cohort 1 Treatment A = CAB 30 mg current formulation, reference	3.35 (24)	2.01 (0.5 – 6.0)	131 (33)	39.1 (23)	m5.3.1.1
				Treatment B = CAB 30 mg new formulation [redacted] mg [redacted]	3.43 (21)	3.00 (1.0 – 4.0)	135 (26)	38.4 (24)	
				Treatment C = CAB 30 mg new formulation [redacted] mg [redacted]	2.65 (29)	2.00 (1.0 – 4.0)	106 (27)	36.8 (23)	
				Cohort 2 Treatment A = CAB 30 mg current formulation, reference	3.48 (29)	2.01 (0.5 – 6.0)	142 (25)	38.6 (12)	
				Treatment D = CAB 30 mg new formulation					

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean (Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)				Study Report Location
					Cmax (μg/mL)	tmax(h) Median (Range)	AUC0-inf (h.μg/mL)	t1/2 (h)	
				[redacted], [redacted] mg [redacted] [redacted]	3.15 (27)	2.01 (0.5 – 6.0)	129 (26)	37.4 (14)	
				Treatment E = CAB 30 mg new formulation [redacted], [redacted] mg [redacted] [redacted]	2.60 (36)	2.00 (0.5 – 4.0)	106 (33)	38.0 (14)	
LAI117020	Part A: To evaluate the relative bioavailability of 2 new CAB 30 mg sodium salt tablet formulations compared to a tablet of the current sodium salt formulation in the fasted state. Part B: To evaluate the effect of a moderate-fat meal on the bioavailability of	R, O, XO	24: 14/10 41.8 (20 – 60) Healthy subjects	Treatment A: CAB 30 mg current formulation, fasted	3.70 (23)	2.00 (1.00 – 6.00)	141 (20)	37.8 (18)	m5.3.1.1
				Treatment B: CAB 30 mg formulation [redacted], fasted	2.38 (30)	3.00 (1.00 – 6.00)	98.8 (33)	38.4 (18)	
				Treatment C: 30 mg formulation [redacted], fasted	1.98 (40)	3.00 (1.00 – 6.00)	82.0 (42)	36.3 (20)	
				Treatment D = CAB 30mg treatment B, fed (moderate-fat meal)	2.71 (16)	3.03 (2.00 – 8.00)	113 (25)	37.2 (16)	

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean (Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)				Study Report Location
					Cmax (μg/mL)	tmax(h) Median (Range)	AUC0-inf (h.μg/mL)	t1/2 (h)	
	the selected tablet formulation								
LAI116585	To evaluate the relative bioavailability of 2 new GSK1265744 30 mg free acid capsule formulations compared to a tablet of the current sodium salt formulation in the fasted state	R, O, XO	18: 10/8 36.7 (21 – 60) Healthy subjects	Treatment A: CAB 30 mg sodium (Na) salt as current formulation, tablet, fasted	4.24 (19)	2.00 (1.0 – 4.0)	174 (25)	39.9 (21)	m5.3.1.1
				Treatment B: CAB 30 mg free acid [redacted], capsule formulation, fasted	3.43 (21)	3.00 (1.0 – 6.0)	152 (22)	41.4 (18)	
				Treatment C: CAB 30 mg free acid [redacted], capsule formulation, fasted	1.96 (28)	3.00 (2.0 – 4.0)	89.4 (29)	42.8 (23)	
LAI114433	To investigate the safety, tolerability, and PK of CAB LA following single dose IM or SC administration in healthy subjects	PLC, R	72: 39/33 35.1 (18-55) Healthy subjects	Single dose CAB 100 mg IM	0.2 (58.6)	9.00 (4.0 - 83.0)	920 (12.3)[a]	33.3 (66.8)[d, f]	m5.3.3.1
				CAB 200 mg IM	0.3 (28.9)	44.50 (27.0 - 170.1)	1234 (34.6)	53.9 (32.2)[f]	
				CAB 400 mg IM	0.7 (55.2)	69.0 (2.0 - 213.0)	2652 (29.8)[b]	38.3 (57.3)[b, f]	
				CAB 400 mg (2x100 mg) IM	1.4 (53.4)	13.00 (4.0 - 84.2)	2687 (53.0)	31.7 (61.8)[e, f]	

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean (Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)				Study Report Location
					Cmax (μg/mL)	tmax(h) Median (Range)	AUC0-inf (h.μg/mL)	t1/2 (h)	
				CAB 800 mg IM	3.3 (75.1)	7.58 (5.0 - 147.0)	5872 (12.6)	25.4 (51.7)[f]	
				CAB 100 mg SC	0.2 (62.1)	16.50 (4.0 - 55.0)	689 (24.0)[c]	50.4 (76.9)[c, f]	
				CAB 200 mg SC	0.5 (48.6)	6.00 (3.0 - 27.0)	1706 (2.6)[a]	42.7 (53.1)[a, f]	
				CAB 400 mg SC	0.9 (83.4)	27.00 (3.0 - 83.0)	2734 (22.3)	42.8 (52.0)[f]	
LAI116815	To evaluate the RBA of two new formulations of CAB 400 mg LA given IM compared to the current formulation ([redacted] nm [redacted])	R, OL, PRL	43: 35/8; 34.8 (20-64) Healthy subjects	Lead in (all treatments) CAB 30mg for 14 days Midazolam 3 mg probe x 2 doses (n=12)					m5.3.1.1
				Treatment A: 400 mg [redacted] ([redacted] nm)	0.91 (101)	28.00 (4.0 - 84.1)	2664 (20)[c]	15.5 (40)[f]	
				Treatment B: 400 mg [redacted] ([redacted] μm)	1.27 (131)	10.00 (2.0 - 56.9)	2717 (28)[c]	17.5 (26)[f]	
				Treatment C: 400 mg [redacted] ([redacted] μm)	0.70 (121)	21.00 (4.0 - 84.0)	2313 (18)[a]	25.6 (29)[f]	
ITZ111682	To evaluate the single-dose relative bioavailability of CAB 10 mg administered in either oral solution fasted, two 5 mg tablets	R, O, PRL	45: 36/9 33.2 (19 – 55) Healthy subjects	Treatment A: CAB 10 mg oral solution, single dose, fasted	1.93 (16)	1.00 (0.50 – 2.00)	62.4 (21)	41.2 (14)	m5.3.1.1
				Treatment B: CAB 10 mg (2x5 mg) tablets, single dose, fasted	1.13 (23)	2.50 (1.50 – 3.50)	44.7 (37)	38.5 (15)	
				Treatment C: CAB 10	1.18	4.00	51.6	42.2	

2.7.1 Summary of Biopharmaceutic Studies
and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean (Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)				Study Report Location
					Cmax (μg/mL)	tmax(h) Median (Range)	AUC0-inf (h.μg/mL)	t1/2 (h)	
	fasted, or two 5mg tablets following a moderate-fat content meal.			mg (2x5 mg) tablets, single dose, fed (moderate-fat meal)	(13)	(2.50 – 6.00)	(19)	(15)	
205696	To evaluate the effect of a high-fat meal on the PK of CAB following a single 30 mg dose using the Phase III formulation	R, O, XO	24: 16/8 39.7 (23 – 66) Healthy subjects	Treatment A: 30 mg Phase III tablet formulation, [redacted], [redacted] mg [redacted], fasted	3.33 (27)	3.0 (1.0 – 4.0)	143 (28)	40.6 (15)	m5.3.3.1
				Treatment B: 30 mg Phase III tablet formulation, [redacted], [redacted] mg [redacted], fed (high-fat meal)	3.85 (24)	3.0 (1.0 – 8.0)	163 (29)	40.6 (16)	

M/F = Male/Female; CAB = Cabotegravir; CV% = Coefficient of variance; Cmax = Maximum observed concentration; tmax = Time of occurrence of Cmax; AUC(0-inf) = Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time; t1/2 = Terminal phase half-life; R = Random; OL = Open label; XO = Crossover; PLC = Placebo control; PRL = Parallel; LA = Long acting; IM = Intramuscular; RBA = Relative bioavailability; SC = Subcutaneous;

a. n = 4
b. n = 10
c. n = 5
d. n = 3
e. n = 7
f. t1/2 is presented in days

Module 2.7.2

Summary of Clinical Pharmacology Studies

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6. APPENDIX 194

ABBREVIATIONS

3TC	Lamivudine
ddQTcF	Baseline-adjusted, maximum time-matched QTcF effect when compared with placebo
AAG	α1-acid glycoprotein
ABC	Abacavir
Add Err	Additive component of residual variability
ADME	Absorption, Distribution, Metabolism, Excretion
AE	Adverse event
ALAG1	Lag time (time between administration and measurable concentrations)
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ART	Antiretroviral treatment
ARV	Antiretroviral
AUC	Area under concentration-time curve
AUC(0-24h)	Area under the concentration-time curve from zero (pre-dose) to 24 h
AUC(0-28d)	Area under the concentration-time curve from zero (pre-dose) to 28 days (4 weeks)
AUC(0-inf) or AUCinf	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-inf) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-tau), AUCtau	Area under the concentration-time curve over the dosing interval
AUClast	Area under the concentration-time curve from time zero (pre-dose) until last measured time point
AUCtd	Area under the plasma concentration-time curve from time of administration to t days after dosing
AZT or ZDV	Zidovudine
BCRP	Breast cancer resistance protein
BID	Twice daily
BMI	Body mass index
BSEP	Bile salt export pump
BWT	Baseline body weight
C0, C0h, or Cpre-dose	Pre-dose concentration
C2h_unb	Change in the unbound concentration at 2 hours
C24	Plasma concentration 24 hours after dosing
C28d	Plasma concentration 28 days (4 weeks) after dosing
CAB	Cabotegravir (GSK1265744)
CAR	Continued/current antiretroviral treatment
Cavgi	Average concentration
CDC	Center for Disease Control

CFB	Change from Baseline
CBZ	Carbamazepine
CI	Confidence Interval
Clast	Last measurable plasma concentration
CLcr	Creatinine clearance
CLr	Renal clearance
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral and LA dosing
Cmax	Maximum observed plasma concentration
Cmax,ss	Maximum observed plasma concentration at steady state
Cmin	Minimum observed plasma concentration
CSF	Cerebrospinal fluid
CSR	Clinical study report
Css,av	Average steady state plasma concentration
Ctau	Trough concentration at the end of the dosing interval
CV	Coefficient of variance
CVb%	Between-subject coefficient of variance
CVF	Confirmed virologic failure
CYP	Cytochrome P450
CVT	Cervicovaginal tissue
CVw%	Within-subject coefficient of variance
D1	Dosing interval 1
ddI	Didanosine
ddQTcF	Individual time-matched GSK1265744 treatment groups -placebo QTcF in change from Baseline difference
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRV/RTV	Darunavir/ritonavir
DTG	Dolutegravir
EBE	Empirical Bayes' estimates
ECG	Electrocardiogram
EE	Ethinyl estradiol
EFV	Efavirenz
Emax	Maximum efficacy which can be expected by a drug
EPK50	PK parameter value associated with the 50% maximum effect (Emax)
eq	Equivalents
Err	Error
ESRD	End-stage renal disease
ETV	Etravirine
F	Bioavailability
F1	Bioavailability of oral CAB relative to CAB LA
F4	Relative bioavailability after oral administration
Fe	Fraction excreted
Fm	Fraction metabolized
Frac	Fraction of the IM dose absorbed via a fast absorption pathway
FSH	Follicle-stimulating hormone

FTC	Emtricitabine
Fu	Unbound fraction
Fu2h	Unbound fraction at 2 hours post-dose
Fu24h	Unbound fraction at 24 hours post-dose
GFR	Glomerular filtration rate
GI	Gastrointestinal
GLS	Geometric Least-Squares
h or hr	Hour(s)
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HI	Hepatic impairment
HIV-1	Human immunodeficiency virus 1
HMG-CoA	β-Hydroxy β-methylglutaryl-CoA
IC50	50% inhibitory concentration
IC90	90% inhibitory concentration
ID	Identity
IIV	Inter-individual variability
IM	Intramuscular
IMG	Intramuscular gluteus maximus
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
ITT-E	Intent to treat exposed
ITT-ME	Intent to treat-maintenance exposed
IV	Intravenous
KA1, KA2	First-order absorption rate constant (for CAB KA1=oral and KA2=IM)
Kel	First order elimination constant
Ki	Inhibitory constant
KTZ	Ketoconazole
λz	Terminal phase rate constant
L	Liter
LA	Long-acting injectable, extended release suspension for injection, or prolonged release suspension for injection
LH	Luteinizing hormone
LLOD	Lower limit of detection
LLQ	Lower limit of quantification
LNG	Levonorgesterol
LP	Lumbar puncture
LPV/RTV	Lopinavir/ritonavir
LTFU	Long-term follow-up
MATE	Multidrug and toxin extrusion transporter
max	Maximum
MDZ	Midazolam
mg	Milligram
min	Minimum
mL	Milliliter

MRP	Multidrug resistance protein
ms	Millisecond
MSDF	Missing, Switch or Discontinuation = Failure
MVA	Multivariable analysis
NA	Not applicable
NC	Not calculated
ND	Not done or Not detected
NDL	Needle length
ng	Nanogram
nm	Nanometer
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOAEL	No observed adverse effect level
NQ	Non-quantifiable concentration measured as below lower limit of quantification
NR	Not reported
NRTI	Nucleoside reverse transcriptase inhibitor
N(t)RTI	Nucleotide HIV-1 reverse transcriptase inhibitor
NVP	Nevirapine
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
OLI	Oral lead-in
OMP	Omeprazole
OR	Odds ratio
OT	Optimized therapy
PA-IC90	Protein binding adjusted IC90
PBMC	Peripheral blood mononuclear cell
PBO	Placebo
PBPK	Physiologically based PK
pcVPC	Prediction corrected visual predictive check
PD	Pharmacodynamic
PDVF	Protocol-defined virological failure
pg	Picogram
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PI	Prediction interval
PK	Pharmacokinetic
PO	By mouth (oral)
PopPK	Population Pharmacokinetic
Prop Err	Proportional component of residual variability
[redacted]	[redacted]
Q	Inter-compartment clearance
Q/F	Apparent inter-compartmental clearance
Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
Q/F	Apparent inter-compartmental clearance

QTcF	QT duration corrected for heart rate by Fridericia's formula
QWBA	Quantitative whole-body autoradiography
R2	Coefficient of determination
R	Resuming
RAL	Raltegravir
RAM	Resistance-associated mutation
RAUC	AUCtau on Day 10/AUC24 on Day 1
RBA	Relative bioavailability
RBT	Rifabutin
RELF	Relative bioavailability factor with Phase I as reference (i.e., 1 or 100%)
RI	Reinitiating
RIF	Rifampin
RNA	Ribonucleic acid
RPV	Rilpivirine (TMC278)
RSE	Relative standard error
%RSE	Percent relative SE of the estimate calculated as SE/parameter estimate*100%
SAS	Statistical Analysis Software
SC	Subcutaneous
SCM	Stepwise covariate model
SD	Standard deviation
SE	Standard error
SOC	Standard of care
SVF	Suspected virologic failure
t	Time of last observed quantifiable concentration
t1/2	Terminal phase elimination half-life
tau	Dosing interval
TBL	Total bilirubin
TDF	Tenofovir disoproxil fumarate
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
TQT	Thorough QT
µg	Microgram
UDP	Uridine diphosphate
UGT1A1	UDP-glucuronosyltransferase 1A1
UGT1A9	UDP-glucuronosyltransferase 1A9
ULN	Upper limit of normal
V2	Central compartment volume of distribution
V2/F	Apparent central volume of distribution
V3	Peripheral compartment volume of distribution
V3/F	Apparent peripheral compartment volume of distribution
Vc	Volume of distribution of the central compartment
Vc/F, V2/F	Apparent volume of the central compartment

V/F or Vz/F	Apparent volume of distribution after extravascular (e.g., oral) administration
VF	Virologic failure
VPC	Visual predictive check
Vp/F, V3/F	Apparent peripheral volume

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1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

1.1. Organization of Data

This module provides a summary of human PK and PD, and evaluation of exposure-response relationships to support administration of CAB, when used in combination with RPV, for the treatment of HIV-1 infection in adults to replace the CAR in those patients who are virologically suppressed (HIV-1 RNA <50 c/mL) and who have no known or suspected resistance to either CAB or RPV.

This module describes the clinical pharmacology characteristics of CAB, which are based upon studies evaluating oral and LA formulations of CAB, either alone or in combination with RPV.

Key clinical PK and PK/PD characteristics for CAB are summarized in Table 1.

In Section 2, where relevant, study data are presented by formulation in the following sections:

- CAB LA + RPV LA combined (Section 2.1)
- CAB LA (Section 2.3)
- Oral CAB + Oral RPV combined (Section 2.4)
- Oral CAB (Section 2.6)

Each of the sections presents CAB PK parameter data in healthy subjects, HIV-infected subjects (target population), special populations, DDIs, and PD in healthy subjects and PK/PD in HIV-infected subjects. In general, objectives, study designs, and methods are described for each study with the first mention of the study in Section 2.

In Section 3, comparisons and analyses of results across studies describe pertinent CAB clinical pharmacology characteristics, including population PK modeling and simulation, and evaluation of (as relevant) intrinsic and extrinsic factors influencing exposures following oral and/or LA dosing. Model-based simulations have been generated to evaluate the impact on CAB PK of aberrations in dosing, including, where relevant, underdosing and higher than planned doses, delayed and missed injections, use of oral therapy for planned missed injections, altered metabolism due to intrinsic factors and extrinsic factors (injection-related factors, DDI with inducers or inhibitors).

Clinical pharmacology conclusions are provided in Section 5. A summary of safety data from CAB clinical pharmacology studies is included in m2.7.4.

Background information and PK results from relevant CAB studies are listed in Appendix Table 1, Appendix Table 2, Appendix Table 3, Appendix Table 4, Appendix Table 5, Appendix Table 6, and Appendix Table 7.

1.2. Key Characteristics of Clinical Pharmacology of Cabotegravir

The data presented in Table 1 support the following key PK characteristics for CAB:

Table 1 Key PK Characteristics for CAB

	Cabotegravir	
	Oral	**LA**
Absorption		
Relative bioavailability of oral to LA [a]	0.756	
tmax [b]	3 hours	7 days
Effect of moderate-fat meal (relative to fasting): AUC(0-inf) ratio [c]	1.08 (0.978, 1.20)	NA
Effect of high-fat meal (relative to fasting): AUC(0-inf) ratio [c]	1.14 (1.02, 1.28) Administer oral CAB with or without food	NA
Polyvalent cations [d]	Chelation effect in vitro ↓plasma CAB exposure; dose separation with antacids	NA
Distribution		
% bound to human plasma proteins [e]	>99.8	
Blood-to-plasma ratio [f]	0.52	
Cervical tissue-to-plasma ratio [g]	0.16 - 0.20	
Vaginal tissue-to-plasma ratio [g]	0.19 - 0.28	
Rectal tissue-to-plasma ratio [g]	0.00 - 0.08	
CSF-to-plasma ratio [h]	0.003 (CSF-to-plasma unbound >1.0)	
Metabolism		
Metabolism [i]	UGT1A1 UGT1A9 (minor)	
Elimination		
Major route of elimination	Metabolism	
CL/F [j]	0.21 L/h	0.151 L/h
t1/2 [k, l]	41 hours	5.6 to 11.5 weeks
% of dose excreted as total radioactivity (unchanged drug) in feces [m, n]	58.5 (46.8)	ND
% of dose excreted as total radioactivity (unchanged drug) in urine [n]	26.8 (0.0)	ND

a. Relative bioavailability of oral CAB vs. CAB LA is based on PopPK estimate (F1); Data Source: GSK Doc. # 2018N384611_01, Table 15
b. tmax presented as median; Data Source: GSK Doc. # 2015N246053_00 Week 32 Table 10.1003; GSK Doc. # 2016N273084_00 Week 48 Table 10.1003, Table 11.
c. Food effect results presented as geometric mean ratio (90% CI) of fed vs. fasted; CAB Data Source: GSK Doc. # 2014N206383_00 Table 11; GSK Doc. # 2016N298724_00 Table 9. The moderate-fat meal was comprised of approximately 670 kcal and 30% fat, and the high-fat meal was comprised of approximately 870 kcal and 53% fat.
d. Polyvalent cation interaction. Data Source: GSK Doc. # 2019N401615_00. In Phase III studies,

polyvalent cation antacids were administered at least 2 hours before or 4 hours after oral CAB for consistency with the recommendation for oral RPV. Dose separation is not relevant for CAB LA administered IM because the interaction with oral CAB occurs in the GI tract.

e. Plasma protein binding based on average values for oral CAB 30 mg {Data Source: GSK Doc. # 2016N274024_00 Table 10; GSK Doc. # 2016N273991_00] and CAB LA Q4W IM and Q8W IM (Table 20; GSK Doc. # 2018N367168_00 Table 6).
f. Blood-to-plasma ratio represents ratio of geometric mean total radioactivity AUC(0-inf) for blood vs. plasma for oral [^{14}C]-CAB. CAB Data Source: GSK Doc. # 2013N167401_01 Table 11.
g. Tissue-to-plasma ratios presented as range of overall median values for single doses of CAB LA 400 mg (1 x 400 mg) IM (samples collected at 2 and 8 weeks) and CAB LA 400 mg (2 x 200 mg) IM (samples collected at 4 and 12 weeks); Data Source: GSK Doc. # 2013N159605_00 Table 11.10.
h. CSF-to-plasma ratio presented as median for CAB LA Q4W and Q8W IM. Data Source: GSK Doc. # 2018N367168_00 Table 3.1 and Table 3.5. CSF-to-unbound plasma ratio based on overall median concentration in CSF vs. overall median unbound concentration in plasma at corresponding time point. Data Source: GSK Doc. # 2018N367168_00 Table 3.1 and Table 3.5.
i. Metabolism; Data Source: Section 2.6.1.2; m2.6.4, Section 5.1.1, Section 5.1.2.
j. CL/F presented as geometric mean for oral CAB [Data Source: GSK Doc. # 2016N298724_00 Table 3.3] and as estimate from the CAB PopPK analysis for CAB LA; Data Source GSK Doc. # 2018N384611_01 Table 15
k. t1/2 presented as geometric mean for oral CAB [Data Source: GSK Doc. # 2016N298724_00 Table 3.3] and as PopPK estimates for males and females for CAB LA [Data Source: GSK Doc. # 2018N384611_01 Section 5.2.3.1].
l. CAB LA exhibits absorption-rate limited PK, which is reflected in a long apparent t1/2 following IM administration compared with oral CAB administration.
m. Data obtained following oral CAB human radiolabeled studies. Data Source: GSK Doc. # 2013N167401_01 Table 8.
n. The mean total recovery of radioactivity in urine and feces was 85.3% of the administered dose; Data Source: GSK Doc. # 2013N167401_01 Table 8.

The data presented in Table 2 support the following conclusions for the intrinsic and extrinsic factors and PK/PD relationships of CAB:

Table 2 Summary of Effect of Intrinsic and Extrinsic Factors, and PK/PD on CAB

	CAB Oral/LA
Intrinsic Factors	
Hepatic Impairment [a] (Child Pugh A/B)	Moderate: AUC(0-inf) ↓27% Fu ↑90 to 114% Geometric mean ratio (90% CI) C2h_unb 1.401 (0.798, 2.46) Administer in mild/moderate HI without dose adjustment Not studied in severe HI
Renal Impairment [a]	Severe renal impairment (CLCr <30 mL/minute) AUC(0-inf) ↔ Fu ↑31 to 51% Geometric mean ratio (90% CI) C2h_unb 1.32 (0.807, 2.15) Administer without dose adjustment in mild to severe renal impairment (not on renal replacement therapy)
HCV co-infection	CAB concentrations in subjects who were HCV antibody positive at Baseline were similar to the overall study population. None of these subjects met CVF criteria at Week 48 or Week 96.
Demographic factors	No clinically relevant effect of age, gender, race, body measure, or metabolic polymorphism.
Extrinsic Factors [b]	
General drug interaction profile	CAB is a UGT1A1 substrate. CAB exhibits few clinically relevant interactions with other drugs. There is no clinically relevant DDI between CAB and RPV (oral or LA).
Inducers (victim)	Co-administration of strong UGT1A1 inducers is contraindicated with CAB due to potential for loss of therapeutic effect and development of resistance; RIF, rifapentine, CBZ, oxcarbazepine, phenobarbital, and phenytoin.
Inhibitors (victim)	CAB may be co-administered with UGT1A1 inhibitors without dose adjustment.
Perpetrator	Based on clinical drug interaction, PBPK modelling, mechanistic static modelling, and in vitro data, no clinical drug interaction risk was identified for CAB with co-administrated substrates of drug metabolizing enzymes CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17 and substrates of drug transporters Pgp, BCRP, BSEP, MRP2, OCT1, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2K, MRP4, and OCT2.
ARV use following discontinuation of LA dosing	There are no limitations (related to drug interactions) to the ARV regimens that can be given after discontinuation of CAB LA. Based on the in vitro and clinical drug interaction profile, CAB is not expected to alter concentrations of other ARV medications including PIs, NNRTIs, NRTIs, INIs, entry inhibitors, and ibalizumab

	CAB Oral/LA
Pharmacodynamics in Healthy Subjects	
TQT Results	A supratherapeutic dose of oral CAB 150 mg Q12h x 3 doses had no effect on cardiac repolarization, there was no relationship between plasma CAB concentrations and ddQTcF, and there were no other safety findings with this regimen.
PK-PD Relationships for CAB LA + RPV LA in HIV-infected Subjects	
Concentration – Efficacy	In the individual studies as well as the MVA of studies 201585 (ATLAS), 201584 (FLAIR), and 207966 (ATLAS 2M), the rate of CVF was low, 1.25% (pooled), across both monthly and every 2 months regimens at Week 48. CAB and RPV plasma concentrations at the SVF visit for subjects with CVF overlapped with plasma concentrations of subjects with HIV-RNA <50 c/mL at the corresponding visit, making it difficult to establish a relationship between plasma concentrations and the occurrence of virologic failure. Multiple factors, including plasma concentrations and viral phenotype, may be associated with the occurrence of virologic failure.
Concentration – Safety	There are no apparent relationships between CAB concentrations and safety parameters of interest in Phase III studies.

a. Elimination pathways of CAB are independent of formulation and route of administration; therefore, results from HI and renal impairment studies evaluated following oral administration inform the recommendations for the CAB LA regimen.

b. Metabolic pathways of CAB are independent of formulation and route of administration [Data Source: GSK Doc. # 2011N115920_00], and exposures are similar following oral CAB and CAB LA administration; therefore, results from oral DDI studies inform the recommendations for the CAB LA regimen.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Table 3 List of Clinical Pharmacology Studies in m2.7.2 by Regimen

Study	Study Design	Phase	Population	Treatment Category			
				CAB LA + RPV LA Section	CAB LA Section	CAB Oral + RPV Oral Section	CAB Oral Section
LAI115428	Phase I repeat dose escalation	Phase I	Healthy Subjects	2.1.1.1	2.3.1.2		2.6.1.3
201585 (ATLAS)	Phase III evaluation of the efficacy, safety, and tolerability of switching to CAB + RPV Q4W from current INI- NNRTI-, or PI-based antiretroviral regimen	Phase III	HIV-infected Subjects	2.1.2.1 2.1.4.1			
201584 (FLAIR)	Phase III evaluation of the efficacy, safety, and tolerability of CAB + RPV Q4W for maintenance of virologic suppression following switch from an integrase inhibitor single tablet regimen	Phase III	HIV-infected Subjects	2.1.2.2 2.1.4.2			
207966 (ATLAS-2M)	Phase IIIb evaluation of the efficacy, safety, and tolerability of CAB LA + RPV LA administered every 8 weeks or every 4 weeks	Phase IIIb	HIV-infected Subjects	2.1.2.3			
200056 (LATTE-2)	Phase IIb maintenance of viral suppression following switch from current ART vs. CAB + RPV Q4W or Q8W	Phase IIb	HIV-infected Subjects	2.1.2.4 2.1.4.4		2.4.1.1	
200056 (LATTE-2)	Distribution into CSF	Phase IIb	HIV-infected Subjects	2.1.2.5			
200056 (LATTE-2)	PGx analysis [a]	Phase IIb	HIV-infected Subjects	2.1.3.1			
201120 (ÉCLAIR)	Phase IIa repeat dose PK and safety	Phase IIa	Healthy Subjects		2.3.1.1		
LAI114433	Phase I single dose escalation	Phase I	Healthy Subjects		2.3.1.3 m2.7.1, 2.1.2.1		

Study	Study Design	Phase	Population	Treatment Category			
				CAB LA + RPV LA Section	CAB LA Section	CAB Oral + RPV Oral Section	CAB Oral Section
LAI114433	Distribution into genital tract tissues	Phase I	Healthy Subjects		2.3.1.4		
LAI116482 (LATTE)	Phase IIb maintenance of virologic suppression following induction	Phase IIb	HIV-infected Subjects			2.4.1.2 2.5.1	2.6.3.1 2.6.4.1
ITZ111451	Phase I single and repeat-dose escalation PK	Phase I	Healthy Subjects				2.6.1.1
	Phase IIa monotherapy PK	Phase IIa	HIV-infected Subjects				2.6.3.3 2.6.4.2
LAI117008	Single dose mass balance PK and single supratherapeutic dose PK	Phase I	Healthy Subjects				2.6.1.2
LAI117009	Repeat dose (supratherapeutic dose) Thorough QTc study	Phase I	Healthy Subjects				2.6.2.1
ITZ112929	Phase IIa monotherapy PK	Phase IIa	HIV-infected Subjects				2.6.3.2 2.6.4.2
201479	Phase I HI PK	Phase I	Moderate Hepatic Impaired Subjects				2.6.5.1
201480	Phase I renal impairment PK	Phase I	Severe Renal Impaired Subjects				2.6.5.2
LAI116181 (DDI)	Phase I RPV DDI PK	Phase I	Healthy Subjects				2.6.6.1
205712 (DDI)	Phase I RBT DDI PK	Phase I	Healthy Subjects				2.6.6.2
LAI117010 (DDI)	Phase I RIF DDI PK	Phase I	Healthy Subjects				2.6.6.3
LAI117011 (DDI)	Phase I Contraceptives DDI PK	Phase I	Healthy Subjects				2.6.6.4
LAI116815 (DDI)	Cytochrome P450 3A (CYP3A) enzymes study	Phase I	Healthy Subjects		m2.7.1, 2.1.2.2		2.6.6.5
ITZ111839 (DDI)	Phase I ETV DDI PK	Phase I	Healthy Subjects				2.6.6.6
205162	PGx meta-analysis in 4 Phase I and 2 Phase II studies	Phase I Phase IIb	Healthy Subjects HIV-infected Subjects				2.6.7.1

For CAB, the DDIs are based on DDI studies and extrapolation from the oral CAB data.

2.1. Cabotegravir LA + Rilpivirine LA

Table 4 Listing of Studies with CAB + RPV

Study	Population	Regimens	Study Design	PK Section	PK/PD Section
LAI115428 (Cohorts 2 and 3)	Healthy Subjects	CAB LA + RPV LA	Phase I repeat dose escalation	2.1.1.1	-
201585 (ATLAS)	HIV-infected Subjects	CAB LA + RPV LA Q4W	Phase III maintenance of viral suppression following switch from current ART	2.1.2.1	2.1.4.1
201584 (FLAIR)	HIV-infected Subjects	CAB LA + RPV LA Q4W	Phase III maintenance of viral suppression following induction	2.1.2.2	2.1.4.2
207966 (ATLAS-2M)	HIV-infected Subjects	CAB + RPV Q8W or CAB + RPV Q4W	Phase IIIb maintenance of viral suppression following induction	2.1.2.3	2.1.4.3
200056 (LATTE-2)	HIV-infected Subjects	CAB LA + RPV LA Q4W and Q8W	Phase IIb maintenance of viral suppression following induction	2.1.2.4	2.1.4.4
			Distribution into CSF	2.1.2.5	-
			PGx analysis	-	2.1.3.1

2.1.1. Pharmacokinetics in Healthy Subjects

2.1.1.1. Study LAI115428: Repeat Dose PK of CAB and RPV (Cohorts 2 and 3)

Study Title: A randomized, open label study to investigate the safety, tolerability and pharmacokinetics of repeat dose administration of long acting GSK1265744 and long-acting TMC278 intramuscular and subcutaneous injections in healthy adult subjects

Location of Report: m5.3.3.1, LAI115428

Objectives: The primary objectives were to investigate the safety, tolerability, and PK of CAB LA following each IM or SC dose in healthy subjects and to investigate the safety, tolerability, and PK of RPV LA IM doses when given in combination with CAB LA IM doses in healthy subjects. A secondary objective was to investigate the safety, tolerability, and PK following repeat oral administration of CAB 30 mg once daily in healthy subjects. PK results following repeat dose administration of oral CAB tablets to healthy subjects are presented in Section 2.6.1.3.

Study Design and Methods: This was a Phase I, randomized, open-label study to investigate the safety, tolerability, and PK of repeat-dose administration of CAB LA IM and SC injections in healthy adult subjects. Ten subjects per cohort were randomized (1:1) to receive CAB LA IM and SC alone (Cohort 1, see GSK Doc. # 2013N159813_01 for data), CAB LA IM alone and with RPV LA (Cohorts 2 and 3), and CAB LA IM alone (Cohort 4, Section 2.3.1.2). In Cohorts 2 and 3, subjects received CAB LA Q4W on 2 occasions (Month 1 and Month 2) and with RPV LA on 2 occasions (Month 3 and Month 4). In Cohort 4, subjects received CAB LA once quarterly on 2 occasions (Quarter 1 and

Quarter 2). All subjects received a 14-day OLI with CAB 30 mg once daily followed by a 7-day washout period prior to receiving LA injections.

Table 5 CAB LA + RPV LA Q4W Dosing Cohorts

Cohort	Lead-in Day-21 to -8	Month 1	Month 2	Month 3	Month 4
2 (n=10)	Oral CAB 30 mg q24h × 14 days	CAB LA 800 mg IM (2 × 400 mg split initial injection)	CAB LA 200 mg IM	CAB LA 200 mg IM + RPV LA 1200 mg IM split initial injection [a]	CAB LA 200 mg IM + RPV LA 900 mg IM
3 (n=10)			CAB LA 400 mg IM	CAB LA 400 mg IM + RPV LA 1200 mg IM split initial injection [a]	CAB LA 400 mg IM + RPV LA 600 mg IM

a. RPV LA 1200 mg initial injection was split into 2 x 600 mg doses. One 600-mg dose was given with the CAB LA dose and the second dose was administered 1 h after the first dose.

Results: Selected plasma PK parameters are summarized in Table 6 following CAB IM and in Table 7 following RPV IM (in combination with CAB IM) administration. Parameters following oral CAB administration are included in Appendix Table 6. Parameters following SC administration are not included. Data following all treatments are included in GSK Doc. # 2013N159813_01.

CAB PK Parameters

Table 6 Summary of Select Plasma CAB PK Parameters Following Q4W IM Dose Administration

Treatment	n	AUC(0-tau) [a] (μg.h/mL)	Cmax [a] (μg/mL)	Ctau [a] μg/mL)	tmax [b] (Day)
CAB LA 800mg IM Initial Injection Overall Cohorts 1-3	30	1178 (63)	2.50 (80)	1.76 (47)	13.00 (6.0-28.0)
Cohort 2					
CAB LA 200mg IM (Month 2)	9	1348 (39)	2.68 (45)	1.71 (25)	6.00 [c] (2.0-28.0)
CAB LA 200mg IM + RPV LA 1200mg IM Initial Injection (Month 3)	9	1365 (17)	2.53 (20)	1.64 (36)	6.00 (2.0-28.0)
CAB LA 200mg IM + RPV LA 900mg IM (Month 4)	9	1242 (39)	2.15 (31)	1.61 (64)	6.00 (2.0-27.0)
Cohort 3					
CAB LA 400mg (Month 2)	10	2010 (31)	3.79 (40)	2.60 (24)	6.01 (2.0-28.0)
CAB LA 400mg IM + RPV LA 1200mg IM Initial Injection (Month 3)	10	2182 (28)	4.03 (40)	2.69 (28)	6.00 (2.0-28.0)
CAB LA 400mg IM + RPV LA 600mg IM (Month 4)	10	2473 (26)	4.41 (31)	3.27 (27)	6.00 (2.0-13.1)

Data Source: GSK Doc. # 2013N159813_01 Table 3.4
a. Geometric mean (CV%)
b. Median (range)
c. n=10

RPV PK Parameters

Table 7 Summary of Plasma RPV PK Parameters Following Q4W IM Dose Administration

Treatment	n	AUC(0-tau) [a] (ng.h/mL)	Cmax [a] (ng/mL)	Ctau [a] (ng/mL)	tmax [b] (day)
Cohort 2					
CAB LA 200mg IM + RPV LA 1200mg IM Initial Injection (Month 3)	9	52,762 (51)	109 (53)	61.6 (64)	6.00 (1.8-20.0)
CAB LA 200mg IM + RPV LA 900mg IM (Month 4)	9	74,420 (35)	168 (37)	79.1 (44)	6.00 (2.0-13.0)
Cohort 3					
CAB LA 400mg IM + RPV LA 1200mg IM Initial Injection (Month 3)	10	52,703 (29)	108 (30)	64.0 (34)	6.00 (2.0-28.0)
CAB LA 400mg IM + RPV LA 600mg IM (Month 4)	10	63,656 (34)	126 (32)	78.9 (39)	9.50 (2.0-27.0)

Data Source: GSK Doc. # 2013N159813_01 Table 3.6
a. Geometric mean (CV%)
b. Median (range)

Conclusions:

- The concentrations at the end of the dosing interval for the CAB LA 400 mg Q4W IM dose were approximately 1.5 to 2 times higher than the CAB LA 200 mg Q4W IM dose.
- Variability in this study was low to moderate with the LA form of CAB.
- PK data were as anticipated for both drugs, with no indication of a drug interaction between CAB and RPV.

2.1.2. Pharmacokinetics in HIV-infected Subjects

2.1.2.1. Study 201585 (ATLAS): Switching to CAB + RPV from Current ART in Treatment Experienced Subjects (Phase III)

Study Title: A Phase III, randomized, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI- NNRTI-, or protease inhibitor-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed

Location of Report: m5.3.5.1, 201585 Week 48 and Week 96

Objectives: The primary objective was to demonstrate the non-inferior antiviral activity of switching to intramuscular CAB + RPV every 4 weeks (Q4W, monthly) compared with continuation of current first line ARV regimen over 48 weeks in HIV-1-infected

ART-experienced participants. A secondary objective was to characterize CAB concentrations and population PK and identify important determinants of variability (Section 2.2). An exploratory objective was to explore relationship(s) between plasma concentrations of CAB and PD endpoints (Section 2.1.4.1).

Study Design and Methods: Study 201585 is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a 2-drug regimen of CAB + RPV compared with maintenance on current ART. A total of 618 HIV-1-infected adult patients who were on a stable ARV regimen containing 2 NRTIs plus an INI, NNRTI, or a protease inhibitor were randomized 1:1 to continue current ART or be switched to the Q4W CAB + RPV regimen through 52 weeks. Following the Week 52 visit, eligible subjects were given the option to transition to Study 207966 (comparing CAB + RPV Q8W with CAB + RPV Q4W or to continue within Study 201585 Extension Phase. This 201585 study continued (Extension Phase) for at least 96 weeks. After Week 52, the majority of subjects transitioned to Study 207966 (CAB + RPV group, 253; Extension Switch Population, 251) and 23 subjects in the CAB + RPV group and 28 subjects in the Extension Switch Population continued on the Study 201585 Extension Phase to Week 96. Subjects randomized to the CAB + RPV group first received oral CAB 30 mg + RPV 25 mg once daily with a meal for 4 to 5 weeks as OLI. Following safety and virology assessments at Week 4 (referred to as Visit 4a), subjects received initial injections at Week 4 (referred to as Visit 4b) of CAB LA 600 mg + RPV LA 900 mg followed by CAB LA 400 mg + RPV LA 600 mg at Week 8 and every 4 weeks for 48 weeks. PK samples were collected for plasma CAB concentrations prior to each injection and at 2-hours post injection dose at Weeks 4b, 48, 56b, 60 and 96, and 1-week (3 to 10 days) post injection at Weeks 5 and 41.

PK data during LTFU after discontinuation of CAB LA + RPV LA and CAB concentrations in subjects who were HCV positive at Baseline are provided in this section.

CAB PK concentration data were included in separate population PK analyses (Section 2.2).

Results:

CAB Concentrations

Plasma CAB concentration-time data are summarized at select visits in Table 8. Following completion of the 4-week OLI, Week 4b CAB concentrations were consistent with oral dosing of CAB 30 mg once daily in the Phase IIb Studies LAI116482 and 200056. Plasma CAB concentrations at Week 8 following the initial 600 mg IM injection at Week 4b were 7.4-fold higher than the PA-IC90 and similar to steady-state trough concentrations following the 10 mg oral dose observed in Study LAI116482 (Section 2.6.3.1, Table 60). By Week 48, CAB concentrations were 17-fold above the PA-IC90 (0.166 μg/mL), between the 10 mg and 30 mg oral dose and consistent with Week 48 concentrations following Q4W dosing in Study 200056 (Table 8).

Geometric mean (95% CI) Week 96 CAB pre-dose concentration of 2.99 μg/mL (2.41, 3.70) for subjects in the CAB + RPV group after receiving injections for 92 weeks was similar to the previously reported value for Week 48 of 2.84 μg/mL after receiving injections for 44 weeks (Table 8) and slightly higher than for the Extension Switch Population of 2.61 μg/mL after receiving injections for 40 weeks (Table 8), which is consistent with achievement of CAB steady state by approximately Week 44. Steady-state Week 96 geometric mean (95% CI) CAB concentrations of 3.13 μg/mL (2.61, 3.76) in this study were similar to those of 3.16 μg/mL (2.95, 3.38) observed following CAB LA + RPV LA Q4W in Study 201584 [Data Source: GSK Doc. # 2019N421511_00].

Table 8 Summary of Evaluable Plasma CAB Concentrations During the Maintenance (Week 48) and Extension (Through Week 96) Phases of Study 201585

Visit [a]		Plasma CAB Concentration (µg/mL) [b] (n=259)		Plasma CAB Concentration (µg/mL) [b] (n=259)
	n	CAB + RPV	n	Extension Switch to CAB + RPV (Initiation Dose at Week 56b)
Week 4b [c] (pre-dose) (Following last oral dose)	259	4.69 [4.47, 4.92] (41)	-	-
Week 8 [d] (pre-dose) (4 weeks after initiation injection)	252	1.23 [1.13, 1.33] (76)	-	-
Week 24 (pre-dose)	234	2.25 [2.12, 2.40] (51)	-	-
Week 41 (1-week post-dose)	251	3.39 [3.18, 3.61] (54)	-	-
Week 48 (pre-dose)	217	2.84 [2.68, 3.01] (46)	-	-
Week 56 (pre-dose) (Following last oral dose)	-	NC [e]	167	5.22 [4.89, 5.57] (45)
Week 56 (2 hours post-dose)	-	NC [e]	166	8.83 [8.26, 9.44] (46)
Week 60 (pre-dose) (4 weeks after initiation injection)	-	NC [e]	155	1.44 [1.31, 1.59] (68)
Week 96 (pre-dose)	23	2.99 [2.41, 3.70] (52)	28	2.61 [2.25, 3.02] (39)
Week 96 (2 hours post-dose)	22	3.13 [2.61, 3.76] (43)	26	2.77 [2.42, 3.17] (34)

Data Source: GSK Doc. # 2018N370336_00 Week 48 Table 4.3, GSK Doc. # 2019N399072_00 Table 14.1, Table 14.2.

a. Evaluable windows: 20 to 28 hours from prior oral dose (4b), 3 to 10 days from injection (W41), and 24 to 32 days from prior injection (Week 8 and Week 48)
b. Geometric mean [95% CI] (CVb%)
c. CAB LA 600 mg + RPV LA 900 mg IM at Week 4b
d. CAB LA 400 mg + RPV LA 600 mg IM at Week 8 and Q4W thereafter
e. NC = not collected for the CAB + RPV arm at Week 56b or Week 60.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W, and Extension Switch to CAB + RPV subjects are listed as CAR group.

Pharmacokinetics During LTFU following Discontinuation of Maintenance Treatment

Subjects who discontinued CAB LA + RPV LA during the Maintenance Phase of the study entered the LTFU Phase with PK sampling at 1, 3, 6, 9, and 12 months after the final injection visit. The final injection visits varied from 8 weeks to 52 weeks after the initiation dose. Thirteen subjects completed the LTFU Phase as planned. Four of 13 subjects presenting for the 12-month follow-up visit had measurable CAB concentrations ranging from 0.034 μg/mL to 0.152 μg/mL, all below the in vitro PA-IC90 of 0.166 μg/mL, and CAB was below the LLOQ of 0.025 μg/mL for the remaining 9 subjects [Data Source: GSK Doc. # 2019N399072_00 Table 10].

One subject (CAB + RPV Q4W) was withdrawn due to pregnancy at Week 36, 1-month following final injections at Week 32. CAB concentrations were 5.0 μg/mL and 0.295 μg/mL at the 1- and 3-month LTFU visits, respectively, and NQ at the 6- and 9-month LTFU visits. The pregnancy resulted in a healthy term delivery.

Maintenance Phase Pharmacokinetics in Subjects with Hepatitis C Virus Antibody Positive Status at Baseline

Twenty-three subjects originally randomized to CAB + RPV were HCV antibody positive at Baseline. CAB + RPV PK observed in subjects with HCV antibody positive at Baseline were within the range observed for all subjects. None of these subjects met CVF criteria at Week 48.

Conclusion:

- CAB concentrations were consistent with those observed in Phase II studies and within the range of exposures following efficacious oral dosing.
- CAB concentrations (Week 96 visit) were similar for CAB + RPV subjects after 96 weeks of treatment in the Maintenance Phase and after 48 weeks of treatment in the Extension Switch, which is consistent with the achievement of steady state after 44 weeks.
- Following discontinuation of CAB LA + RPV LA injections, CAB was detectable in 4/13 (31%) subjects completing the 12-month LTFU visit.
- CAB concentrations in subjects who were Hepatitis C antibody positive at Baseline were similar to the overall population and none of these subjects met CVF criteria at Week 48.

2.1.2.2. Study 201584 (FLAIR): Switching to CAB + RPV After Induction of Virologic Suppression in Treatment Naïve Subjects

Study Title: A Phase III, randomized, multicenter, parallel-group, open- label study evaluating the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch from an

integrase inhibitor single tablet regimen in HIV-1-infected antiretroviral therapy naive adult participants

Location of Report: m5.3.5.1, 201584 Week 48 and Week 96

Objectives: The primary objective was to demonstrate the non-inferior antiviral activity of switching to IM CAB LA + RPV LA every 4 weeks compared with continuation of ABC/DTG/3TC over 48 weeks in HIV-1 ARV naïve participants. A secondary objective was to characterize CAB concentrations and population PK and identify important determinants of variability (Section 2.2). An exploratory objective was to explore relationship(s) between plasma concentrations of CAB and PD endpoints (Section 2.1.4.2).

Study Design and Methods: Study 201584 is a Phase III, multi-phase, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to demonstrate the non-inferior antiviral activity of switching to a 2-drug regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks (Q4W: monthly) compared with remaining on ABC/DTG/3TC over 48 weeks (4 weeks oral CAB + RPV, 44 weeks LA therapy). HIV-1, ART-naïve adult patients were enrolled into the Induction Period of the study and received ABC/DTG/3TC for 20 weeks (Week [-20] to Day 1). Patients who had an HIV-1 RNA <50 c/mL at Week (-4) were randomized 1:1 into the Maintenance Period at Day 1 to either continue ABC/DTG/3TC or to commence oral therapy with CAB 30 mg + RPV 25 mg once daily for 4 to 5 weeks (to determine individual safety and tolerability prior to administration of CAB LA + RPV LA). Study 201584 allowed for characterization of long-term antiviral activity, safety, and tolerability and participant satisfaction of the regimens through Week 96. PK samples were collected prior to each injection and at 2-hours post injection at Week 4b, Week 48, and Week 96, and 3 to 10 days after the Week 4b and Week 40 injection at Weeks 5 and 41. Subjects who continued their CAB LA + RPV LA regimens after Week 48 underwent PK sampling every 4 weeks to Week 60 and every 8 weeks from Week 64 to Week 96. PK samples were assayed for CAB and RPV concentrations at Weeks 52, 56, 60, 80, 88 and 96.

An additional objective of the study was to examine plasma concentrations of CAB in Japanese subjects compared with the overall study population. Twenty Japanese subjects (8, CAB LA + RPV LA group; 12, CAR group) were randomized to CAB LA and RPV LA from Week 4b through Week 96 of the Maintenance Phase. Following the first oral dose of CAB + RPV, sequential plasma samples were collected on Day 1 of the OLI phase to determine PK of oral CAB in the Japanese subjects.

PK data during LTFU after discontinuation of CAB LA + RPV LA and CAB concentrations in subjects who were HCV positive at Baseline are provided in this section.

All CAB PK concentration data were included in separate population PK analyses for each respective agent (Section 2.2).

Results:

CAB Concentrations

Plasma CAB concentration-time data are summarized at select visits in Table 9. Following completion of the 4-week OLI, Week 4b CAB concentrations were consistent with oral dosing of CAB 30 mg once daily in the Phase IIb Studies LAI116482 and 200056. Plasma CAB concentrations at Week 8 following the initial 600 mg IM injection at Week 4b were 9.4-fold higher than the PA-IC90 and similar to steady-state trough concentrations following the 10 mg oral dose observed in Study LAI116482 (Section 2.6.3.1, Table 60). By Week 48, CAB concentrations were 19-fold above the PA-IC90, between the 10 mg and 30 mg oral dose and consistent with Week 48 concentrations following Q4W dosing in 200056 (Table 9).

Week 96 geometric mean (95% CI) CAB pre-dose concentration was 2.80 μg/mL similar to the Week 48 pre-dose concentration of 3.13 μg/mL (Table 9). Achievement of steady state was confirmed at Week 44 [Data Source: GSK Doc. # 2017N345267_00] and was not reassessed using data through Week 96. Graphical inspection of the observed data demonstrated that trough concentrations plateau from Week 44 to Week 96 and steady state was maintained through Week 96 [Data Source: GSK Doc. # 2019N421511_00, Figure 4.8]. CAB trough concentrations, including 95% CIs, from Week 48 to Week 96 were above the mean trough values associated with a 10 mg oral dose (1.35 μg/mL) and below the mean trough value associated with a 30 mg oral dose (4.2 μg/mL) [Data Source: GSK Doc. # 2013N180642_00 Week 48 Table 9.4 and Table 9.9]. Steady-state CAB concentrations at Week 96 were similar to the geometric mean (95% CI) of 3.13 μg/mL (2.61, 3.76) following CAB LA + RPV LA Q4W for 96 weeks in Study 201585 [Data Source: GSK Doc. # 2019N399072_00].

Table 9 Summary of Select Evaluable Plasma CAB Concentrations Following Oral CAB 30 mg and CAB LA Q4W at Selected Visits

Visit [a]	n	Plasma CAB Concentration (μg/mL) (n=278) [b]
Week 4b (pre-dose) (Following last oral dose)	243	5.22 [4.88, 5.57] (56)
Week 8 (pre-dose) (4 weeks after initiation injection)	250	1.56 [1.45, 1.68] (65)
Week 24 (pre-dose)	227	2.38 [2.27, 2.50] (37)
Week 41 (1-week post-dose)	236	4.03 [3.85, 4.23] (38)
Week 48 (pre-dose)	197	3.13 [2.95, 3.33] (46)
Week 52 (pre-dose)	194	3.10 [2.94, 3.26] (37)
Week 56 (pre-dose)	204	3.05 [2.90, 3.21] (38)
Week 60 (pre-dose)	206	3.16 [3.00, 3.32] (39)
Week 80 (pre-dose)	192	2.64 [2.51, 2.78] (37)
Week 88 (pre-dose)	195	2.78 [2.65, 2.92] (36)
Week 96 (pre-dose)	194	2.80 [2.64, 2.97] (43)
Week 96 (2 hr post-dose [c])	239	3.16 [2.95, 3.38] (59)

Data Source: GSK Doc. # 2017N345267_00 Week 48 Table 4.3; GSK Doc. # 2019N421511_00 Table 4.4.

a. Evaluable trough windows: 20 to 28 hours from prior oral dose (4b), 3 to 10 days from injection (Week 41), 26 to 30 days from prior injection (Week 8 and Week 48), and 24 to 32 days from prior injection.
b. Geometric mean [95% CI] (CVb%)
c. Evaluable 2 hr post-dose window: 1 to 5 hr from prior injection.

CAB Concentrations in HIV-1 Infected Japanese Subjects

Subjects received oral CAB 30 mg + RPV 25 mg once daily from Day 1 to Week 4b when they started injections. Selected PK parameters following the first oral dose of CAB 30 mg in the Japanese HIV-1 subjects are summarized in Table 10. The variability in CAB PK parameters in the subjects in Japan was low, CVb% ranged from 15% to 18%. Absorption was rapid with CAB plasma concentrations peaking at 3 h (tmax). Cmax and C24 values tended to be higher (29 - 42%) in the Japanese subjects compared to previous reports in healthy subjects in the West (Studies 201741, 205696, 201479, 201480); principally White/European/Caucasian subjects. However, the higher exposure observed in the Japanese subjects, associated with a CAB 30 mg oral dose, was below the long-term safety threshold (13.1 μg/mL).

Table 10 Summary of Plasma CAB PK Parameters following Single Oral Dose Administration of CAB 30 mg to HIV-1 Infected Japanese Subjects

	Plasma CAB PK Parameter[a]			
Study	**AUC(0-t)[b] (μg.h/mL)**	**Cmax (μg/mL)**	**C24 (μg/mL)**	**tmax[c] (h)**
201584 (n=8) Japan HIV-1	69.4 [61.3, 78.6] (15)	4.63 [3.99, 5.37] (18)	2.23 [1.96, 2.52] (15)	2.93 (0.98 -4.0)

Data Source: GSK Doc. # 2019N421511_00 Table 14.7

a. Geometric Mean [95% CI], (CVb%)
b. AUC(0-t) = AUC(0-24)
c. tmax values presented as median (range)

Geometric mean (95% CI) plasma CAB concentrations in Japanese subjects at selected visits are summarized in Table 11. CAB pre-dose concentrations were moderately variable with intersubject CVb% values ranging from 22% to 69% in Japanese subjects similar to CVb% observed in the overall study population. Following the last dose of oral CAB 30 mg once daily, the geometric mean CAB trough concentration of 6.96 μg/mL was higher than the geometric mean trough concentration (4.2 μg/mL) in subjects in the West. Following IM administration, accumulation of CAB plasma concentrations from pre-dose Week 8 to Week 24 was ~50%, and there was little accumulation from Week 24 to Week 48, suggesting steady state had been achieved in these subjects by Week 48. Geometric mean trough concentrations from Week 48 to Week 96 were 14 to 46% higher in Japanese subjects (Table 11) compared with the overall PK population (Table 9).

Table 11 Summary of Evaluable Plasma CAB Concentrations Following CAB LA 400 mg + RPV LA 600 mg Q4W at Selected Visits in Japanese HIV-1 Infected Subjects

Visit [a]	n	Plasma CAB Concentration (μg/mL) [b]
Week 4b pre-dose (following last oral dose)	8	6.96 [5.42, 8.95] (31)
Week 4b 2hr post-dose[c]	8	9.32 [6.53, 13.3] (45)
Week 8 pre-dose (after initiation injection)	8	2.26 [1.49, 3.44] (54)
Week 24 pre-dose	5	3.41 [2.24, 5.20] (35)
Week 41[d] 1-week post-dose	7	4.65 [3.84, 5.64] (21)
Week 48 pre-dose	5	3.67 [2.06, 6.52] (49)
Week 52 pre-dose	6	3.68 [2.33, 5.82] (46)
Week 56 pre-dose	6	3.48 [1.81, 6.69] (69)
Week 60 pre-dose	6	3.86 [2.29, 6.52] (53)
Week 80 pre-dose	5	3.16 [2.25, 4.43] (28)
Week 88 Pre-dose	5	4.05 [3.08, 5.33] (22)
Week 96 Pre-dose	7	3.97 [2.73, 5.78] (42)

Data Source: GSK Doc. # 2019N421511_00 Table 14.3.

a. Evaluable trough window: 24 to 32 days from prior injection.
b. Geometric mean [95% CI] (CVb%)
c. Evaluable 2hr post dose window:1 to 5 hrs from prior injection.
d. Evaluable 1-week post dose window: 3 to 10 days from prior injection.

Pharmacokinetics During LTFU following Discontinuation of Maintenance Treatment

Thirty-six subjects entered the LTFU Phase of the study following discontinuation of CAB LA + RPV LA received during the Maintenance Phase. Plasma CAB concentrations were available for 32 of these subjects. PK sampling occurred at follow-up visits 1, 3, 6, 9, and 12 months after the final injection visit. The final injection visits for the individuals in the LTFU Phase varied from having only the first injection at Week 4b to having injections out through Extension Week 108.

Eleven subjects completed the 12-month LTFU visit. Six of the 11 subjects had CAB concentrations below the LLQ of 0.025 μg/mL. The remaining 5 subjects had measurable CAB concentrations ranging from 0.0656 μg/mL to 0.762 μg/mL; 3 of which were greater than the in vitro PA-IC90 of 0.166 μg/mL [Data Source: GSK Doc. # 2019N421511_00 Table 46].

Three subjects withdrew from the study because of pregnancies and were then followed in the LTFU Phase. One subject became pregnant during the Maintenance Phase, received her last dose at Week 72, and the pregnancy ended in an elective abortion during the first trimester. CAB concentration was 0.027 μg/mL at the 9-month LTFU for this subject. Another subject received her last dose during Week 108 of the Extension Phase. She had a spontaneous abortion on [redacted] 2019; the 1-month LTFU CAB concentration on [redacted] 2019 was 2.77 μg/mL. A third subject received her last dose at the Week 112 Extension Phase visit on [redacted] 2019. The subject had a positive pregnancy test on [redacted] 2019. Her plasma CAB pre-dose concentration was 5.58 μg/mL at the Week 108 visit on [redacted] 2019 one month prior to withdrawal and was not obtained on [redacted] 2019. On [redacted] 2019, this subject's 1-month LTFU CAB concentration was 4.27 μg/mL. No additional LTFU PK data were available at the time of the Week 96 data cut. She gave birth to a normal male live infant on [redacted] 2020.

Maintenance Phase Pharmacokinetics in Subjects with Hepatitis C Virus Antibody Positive Status at Baseline

Nineteen subjects originally randomized to CAB + RPV Q4W were HCV antibody positive (HCV Reactive) at Baseline. One subject withdrew prior to the first CAB + RPV injection and did not provide any PK concentration data. The CAB PK concentrations observed in 18 subjects with HCV reactive at Baseline were within the range observed for all subjects [Data Source: GSK Doc. # 2019N421511_00 Table 47]. None of these subjects met CVF criteria at Week 48 or Week 96.

Conclusion

- Week 96 CAB plasma concentrations were similar to CAB + RPV Q4W treated subjects in other Phase III studies (Study 201585 and Study 207966).
- Week 96 CAB plasma concentrations were similar to Week 48 CAB concentrations, consistent with the achievement of steady state after 44 weeks.

- In the Japanese subjects, mean trough and Cmax values for CAB concentrations tended to be higher than observed in the overall study population but were within the clinically appropriate ranges as determined by the overall population results. Therefore, the higher exposures are not considered to be of clinical concern.
- High 2-hour CAB concentrations due to suspected dosing errors were infrequent, random, and did not result in virologic failure or AEs leading to withdrawal.
- At the 12-month LTFU following discontinuation of maintenance treatment visit, following discontinuation of CAB LA + RPV LA injections, CAB was detectable in 5/11 (45%) subjects.
- CAB concentrations in subjects who were hepatitis C antibody positive at Baseline were similar to the overall population and none of these subjects met CVF criteria at Week 48 or Week 96.

2.1.2.3. Study 207966 (ATLAS-2M): Maintenance of Virologic Suppression with CAB + RPV Q8W or CAB + RPV Q4W in Treatment Experienced Subjects (Phase IIIb)

Study Title: A Phase IIIb, randomized, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety, and tolerability of long-acting cabotegravir plus long-acting rilpivirine administered every 8 weeks or every 4 weeks in HIV-1-infected adults who are virologically suppressed

Location of Report: m5.3.4.2, 207966 Week 48

Objectives: The primary objective of the study was to demonstrate the non-inferior antiviral activity of CAB LA + RPV LA Q8W compared with CAB LA + RPV LA Q4W over 48 weeks in suppressed HIV-1 infected ART-experienced subjects. A secondary PK objective was to characterize CAB concentrations and population PK and to identify important determinants of variability. An exploratory objective was to explore relationship(s) between plasma concentrations of CAB and RPV and PD endpoints.

Study Design and Methods: Study 207966 is a Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of IM CAB + RPV Q8W compared with IM CAB + RPV Q4W in HIV-1 infected adult subjects.

A total of 1049 subjects were randomized (1:1) to receive either CAB + RPV Q8W (524 subjects) or CAB + RPV Q4W (525 subjects) for at least 100 weeks. Randomization was stratified by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks). Two groups of subjects were randomized:

> **Group 1:** Subjects currently receiving ART SOC therapy, including those enrolled to the CAR arm of Study 201585 (following completion of the Week 52 visit at minimum), received oral therapy with CAB 30 mg + RPV 25 mg once daily for 28 days (±3 days) followed by IM injections of CAB + RPV Q8W (IM CAB 600 mg + RPV 900 mg at Week 4b and Week 8 and every 8 weeks thereafter) or IM

injections of CAB + RPV Q4W (IM CAB 600 mg + RPV 900 mg at Week 4b, IM CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter). Subjects were to receive IM injections of CAB + RPV for at least 96 weeks.

Group 2: At Baseline (Day 1), subjects entering Study 207966 from Study 201585 and currently receiving IM CAB + RPV Q4W (including both those who were originally randomized to Q4W in the Maintenance Phase of Study 201585 and those who transitioned from SOC to the Q4W regimen within the Extension Phase of Study 201585) were randomized 1:1 to either continue to receive IM CAB 400 mg + RPV 600 mg Q4W or switched to IM CAB 600 mg + RPV 900 mg Q8W for at least 100 weeks. There was no intermediate loading dose 4 weeks after the initial injection for subjects transitioning from Q4W to Q8W.

Any subject who received at least a single dose of IM CAB and/or RPV and discontinued the regimen for any reason entered a 52-week LTFU Phase. Subjects were to remain on suppressive HAART for at least 52 weeks after the last dose of IM CAB and/or RPV.

PK samples for plasma CAB and RPV concentrations were collected prior to an injection at Weeks 4b, 8, 16, 24, 32, 40, 48, and 96. Regardless of the prior treatment strata, the first on-study CAB and RPV pre-dose concentrations were obtained at Week 8 (after their first injection in Study 207966).

Results:

CAB Concentrations

Overall plasma CAB pre-dose concentrations at Week 48 in Study 207966 are summarized by regimen, irrespective of strata of prior exposure, in Table 12. Plasma CAB pre-dose concentrations are summarized by regimen and strata of prior exposure to CAB + RPV at select visits in Table 13 and Table 14 for Q8W and Q4W, respectively.

Table 12 Summary of Overall (Irrespective of Prior Exposure) Evaluable Week 48 Plasma CAB Pre-dose Concentrations following CAB LA + RPV LA Q8W and Q4W (PK Population)

Visit	Plasma CAB (μg/mL)[a]	
	Q8W (n=353)	Q4W (n=386)
Week 48 pre-dose	1.67 [1.58, 1.75] (52)	2.74 [2.63, 2.85] (41)

Data Source: GSK Doc. # 2019N406358_01 Table 4.3.
Note: Evaluable pre-dose windows: 52 to 60 days from prior Q8W injection and 24 to 32 days from prior Q4W injection)
a. Geometric mean [95% CI] (CVb%).

For subjects randomized to the Q8W regimen from Q4W in Study 201585, geometric mean Day 1 CAB concentrations were 1.79 μg/mL in subjects with 1 to 24 weeks prior exposure to CAB + RPV, consistent with pre-dose concentrations following initial injections, and 3.17 μg/mL in subjects with >24 weeks prior exposure to CAB + RPV,

consistent with steady-state CAB pre-dose concentrations for CAB LA Q4W. The geometric mean Week 4b pre-dose concentration of 5.18 μg/mL observed in subjects entering Study 207966 from SOC (0 prior exposure) prior to initial Q8W injections was consistent with historical data from oral dosing following 4 weeks of OLI. CAB pre-dose concentrations were similar at Week 8 following an initial 600 mg IM injection as compared with those at Week 48 in Q8W subjects with 0 prior exposure and 1 to 24 weeks prior exposure to CAB + RPV, reflecting establishment of steady-state concentrations following initiation injections. For subjects transitioning from the Q4W to the Q8W regimen with >24 weeks prior exposure, CAB pre-dose concentrations decreased from Day 1 to Week 48 as subjects received a lower annual dose rate during the Q8W regimen. Week 48 geometric mean pre-dose concentrations for the Q8W regimen were similar across strata, ranging from 1.58 to 1.83 μg/mL (Table 13).

Table 13 Summary of Evaluable Plasma CAB Concentrations at Select Visits for Subjects Randomized to CAB LA + RPV LA Q8W Stratified by Prior Exposure (PK Population)

Visit (Week)	Strata of Prior Exposure to CAB + RPV					
	0 Weeks (n=326)		1 to 24 Weeks (n=69)		>24 Weeks (n=126)	
	n	Plasma CAB[a] (μg/mL)	n	Plasma CAB[a] (μg/mL)	n	Plasma CAB[a] (μg/mL)
Day 1	-	ND	61	1.79 [1.56,2.04] (56)	112	3.17 [2.94,3.41] (40)
Week 4b[b]	282	5.18 [4.93, 5.45] (45)	1	6.75[c]	-	ND
Week 8[d]	273	1.57 [1.46, 1.69] (67)	62	1.65 [1.42, 1.91] (63)	105	2.52 [2.29, 2.77] (53)
Week 16	262	1.41 [1.32, 1.51] (58)	54	1.61 [1.36, 1.91] (69)	92	2.30 [2.12, 2.50] (41)
Week 24	219	1.44 [1.34, 1.56] (62)	46	1.62 [1.40, 1.88] (54)	96	2.10 [1.92, 2.30] (47)
Week 41	268	3.53 [3.33, 3.75] (53)	61	3.54 [3.13, 4.00] (51)	109	3.67 [3.38, 3.99] (46)
Week 48	217	1.58 [1.49, 1.68] (47)	51	1.77 [1.51, 2.08] (63)	85	1.83 [1.64, 2.04] (55)

Data Source: GSK Doc. # 2019N406358_01 Table 4.5.

a. Geometric mean [95% CI] (CVb%). All concentrations are at pre-dose except for Week 41 which is 1-week post injection (~Cmax).
b. Week 4b pre-dose concentrations were obtained following a 4-week OLI regimen of CAB 30 mg and RPV 25 mg once daily.
c. One subject with 1 to 24 weeks prior exposure received OLI in Study 201585 and restarted OLI in Study 207966. Week 4b pre-dose concentration for this subject was consistent with oral dosing.
d. Week 8 pre-dose concentrations were obtained following a CAB 600 mg IM dose administered either at Week 4b (0 prior exposure) or Day 1 (1 to 24 weeks prior exposure or >24 weeks prior exposure).

For the Q4W regimen, geometric mean Week 4b pre-dose concentrations were 5.29 μg/mL in subjects with 0 prior exposure to CAB + RPV, consistent with oral dosing, 1.8 μg/mL in subjects with 1 to 24 weeks prior exposure, consistent with pre-dose concentrations following initial injections, and 2.98 μg/mL for the >24 weeks prior exposure strata, consistent with steady state for the Q4W regimen and similar to Day 1 pre-dose concentrations of 3.17 μg/mL for subjects with >24 weeks prior exposure in the Q8W arm. Geometric mean CAB pre-dose concentrations increased from 1.52 μg/mL at Week 8 to 2.71 μg/mL at Week 48 for subjects with 0 prior exposure to CAB + RPV, increased from 2.06 μg/mL at Week 8 to 2.59 μg/mL at Week 48 for subjects with 1 to

24 weeks prior exposure to CAB + RPV, and remained consistent with 3.01 μg/mL at Week 8 and 2.91 μg/mL at Week 48 in subjects with >24 weeks prior exposure to CAB + RPV (Table 14).

Table 14 Summary of Plasma CAB Pre-Dose Concentrations at Select Visits for Subjects Randomized to CAB LA + RPV LA Q4W Stratified by Prior Exposure (PK Population)

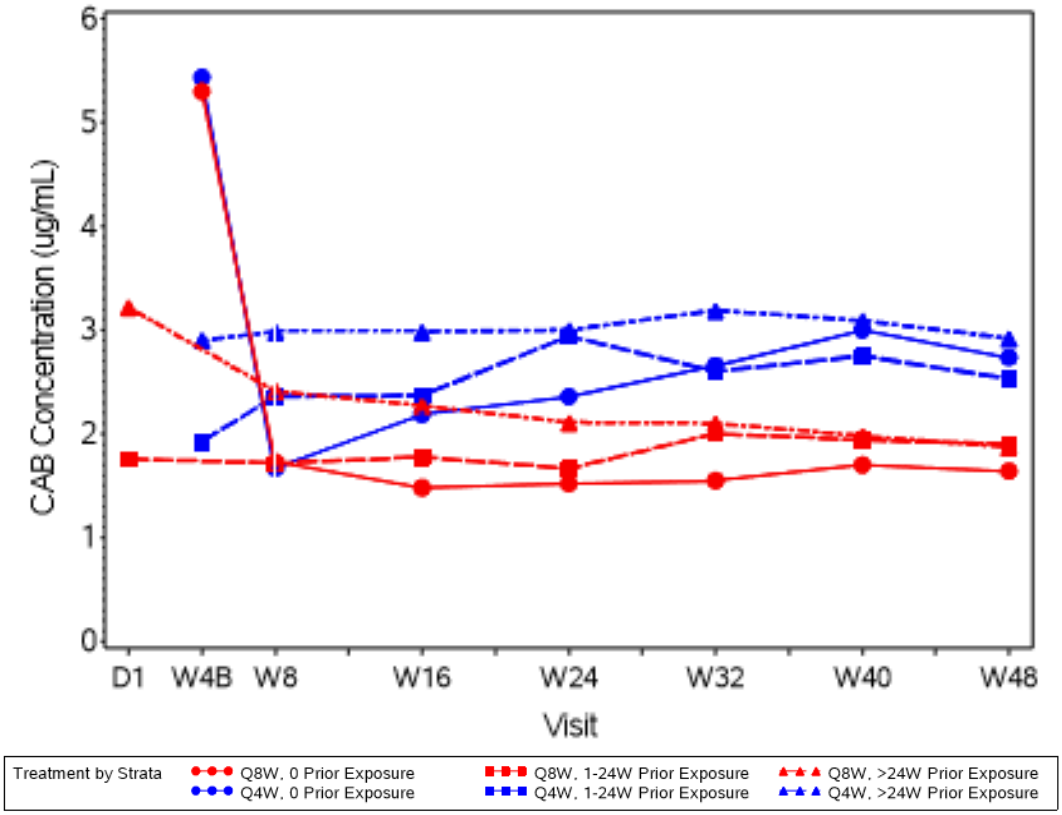
Visit (Week)	Strata of Prior Exposure to CAB + RPV[a]					
	0 Weeks (n=326)		1 to 24 Weeks (n=67)		>24 Weeks (n=128)	
	n	Plasma CAB[a] (μg/mL)	n	Plasma CAB[a] (μg/mL)	n	Plasma CAB[a] (μg/mL)
Week 4b	292	5.29[b] [5.04, 5.55] (43)	54	1.8 [1.56, 2.07] (56)	109	2.98 [2.78, 3.19] (38)
Week 8[c]	267	1.52 [1.40, 1.64] (74)	57	2.06 [1.78, 2.38] (59)	102	3.01 [2.78, 3.25] (42)
Week 16	253	2.13 [2.02, 2.25] (46)	59	2.28 [2.06, 2.53] (41)	104	2.86 [2.63, 3.11] (46)
Week 24	228	2.41 [2.29, 2.54] (41)	40	2.68 [2.38, 3.02] (39)	94	3.08 [2.80, 3.38] (49)
Week 48	236	2.71 [2.58, 2.84] (39)	53	2.59 [2.33, 2.86] (38)	97	2.91 [2.66, 3.17] (45)

Data Source: GSK Doc. # 2019N406358_01 Table 4.5.

a. Geometric mean [95% CI] (CVb%).
b. Week 4b pre-dose concentrations were obtained following a 4-week OLI regimen of CAB 30 mg and RPV 25 mg once daily.
c. Week 8 pre-dose concentrations were obtained following a CAB 600 mg IM dose administered either at Week 4b (0 prior exposure) or Day 1 (1 to 24 weeks prior exposure or >24 weeks prior exposure).

Median CAB pre-dose concentrations by week and strata for each regimen are shown graphically in Figure 1.

Figure 1 Median Plasma CAB Pre-dose Concentrations by Regimen and Strata of Prior Exposure (PK Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 4.16.
Note: For subjects with no prior exposure to CAB + RPV, Week 4b pre-dose concentrations obtained following 4-week oral lead-in regimen of CAB 30 mg and RPV 25 mg once daily.
Red = Q8W regimen, Blue = Q4W regimen

Achievement of Steady State

Achievement of steady state following the Q4W regimen was evaluated in Studies 201584 and 201585 and was not repeated in Study 207966. Achievement of steady state was assessed for the Q8W regimen for each stratum by determining the slope and associated 90% CI of the linear regression of consecutive pre-dose concentrations (Table 15). Steady state was achieved for CAB within 48 weeks on study regardless of stratification of prior exposure.

Table 15 Assessment of Achievement of Steady State of CAB Following CAB + RPV LA Q8W by Strata of Prior Exposure (PK Population)

Drug	Strata of Prior Exposure to CAB + RPV					
	0 Weeks		1 to 24 Weeks		>24 Weeks	
	Visits Included	Slope (90% CI)	Visits Included	Slope (90% CI)	Visits Included	Slope (90% CI)
CAB	Week 32, Week 40, Week 48	0.00072 (-0.0025, 0.0040)	Week 24, Week 32, Week 40, Week 48	0.00387 (-0.0005, 0.0082)	Week 24, Week 32, Week 40, Week 48	-0.00253 (-0.0053, 0.0002)

Data Source: GSK Doc. # 2019N406358_01 Table 4.7

Pharmacokinetics During LTFU following Discontinuation of Maintenance Treatment

LTFU PK concentration data were available in 46 subjects (24 Q4W, 22 Q8W) following withdrawal from CAB LA + RPV LA treatment [Data Source: GSK Doc. # 2019N406358_01 Listing 63], including 32 subjects (18 Q4W, 14 Q8W) without prior exposure to the regimen, 5 subjects (2 Q4W, 3 Q8W) with 1 to 24 weeks prior exposure, and 9 subjects (4 Q4W, 5 Q8W) with >24 weeks prior exposure [Data Source: GSK Doc. # 2019N406358_01 Figure 4.15]. PK concentrations at the 12-month LTFU visit were available in 6 subjects at the time of the 207966 Week 48 report. Of the 6 subjects who completed their 12-month LTFU visit, CAB concentration was measurable in 1 subject at 0.293 μg/mL following their final injection at Week 16; and CAB concentration was NQ in 5 of 6 subjects with final injections ranging from Day 1 to Week 16.

Conclusions:

- Following Q8W dosing, CAB pre-dose concentrations were unchanged from Week 8 to Week 48 in subjects with 0 prior exposure and decreased from Day 1 to Week 48 in subjects with >24 weeks prior exposure on the Q4W regimen. Steady state was confirmed for CAB by Week 48 regardless of stratification by prior exposure. CAB geometric mean (CVb%) pre-dose concentrations at Week 48 for Q8W and Q4W regimens were 1.67 (52%) and 2.74 (41%) μg/mL, respectively.
- CAB concentrations were similar to those observed in Phase IIb/III studies with Q4W regimen and Phase IIb studies with Q8W regimen, for subjects with similar length of exposure to the regimens.

2.1.2.4. Study 200056 (LATTE-2): Switching to CAB + RPV Q8W or Q4W After Induction of Virologic Suppression in Treatment Naïve Subjects (Phase IIb)

Study Title: A Phase IIb study evaluating a long-acting intramuscular regimen of CAB plus RPV for the maintenance of virologic suppression following an induction of virologic suppression on an oral regimen of CAB plus abacavir/lamivudine in HIV-1-infected, antiretroviral therapy-naive adult subjects.

Location of Reports: m5.3.4.2, 200056 Week 32, Week 48, Week 128, and Week 160

Objectives: The primary objective was to select an IM dosing regimen of CAB + RPV based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to CAB 30 mg + ABC/3TC orally once daily. A secondary objective was to characterize CAB LA PK, and to explore PK-PD relationships (see Section 2.1.4.4).

Study Design and Methods: Study 200056 was a Phase IIb, randomized, multicenter, parallel group, open-label, three-part study conducted in HIV-1-infected, ART-naive adults. This study consisted of a Screening Period, Induction Period, Maintenance Period, Extension Period with CSF PK sub-study, and a long-term Follow-up Period (only in subjects who had discontinued IM dosing).

During the Induction Period, subjects received oral CAB 30 mg once daily + ABC/3TC 600/300 mg once daily for 20 weeks (Week -20 to Day 1) with oral RPV 25 mg once daily added for 4 weeks beginning at Week -4. In the Maintenance Period (Day 1 to Week 96), subjects with HIV-1 RNA <50 c/mL at Week -4 were randomized 2:2:1 to receive CAB LA + RPV LA Q4W or Q8W or continue oral CAB 30 mg + ABC/3TC once daily. PK analysis was performed at Week 32 and Week 48 using non-compartmental methods. Individual Average C0 was calculated from multiple trough concentrations to provide a single representative value for each individual prior to summarization.

All oral comparator subjects successfully completing 96 weeks of treatment with HIV-1 RNA <50 c/mL had the option to switch to an optimized IM dosing regimen (either Q8W or Q4W; see Table 16 footnote) of CAB LA + RPV LA in the Extension Period. The loading dose strategy was optimized from what was utilized at the beginning of the Maintenance Period.

Table 16 Post-randomization Study Design of 200056

Phase	Q4W [a]			Q8W [a]		
	Study Visit	**CAB LA (IM)**	**RPV LA (IM)**	**Study Visit**	**CAB LA (IM)**	**RPV LA (IM)**
Maintenance Period Day 1 to Week 96 and continued during Extension Period	Day 1	800mg	600mg	Day 1	800mg	900mg
	Week 4 and Q4W thereafter	400mg	600mg	Week 4	600mg	None
				Week 8 and Q8W thereafter	600mg	900mg
Extension Period [b] Commencing at Week 100 (oral comparator subjects only)	Week 100	600mg	900mg	Week 100	600mg	900mg
	Week 104 and Q4W thereafter	400mg	600mg	Week 104	600mg	900mg
				Week 112 and Q8W thereafter	600mg	900mg

Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)

a. Prior to randomization all subjects underwent 20 weeks of induction with oral CAB + 2 NRTIs with the addition of oral RPV for the last 4 weeks of the induction period.
b. Optimized IM regimen = initial CAB injection given as a single 600 mg injection; initial RPV injection increased to 900 mg (Q4W) and 900 mg repeated at Week 104 (Q8W) prior to resumption of Q8W administration schedule.

PK for oral CAB and oral RPV was evaluated at Day 1 prior to receiving LA injections and 2 hours post injection at Day 1, Week 32 and Week 48, 1-week post injection at Weeks 1, 25, and 41, and at 4-week intervals (trough for Q4W IM arm and trough or mid-cycle concentration for Q8W IM arm) through Week 48 of the Maintenance Period. Additional PK sampling was evaluated at 8-week intervals between Week 56 and Week 96 for those initially randomized to LA treatments at Day 1.

Results:

Maintenance Period Results (Through Week 96)

Table 17 Summary of Maintenance Period CAB PK Parameters Following Repeat Dose Administration of CAB LA + RPV LA Q4W and Q8W

CAB LA Regimen	Endpoint[b]	Plasma CAB PK Parameter [a]			
		AUC(0-tau) (μg•h/mL)	Cmax (μg/mL)	Individual Average C0 (μg/mL)	tmax [c] (day)
800 mg IM/ 400 mg IM Q4W (n=115)	Week 32 (n=97)	1858 [d] [1719, 2007] (37)	3.50 [l] [3.2, 3.8] (39)	2.35 [e] [2.2, 2.5] (32)	6.9 (0 – 29)
	Week 48 (n=95)	2017 [f] [1847, 2203] (41)	3.50 [m] [3.3, 3.8] (37)	2.56 [g] [2.4, 2.7] (32)	6.9 (0 – 28)
800 mg IM/ 600 mg IM Q8W (n=115)	Week 32 (n=98)	3037 [h] [2786, 3310] (42)	3.55 [g] [3.2, 3.9] (56)	1.43 [i] [1.3, 1.6] (54)	6.9 (0 – 59)
	Week 48 (n=104)	3027 [j] [2762, 3322] (47)	3.33 [n] [3.1, 3.6] (47)	1.49 [k] [1.4, 1.6] (42)	7.0 (0 – 57)

Data Source: GSK Doc. # 2015N246053_00 Week 32 Table 10.1003; GSK Doc. # 2016N273084_00 Week 48 Table 10.1003

Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)

a. Geometric mean [95% CI] (CVb%).
b. PK Parameters reported in the CSR tables are identified by the start of the interval during which they were estimated. Week 32 parameters were estimated during the interval starting at Week 24, and Week 48 parameters were estimated during the interval starting at Week 40.
c. tmax median (range)
d. n=84
e. n=108
f. n=80
g. n=98
h. n=86
i. n=100
j. n=93
k. n=112
l. n=97
m. n=95
n. n=104

Using data through Week 48, steady state for CAB was achieved by Week 40 for the Q4W arm and by Week 16 for the Q8W arm.

Subjects randomized on Day 1 to CAB LA + RPV LA continued their long acting regimens after Week 48 and underwent PK sampling every 8 weeks from Week 56 to Week 96. Plasma CAB and RPV were summarized by visit for all subjects and for those with evaluable concentrations within a specified window (troughs 26 to 30 days from

prior injection for Q4W and 52 to 60 days from prior injection for Q8W). CAB trough concentrations obtained at Week 72 and Week 96 are presented in Table 18. Although steady state was not reassessed for data through Week 96, trough concentrations appeared to plateau between Week 72 and Week 96.

Table 18 Summary of Week 72 and Week 96 CAB Trough Concentrations Following Repeat Dose Administration of CAB LA + RPV LA Q4W and Q8W to HIV-infected Subjects in the Second Year of Treatment

Visit	Geometric Mean [95% CI] (CVb%)	
	400 mg IM Q4W	600 mg IM Q8W
Week 72 Pre-dose (μg/mL)	2.94 [2.71, 3.19] (35) (n=69)	1.72 [1.56, 1.89] (49) (n=89)
Week 96 Pre-dose (μg/mL)	2.95 [2.67, 3.26] (42) (n=65)	1.89 [1.73, 2.08] (42) (n=78)

Data Source: GSK Doc. # 2018N380094_00 Week 160 Table 10.1003
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)

Extension Period Results (Week 128): During the Extension Phase for oral comparator subjects switching to CAB LA + RPV LA at Week 100, CAB concentrations were assessed prior to each LA injection beginning at Week 100 and 1-week post injection at Week 101 and Week 121, with a primary endpoint of Week 128 (Table 19).

Table 19 Summary of Select Plasma CAB Trough Concentrations Following the Optimized Q8W and Q4W Regimens in Oral Switch Subjects

Visit	Plasma CAB Ctau [a](μg/mL)			
	Optimized 600 mg IM Q8W		Optimized 400 mg IM Q4W	
	All Data (n=34)	Evaluable [b] (n=29)	All Data (n=10)	Evaluable [b] (n=7)
Week 104 (4 weeks after initiation injection) [c]	1.62 [1.28, 2.05] (77)	1.58 [d] [1.19, 2.09] (82)	1.41 [0.64, 3.11] (156)	1.18 [0.39, 3.50] (174)
Week 128	1.71 [1.45, 2.03] (51)	1.68 [1.43, 1.96] (43)	2.19 [1.58, 3.01] (47)	2.32 [e] [1.37, 3.92] (44)

Data Source: GSK Doc. # 2018N360914_00 Week 128 Table 4.1003 and Table 4.1005
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)

a. Geometric mean [95% CI] (CVb%).
b. Evaluable trough windows: 26 to 30 days from prior injection for Week 104 and Week 128 Q4W, and 52 to 60 days from prior injection Week 128 Q8W.
c. For subjects in both Q4W and Q8W dosing regimens, trough concentrations were assessed 4 weeks after the initial 600 mg CAB dose.
d. n=28
e. n=5

Week 104 geometric mean CAB trough concentrations 4 weeks following an initial CAB LA injection of 600 mg IM were lower than 4 weeks following an initial injection of 800 mg IM, which achieved geometric mean Week 4 CAB concentrations of 1.99 μg/mL (Q8W) and 1.77 μg/mL (Q4W) [Data Source: GSK Doc. # 2015N246053_00 Week 32 and GSK Doc. # 2018N360914_00 Week 128]. Week 128 Ctau were consistent with Individual Average C0 concentrations of 1.49 μg/mL (Q8W) and 2.56 μg/mL (Q4W) observed at the Week 48 primary endpoint (Table 17).

Long-Term Follow-up following Discontinuation of Maintenance Treatment

Plasma CAB concentrations were available in 14 subjects (9 in Q4W and 5 in Q8W) who entered the LTFU phase following discontinuation of CAB LA + RPV LA during the Maintenance Phase of the study. PK sampling occurred at follow-up visits 1-, 3-. 6-, 9- and 12-months after the final injection visit. The final injection visits for the 14 subjects in LTFU varied from Day 1/Week 4 to Week 72, and 12 of 14 subjects had 12-month follow-up visit PK samples ranging from 48 to 60 weeks post-last injection. Four of 12 subjects presenting for the 12-month follow-up visit had measurable CAB concentrations ranging from 0.045 μg/mL to 0.083 μg/mL, all below the in vitro PA-IC90 of 0.166 μg/mL, and CAB was below the LLQ of 0.025 μg/mL for the remaining 8 subjects.

One subject (Q4W) was withdrawn following a final injection visit at Week 16 due to pregnancy and delivered a healthy baby between the 6-month follow-up visit and the 9-

month follow-up visit, which occurred 42-weeks following the final injection visit. One subject (Q4W) who discontinued following a final injection visit at Week 56 had follow-up visits through 9 months post last injection. One subject (Q4W) who discontinued following a final injection visit at Week 72 had follow-up visits through 6 months and had CAB concentrations at the 6-month follow-up visit of 0.324 μg/mL. Details of the subjects who discontinued are described in GSK Doc. # 2018N380094_00 Week 160.

Conclusions:

- At the Week 48 analysis, CAB trough values were 15-fold and 9-fold higher than the in vitro PA-IC90 against wild type virus, respectively, and between trough values for the oral CAB 10 mg once daily and CAB 30 mg once daily observed in LAI116482.
- CAB steady-state was achieved by Week 40 for the Q4W arm and by Week 16 for the Q8W arm.
- At the Week 96 analysis, CAB trough values were 18-fold and 11-fold higher than the in vitro PA-IC90 against wild type virus, respectively, and between trough values for the oral CAB 10 mg once daily and CAB 30 mg once daily observed in LAI116482 (LATTE).
- The optimized Q4W IM dosing strategy reflected lower CAB concentrations at Week 104 consistent with a reduction in initial injection of CAB LA from 800 mg IM to 600 mg IM, as used in Phase III.
- Week 128 CAB concentrations in subjects who transitioned from oral dosing to CAB LA + RPV LA Q8W or Q4W at Week 100 in the Extension Phase (i.e., 28 weeks on LA treatment) were consistent with those observed following a similar duration of treatment for those participating in the Q8W and Q4W dosing arms during the initial Maintenance Phase.
- Four of 12 subjects presenting for the 12-month follow-up visit had measurable CAB concentrations ranging from 0.045 μg/mL to 0.083 μg/mL, all below the in vitro PA-IC90 of 0.166 μg/mL, and CAB was below the LLQ of 0.025 μg/mL for the remaining 8 subjects.

2.1.2.5. Study 200056 (LATTE-2): CSF PK Sub-study

Study Title: An assessment of the pharmacokinetics (PK) of cabotegravir (CAB) and rilpivirine (RPV) in the plasma and cerebrospinal fluid (CSF) following LA intramuscular administration in subjects currently enrolled into the LATTE-2 Phase 2b study.

Location of Report: m5.3.4.2, 200056 CSF PK Sub-study

A CSF PK sub-study was conducted concurrently with the Extension Period of Study 200056. The CSF PK sub-study was designed to assess the potential for CAB and RPV to enter the CSF compartment. Sub-study visits were aligned with a scheduled injection visit during the Extension Period plus 1 or 2 extra visits. For the Q8W IM group, all

subjects had reached at least Week 152 and for the Q4W IM group, all subjects had reached at least Week 153 of the 200056 parent study before screening for this sub-study.

Subjects continued their designated Extension Period IM dosing regimen (Q8W or Q4W dosing). After an injection visit, two time-matched PK samples (one from plasma and the other from CSF) were collected 7 days (±3 days) after an injection visit as per the schedule of events for the CSF PK sub-study to assess peak concentrations of CAB (CSF PK sub-study visit).

Plasma HIV-1 RNA levels were assessed prior to the injection on Day 1. Two samples were collected from plasma and in CSF (via LP) for the assessment of HIV-1 RNA levels 7 days (±3) after the injection visit.

Results:

Table 20 Summary of CAB Concentrations in Plasma and CSF Following Repeat Dose Administration of CAB LA + RPV LA Q4W and Q8W

	Q8W IM (n=15)	Q4W IM (n=3)
	Median (Min, Max)	Median (Min, Max)
Plasma total (μg/mL)	3.92 (1.30, 6.41)	3.02 (2.37, 5.10)
Plasma unbound (μg/mL)	0.0047 (0.0007, 0.0220)	0.0019 (0.0014, 0.0698)
Unbound fraction in Plasma (%)	0.103 (0.056, 0.912)	0.075 (0.062, 1.45)
CSF total (μg/mL)	0.0106 (0.0053, 0.0245) [a]	0.0127 (0.0082, 0.0159)
Ratio CSF:Plasma	0.003 (0.002, 0.004) (CSF-to-plasma unbound >1.0) [a]	0.003 (0.003, 0.004)

Data Source: GSK Doc. # 2018N367168_00 Table 3.1 and Table 3.5
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
a. n=13; 2 subjects had failed attempts at CSF collection during LP

Table 21 Summary of Percentage of Subjects with CSF HIV-1 RNA levels <50 c/mL and <2 c/mL Following Repeat Dose Administration of CAB LA + RPV LA Q4W and Q8W (CSF Efficacy Population)

Visit	Q8W IM (n=13) n/N (%)		Q4W IM (n=3) n/N (%)	
Sub-study Day 8	<50 c/mL	< 2 c/mL	<50 c/mL	<2 c/mL
	13 / 13 (100)	12 / 13 (92)	3 / 3 (100)	3 / 3 (100)

Data Source: GSK Doc. # 2018N367168_00 Table 4.8 and Table 4.9
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
SuperLow Assay LLOD is 2 c/mL

Table 22 Summary of Percentage of Subjects with Plasma HIV-1 RNA Levels on Sub-study Day 8 Following Repeat Dose Administration of CAB LA + RPV LA Q4W and Q8W (Plasma Efficacy Population)

Visit	Q8W IM (n=13) n/N (%)		Q4W IM (n=3) n/N (%)	
Sub-study Day 8	<50 c/mL	< 2 c/mL	<50 c/mL	<2 c/mL
	15 / 15 (100)	9 / 15 (60)	3 / 3 (100)	3 /3 (100)

Data Source: GSK Doc. # 2018N367168_00 Table 4.1 and Table 4.3
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
SuperLow Assay LLOD is 2 c/mL

Conclusions:

- The median CSF:plasma concentration ratio was 0.003 for CAB Q4W.
- Median CAB CSF concentrations were 42-fold above the highest IC50 for wild type HIV-1 viruses reported (0.0003 μg/mL) in the Q4W IM group.
- When CAB is used in combination with RPV, CSF HIV-1 RNA concentrations (n=16) were <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of subjects.
- When CAB is used in combination with RPV, mean plasma HIV-1 RNA levels were <50 c/mL in 18/18 (100%) of subjects across Q8W and Q4W arms using the Abbott RT assay and <2 c/mL in 9/15 (60%) of subjects in the Q8W arm and 3/3 (100%) in the Q4W arm using the SuperLow Assay.

2.1.3. Pharmacogenetics

2.1.3.1. Study 200056 (LATTE-2): Pharmacogenetics Following CAB LA

Study Title: A Phase IIb study evaluating a long-acting intramuscular regimen of CAB plus RPV for the maintenance of virologic suppression following an induction of virologic suppression on an oral regimen of CAB plus abacavir/lamivudine in HIV-1-infected, antiretroviral therapy-naive adult subjects.

Location of report: m5.3.4.2, 200056 Week 160

Study Design: This analysis evaluated the impact of UGT1A1 genotypes on CAB PK in subjects who received both oral CAB and CAB LA in the 200056 (LATTE-2) study. DNA genotyped for UGT1A1 to evaluate the impact of UGT polymorphisms on oral CAB in 205162 (see Section 2.6.7.1) was available in 215 HIV-infected subjects who received oral CAB 30 mg once daily and CAB LA Q4W or Q8W in 200056. UGT1A1 variants (*6, *28, *36 and *37) were used to classify subjects with genetically predicted UGT1A1 low (n=36), reduced (n=103), or normal (n=84) enzyme activity (Table 23). Genetically predicted enzyme activity was assessed for association with CAB LA PK parameters at Study Weeks 32 and 48. Covariates of age, weight, regimen, BMI and

gender were also considered, and linear regression models were applied with adjustment for significant covariates in the model. The impact of UGT1A1 genotypes on oral and LA plasma CAB concentrations was analyzed descriptively.

Table 23 Summary of Carriages for UGT1A1 Alleles and Genetically Predicted Activity Status in Study 200056

rs4148323 *(UGT1A1*6)*	rs8175347 *(UGT1A1 TA5/6/7/8)*	Genetically Predicted UGT1A1 Activity, N (%)		
		Normal	Reduced	Low
G/G (wild-type)	TA5/6	2		
	TA6/6	82		
	TA6/7		98	
	TA6/8		2	
	TA7/7			34
	TA7/8			2
A/G	TA6/6		3	
Total		**84 (37.7)**	**103 (46.2)**	**36 (16.1)**

Data Source: GSK Doc. # 2018N380094_00 Week 160 Table 11.0002

Results:

Genetic Association with CAB LA PK Parameters

Genetically predicted UGT1A1 activity, coded as an additive 0/1/2 variable for Normal/Reduced/Low activity, was significantly associated with CAB LA CAB Cpre-dose, AUCtau, Cmax, and Cavgi at Study Week 32 and 48, respectively, after adjusting for significant ($p<0.05$) covariates (Table 24).

Table 24 Summary of Analysis Results

Parameter	Covariates	Visit	Analyzed Subjects, N	P value	Parameter Estimate for UGT1A1 Activity (Standard Error)
Cpre-dose (μg/mL)	Treatment Weight	Week 32	164	0.0123	0.21 (0.09)
		Week 48	159	0.0037	0.26 (0.10)
AUCtau (hr*μg/mL)	Treatment, Weight	Week 32	215	0.0201	261.42 (126.60)
		Week 48	212	0.0162	250.10 (116.08)
Cmax (ug/mL)	Weight	Week 32	215	0.0310	0.41 (0.22)
		Week 48	212	0.0047	0.41 (0.16)
Cavgi (μg/mL)	Treatment, Weight	Week 32	201	0.0062	0.19 (0.08)
		Week 48	204	0.0094	0.19 (0.08)

Data Source: GSK Doc. # 2018N380094_00 Week 160 Table 11.0003

Mean PK parameters after CAB LA administration increased approximately 1.2-fold in subjects with low vs. normal genetically predicted UGT1A1 activity (Table 25). The impact of UGT1A1 genotypes was smaller than observed for oral CAB (see Section 2.6.7.1). Median Ctrough appeared to increase by 7 to 29% by regimen when comparing low to normal predicted activity.

Table 25 Effects of UGT1A1 Genetically Predicted Activity on CAB LA PK Following Repeat Dose Administration of CAB + RPV LA Q4W and Q8W (200056)

	Visit	Week 32			Week 48		
	UGT1A1 status	Normal	Reduced	Low	Normal	Reduced	Low
Cpre-dose (μg/mL)							
Q4W	N	33	37	12	25	37	8
	Mean (Min, Max)	2.35 (1.11, 4.70)	2.43 (0.85, 4.58)	2.89 (1.07, 5.01)	2.51 (0, 5.13)	2.67 (1.01, 5.49)	3.56 (1.68, 6.11)
	Fold-change [a]	1.23			1.41		
Q8W	N	34	37	11	36	38	15
	Mean (Min, Max)	1.35 (0.50, 2.07)	1.7 (0.27, 3.89)	1.56 (0.21, 3.39)	1.44 (0.55, 3.80)	1.71 (0.19, 2.99)	1.66 (0, 3.13)
	Fold-change [a]	1.16			1.16		
AUCtau (hr*μg/mL)							
Q4W	N	40	49	16	39	49	15
	Mean (Min, Max)	1882.3 (3010.5, 1115.6)	2017.8 (3705.6, 608.6)	2250.9 (4980.3, 977.9)	2188.9 (6501.2, 1209.8)	2001.5 (3466.2, 276.9)	2588.8 (6256.4, 1229.8)
	Fold-change [a]	1.2			1.18		
Q8W	N	42	51	17	42	50	17
	Mean (Min, Max)	3226.4 (1020.5, 6392.4)	3499.4 (838.4, 11312.9)	3864.5 (1191.1, 11091.9)	3167.0 (322.6, 9754.9)	3506.8 (582.8, 9287.6)	3613.5 (2008.4, 4773.3)
	Fold-change [a]	1.2			1.14		
Cmax (μg/mL)							
Q4W	N	40	49	16	39	49	15
	Mean (Min, Max)	3.52 (1.83, 6.69)	3.78 (1.64, 7.47)	4.23 (1.85, 11.70)	3.7 (1.93, 7.26)	3.56 (1.53, 6.66)	4.52 (1.91, 11.50)
	Fold-change [a]	1.2			1.22		
Q8W	N	42	51	17	42	50	17
	Mean (Min, Max)	3.84 (0.91, 9.66)	4.19 (1.08, 21.40)	4.74 (1.10, 11.30)	3.36 (1.56, 8.08)	4.01 (1.03, 10.50)	3.84 (1.66, 6.28)
	Fold-change [a]	1.24			1.14		
Cavgi (μg/mL)							
Q4W	N	40	48	16	36	45	14
	Mean (Min, Max)	2.28 (1.53, 3.19)	2.49 (0.78, 4.30)	2.90 (1.07, 6.67)	2.65 (1.52, 4.51)	2.57 (1.48, 4.12)	3.29 (1.70, 6.73)
	Fold-change [a]	1.27			1.24		
Q8W	N	37	46	14	42	50	17
	Mean (Min, Max)	1.49 (0.33, 3.37)	1.7 (0.34, 3.97)	1.53 (0.25, 2.93)	1.46 (0.46, 2.77)	1.73 (0.41, 4.27)	1.54 (0, 2.71)
	Fold-change [a]	1.03			1.05		

Data Source: GSK Doc. # 2018N380094_00 Week 160 Table 11.0007
Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
a. Fold-change is based on a comparison between low vs. normal UGT1A1 enzyme activity.

Descriptive Comparison of UGT1A1 Genotypes on Plasma CAB Concentration between Oral and LA Injection Administration

CAB LA exhibits absorption rate-limited PK with reduced maximum concentrations and prolonged drug exposure compared with oral administration. A descriptive comparison was conducted to assess the impact of UGT1A1 genotypes on plasma CAB PK parameters following oral administration (during the Induction Period) and LA injection (in the Maintenance Period) in subjects who received both treatments (Table 25 and Table 26). The estimated effect of UGT1A1 genotypes on CAB LA PK parameters was smaller than that observed for oral CAB dosing (Figure 2), suggesting that LA sustained drug delivery may attenuate the impact of reduced UGT1A1 enzymatic activity on CAB PK exposure.

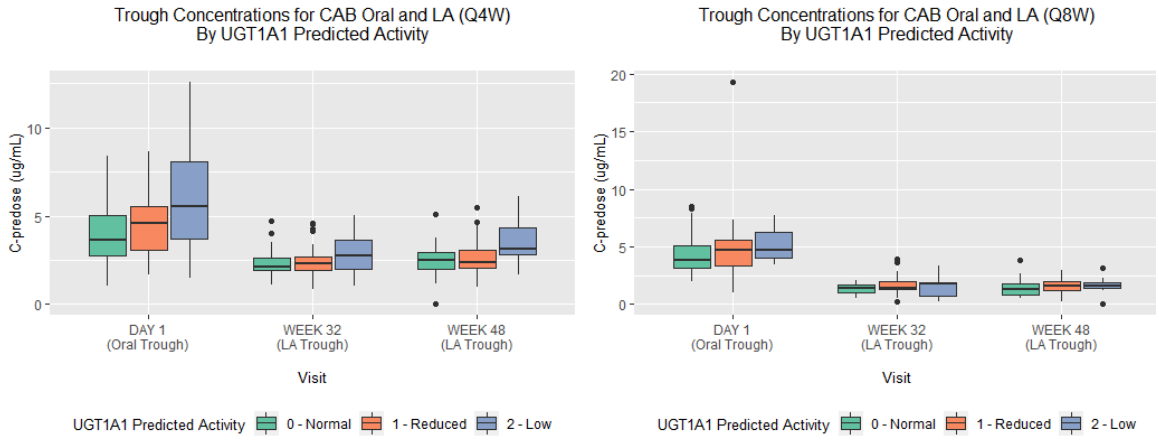
Table 26 Summary of Oral CAB Trough Concentrations by Genetically Predicted UGT1A1 Activity Status

	Normal	Reduced	Low
N	71	85	28
Mean (Min, Max)	4.07 (1.02, 8.51)	4.72 (1.06, 19.3)	5.61 (1.49, 12.6)
Fold-change [a]	1.38		

Data Source: GSK Doc. # 2018N380094_00 Week 160 Table 11.0005

a. Fold-change is based on a comparison between low vs. normal UGT1A1 enzyme activity.

Figure 2 Impact of UGT1A1 Genotypes on CAB PK Parameters Following Oral and LA Administration by Treatment Regimen



		Q4W CAB Cpre-dose (µg/mL)			Q8W CAB Cpre-dose (µg/mL)		
		Day 1	Week 32	Week 48	Day 1	Week 32	Week 48
Normal	N	37	33	25	34	34	36
	Mean (min, max)	3.88 (1.02, 8.41)	2.35 (1.11, 4.70)	2.51 (0, 5.13)	4.28 (2.01, 8.51)	1.35 (0.50, 2.07)	1.44 (0.55, 3.80)
Reduced	N	43	37	37	43	37	38
	Mean (min, max)	4.55 (1.70, 8.64)	2.43 (0.85, 4.58)	2.67 (1.01, 5.49)	4.89 (1.06, 19.3)	1.70 (0.27, 3.89)	1.71 (0.19, 2.99)
Low	N	14	12	8	14	11	15
	Mean (min, max)	6.11 (1.49, 12.6)	2.89 (1.07, 5.01)	3.56 (1.68, 6.11)	5.10 (3.42, 7.70)	1.56 (0.21, 3.39)	1.66 (0, 3.13)

Data Source: GSK Doc. # 2018N380094_00 Week 160 Figure 11.0006

Conclusion

- *UGT1A1*-reduced function polymorphisms modestly increased CAB PK parameters in HIV-infected patients who received CAB by oral or IM injection administration. There was approximately a 1.2-fold difference in mean CAB LA PK parameter values between patients with low vs. normal predicted UGT1A1 activity, which is lower than that observed with oral CAB (1.38-fold).
- Based on the accumulated safety profile of CAB, individuals with UGT1A1-reduced function polymorphisms do not require dose adjustment for either oral or LA CAB administration.

2.1.4. Pharmacokinetic-Pharmacodynamic Relationships in HIV-infected Subjects

2.1.4.1. Study 201585 (ATLAS): Switching to CAB + RPV from Current ART in Treatment Experienced Subjects (Phase III)

Study Title: A Phase III, randomized, multicenter, parallel-group, noninferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI- NNRTI-, or protease inhibitor-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed

Location of Report: m5.3.5.1, 201585 Week 48

The objectives, study design, methods, and PK results are described in Section 2.1.2.1.

Pharmacokinetic/Efficacy Relationships

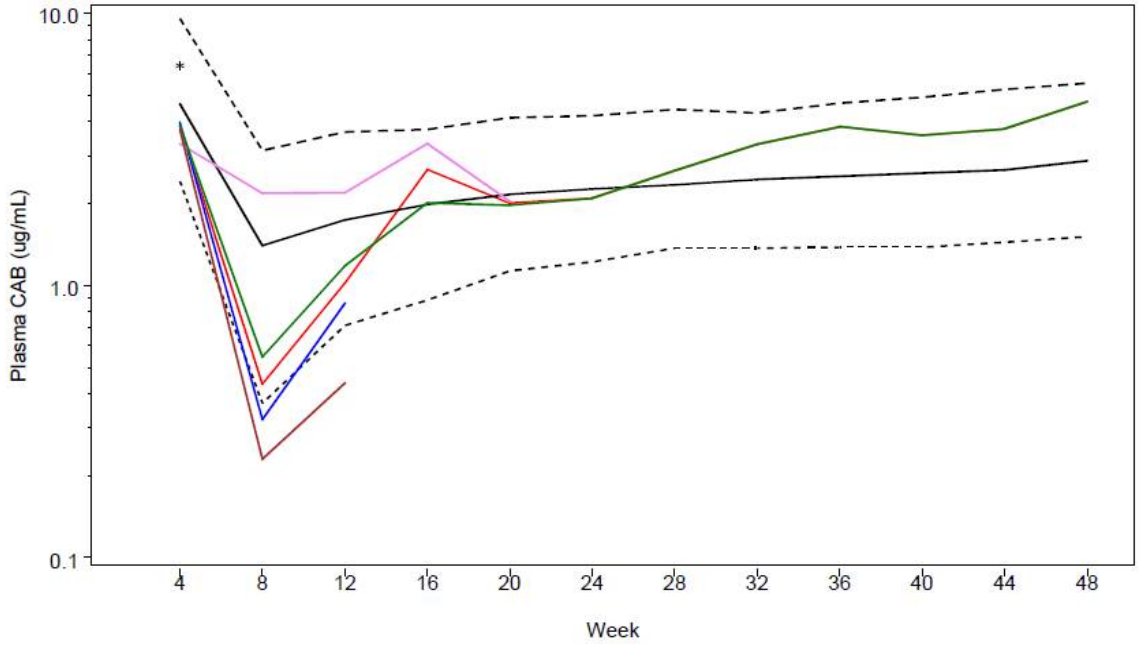
Exposure-response relationships for efficacy endpoints are discussed in Section 3.1.1.

Only five (1.6%) of the 308 subjects included in the ITT-E population in the CAB + RPV group were identified as having HIV-1 RNA ≥50 c/mL at the Week 48 analysis, based on the Snapshot algorithm, limiting the ability for robust evaluation of PK/efficacy relationships. Of these 5 subjects, 3 subjects met the criteria for CVF, all prior to Week 24.

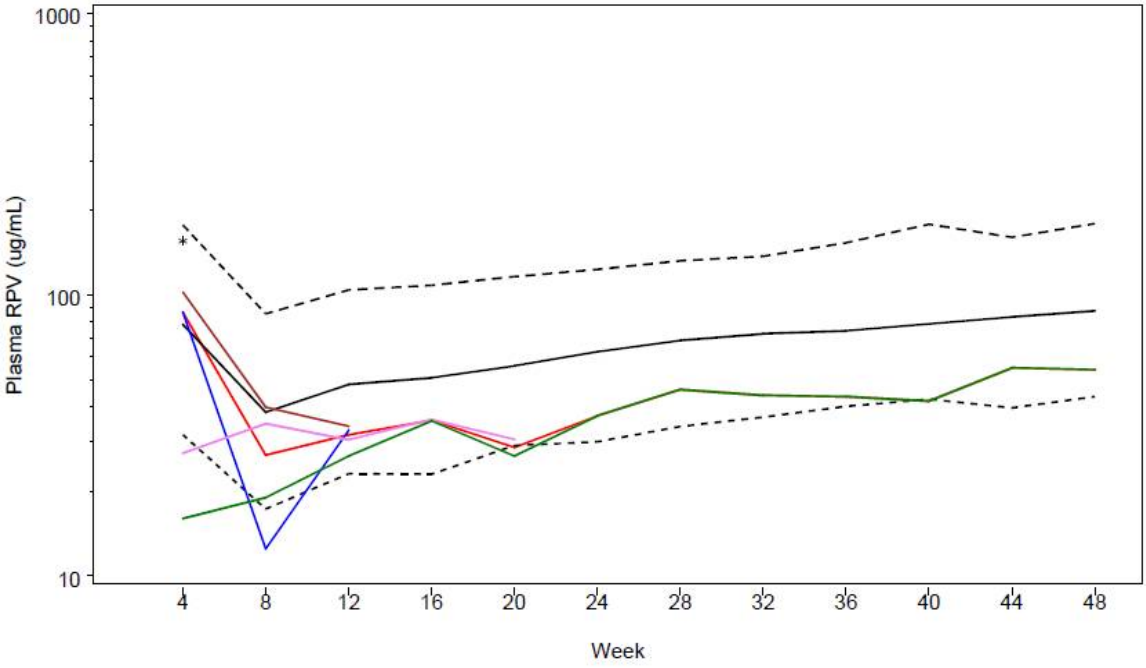
Individual and median plasma CAB and RPV concentration-time data for these 5 subjects were plotted against the median (5th, 95th percentiles) plasma CAB and RPV concentration-time data for subjects identified as virologic successes or no virologic data per the Snapshot algorithm (Figure 3).

Figure 3 **Individual Plasma CAB and RPV Ctau vs. Time for Subjects with Snapshot HIV-1 ≥50 c/mL at Week 48 vs. Median (5th & 95th percentile) of CAB and RPV Ctau for All Other Subjects**

Study 201585 - CAB



Study 201585 - RPV



Snapshot HIV-1 ≥50 c/mL at Week 48 (Study 201585 n=5)	All Other Subjects (Study 201585 n=303)
— Median Failure	— Median Success

Snapshot HIV-1 ≥50 c/mL at Week 48 (Study 201585 n=5)	All Other Subjects (Study 201585 n=303)
—, —, —, —, * * * Individual Subject Data Subjects identified in blue, pink, and brown were confirmed virologic failures.	- - - P5 (5th percentile) and P95 (95th percentile) Success Note: Success is comprised of subjects with HIV<50 c/mL or 'No virologic Data' per the Snapshot algorithm at Week 48

Data Source: GSK Doc. # 2018N370336_00 Figure 5.7, Figure 5.8

The CAB and RPV plasma concentrations for the 3 subjects with CVF are compared to the geometric mean [min, max] values for the overall population at each visit (Table 27). At each SVF visit for these 3 CVF subjects, there were also subjects with virologic success that had lower CAB and RPV concentrations than those observed for subjects with SVF.

Table 27 Summary of CAB and RPV Plasma Concentrations for CVF Subjects at SVF Visit Compared to Overall Population at Corresponding Study Visit Following Repeat Dose Administration of CAB LA + RPV LA Q4W

CVF Subject Number	CVF Visit	SVF Visit	CAB (μg/mL)		RPV (ng/mL)	
			CVF Subject Concentration at SVF Visit	Concentration for Overall Population Geometric Mean (CVb%) [min, max]	CVF Subject Concentration at SVF Visit	Concentration for Overall Population Geometric Mean (CVb%) [min, max]
Subject [redacted]	Week 12	Week 8	0.322	1.233 (77) [0.156, 5.880]	12.5	38.44 (59) [1.9, 180]
Subject [redacted]	Week 16	Week 12	0.44	1.699 (50) [0.294, 6.220]	34.1	47.40 (48) [7.7, 189]
Subject [redacted]	Week 24 Retest	Week 24	2.04	2.260 (49) [0.025, 11.800]	30.6	55.41 (47) [10.6, 255]

Data Source: GSK Doc. # 2018N370336_00 Week 48 Listing 40, Listing 28, Listing 29, Table 4.1, and Table 4.2
Virologic failure (SVF, CVF) was defined as rebound as indicated by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

Relationships between plasma CAB and/or RPV PK concentrations and HIV-1 RNA were analyzed, including factors such as age, weight, BMI, sex at birth, race, Baseline HIV-1 RNA, HIV risk factors, CDC classification, and CD4+ cell count.

Given the few subjects who were identified as cases of CVF on CAB + RPV and the fact that there is a high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it is difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. Multiple factors including plasma concentrations may be associated

with the occurrence of virologic failure (See Data Source: GSK Doc. # 2018N370336_00 Week 48 Section 11).

In a univariate analysis, the last available RPV trough plasma concentration and the Week 8 CAB plasma concentration were identified as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL. In the multivariable analysis (including Baseline viral load and Baseline CDC stage of disease subgroups) and additional subgroup/covariates for PK/PD efficacy analysis (last CAB/RPV trough concentration, CAB/RPV trough concentration at nominal visit of Week 8, Baseline BMI, length of injection needle), only the last available RPV trough concentration was retained as a statistically significant predictor of Week 48 HIV RNA ≥50 c/mL (Odds Ratio [95% CI, p-value] 0.560 [0.315, 0.996, p=0.0486]). However, combining last available concentrations for a subject experiencing CVF early in treatment serves to mix time points with differing accumulation of plasma concentrations, potentially biasing the results. In addition, not all relevant factors could be measured or included in the multivariable analysis and thus results should be interpreted with caution.

Pharmacokinetic/Safety Relationships

No relationships between CAB concentrations and the following parameters of interest were identified: QTc changes, ALT changes from Baseline, or changes in bilirubin [Data Source: GSK Doc. # 2018N370336_00 Week 48 Section 8.5].

Conclusions:

- Given the low incidence of CVF in subjects receiving CAB + RPV, relationships between drug concentrations and CVF are difficult to establish. Multiple factors, including plasma concentrations, may be associated with the occurrence of virologic failure.

- No relationship was identified between drug concentrations and safety parameters of interest.

2.1.4.2. Study 201584 (FLAIR): Switching to CAB + RPV After Induction of Virologic Suppression in Treatment Naïve Subjects

Study Title: A Phase III, randomized, multicenter, parallel-group, open- label study evaluating the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch from an integrase inhibitor single tablet regimen in HIV-1-infected antiretroviral therapy naive adult participants

Location of Report: m5.3.5.1, 201584 Week 48 and Week 96

The objectives, study design, methods, and PK results are described in Section 2.1.2.2.

Pharmacokinetic/Efficacy Relationships

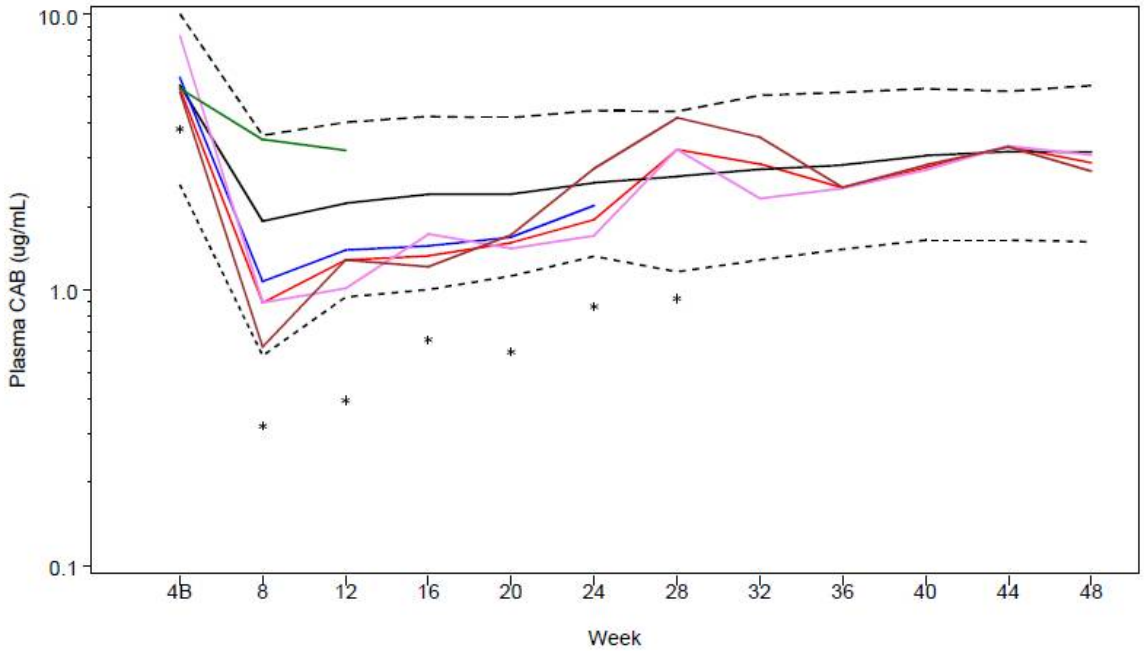
Exposure-response relationships for efficacy endpoints are discussed in Section 3.1.1.

Only 6 (2.1%) of the 283 subjects included in the ITT-E Population in the CAB + RPV group were identified as having plasma HIV-1 RNA ≥50 c/mL at the Week 48 analysis, based on the Snapshot algorithm, limiting the ability for robust evaluation of PK/efficacy relationships. Of these 6 subjects, 1 had virologic rebound during a treatment interruption of oral CAB + RPV during the OLI Period and had no plasma PK data.

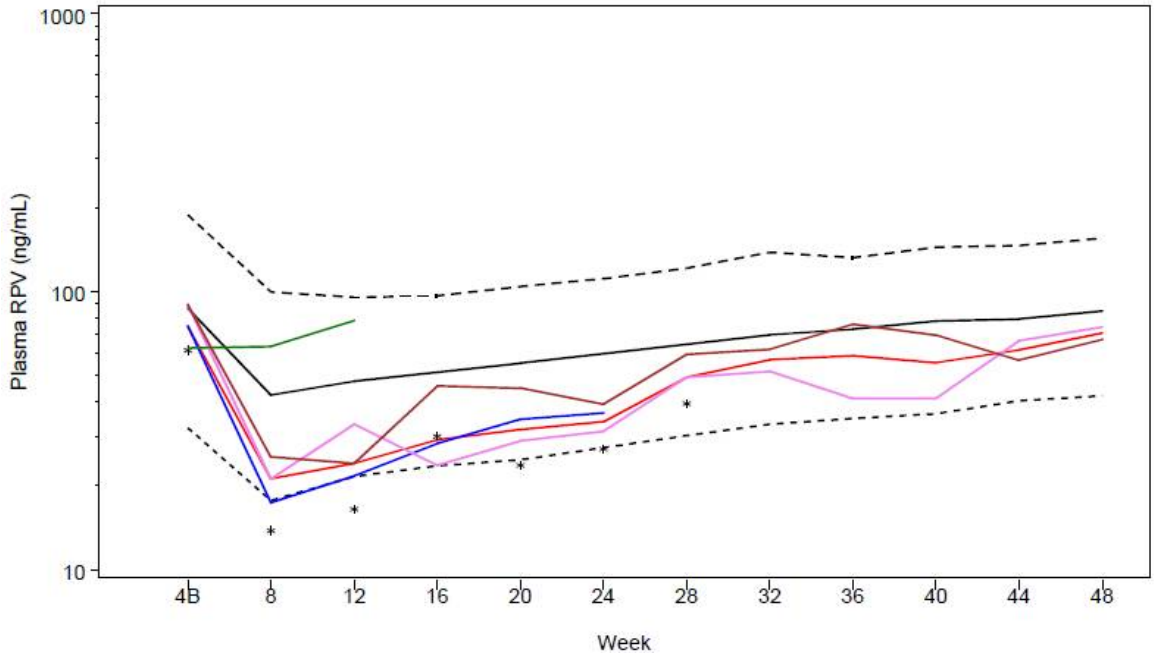
Individual and median plasma CAB and RPV concentration-time data for the other 5 subjects (with PK concentration data available) were plotted against the median (5th, 95th percentiles) plasma CAB and RPV concentration-time data for subjects identified as virologic successes (i.e., those in the category of HIV-1 <50 c/mL or No Virologic Data, per the Snapshot algorithm at Week 48) (Figure 4).

Figure 4 Individual Plasma CAB and RPV Ctau vs. Time for Subjects with Snapshot HIV-1 ≥50 c/mL at Week 48 vs. Median (5th & 95th percentile) of CAB and RPV Ctau for All Other Subjects

Study 201584 – CAB



Study 201584 – RPV



Snapshot HIV-1 ≥50 c/mL at Week 48 (Study 201584 n=6)	All Other Subjects (Study 201584 n=277)
— Median Failure —, —, —, —, * * * Individual Subject Data Note: 1 subject in Study 201584 did not have PK samples and is not included in figure Subjects identified in blue (both studies), pink (both studies), and asterisks were confirmed virologic failures.	— Median Success - - - P5 (5th percentile) and P95 (95th percentile) Success Note: Success is comprised of subjects with HIV<50 c/mL or 'No virologic Data' per the Snapshot algorithm at Week 48

Data Source: GSK Doc. # 2017N345267_00 Figure 5.7, Figure 5.8

Of the 6 subjects with plasma HIV-1 RNA ≥50 c/mL, 4 subjects met the criteria for CVF (3 who had measurable plasma concentrations and the 1 described previously with treatment interruption during OLI). The CAB and RPV plasma concentrations for the 3 subjects with PK data who experienced CVF were compared with the geometric mean (min, max) values for the overall population at each visit (Table 28).

There were no additional subjects who experienced CVF between Week 48 and Week 96 [Data Source: GSK Doc. # 2019N421511_00 Section 8.6].

Table 28 Summary of CAB and RPV Plasma Concentrations for CVF Subjects at SVF Visit Compared to Overall Population at Corresponding Study Visit Following Repeat Dose Administration of CAB + RPV LA Q4W

CVF Subject Number [a]	CVF Visit	SVF Visit	CAB (μg/mL)		RPV (ng/mL)	
			CVF Subject Concentration at SVF Visit	Concentration for Overall Population Geometric Mean (CVb%) [min, max]	CVF Subject Concentration at SVF Visit	Concentration for Overall Population Geometric Mean (CVb%) [min, max]
Subject [redacted]	Week 24	Week 20	1.55	2.18 (44) [0.49, 6.91]	34.7	53.1 (48) [10.7, 158]
Subject [redacted]	Week 32	Week 28	0.93	2.46 (43) [0.74, 8.61]	39.5	61.3 (56) [1.0, 208]
Subject [redacted]	Week 52	Week 48	3.08	3.07 (46) [0.91, 74.2]	74.4	83.1 (40) [22.3, 214]

Data Source: GSK Doc. # 2017N345267_00 Week 48 Listing 45, Listing 30, Listing 31, Table 4.1, and Table 4.2

a. There was one additional CVF subject (Subject [redacted]) who didn't receive CAB LA + RPV LA treatment; hence no PK measurements were conducted.

The relationship between the plasma CAB and RPV concentrations and Snapshot HIV-1 RNA ≥50 c/mL at Week 48 was explored using univariable and multivariable logistic regression analysis (using backwards covariate selection of predictors that were significant in the univariable analysis with $p < 0.15$). Fisher's Exact test was also used as post-hoc analyses when the univariate logistic model could not converge. Variables considered as potential predictors included age, Induction Baseline BMI, sex at birth, race, Induction Baseline HIV-1 RNA, CDC classification, Induction Visit of First HIV-1 RNA <50 c/mL, HIV-1 Subtype, and Induction Baseline and Maintenance Baseline CD4+ cell count, length of Week 4b injection needle, Week 8 CAB/RPV trough concentration, and Last CAB/RPV trough concentration.

In a univariate analysis, HIV-1 subtype (A1 vs. others; post hoc grouping of subtype categories), Induction Baseline BMI (>30 kg/m^2), RPV Week 8 trough concentration, CAB Week 8 trough concentration, and last RPV trough concentration were identified as statistically significant predictors ($p < 0.05$) of having HIV RNA ≥50 c/mL at Week 48 (based on the Snapshot algorithm).

In the multivariable analysis, only HIV-1 subtype A1 vs. others (odds ratio [95% CI; p-value] 114 [9.14, <999; p=<0.001]) and the RPV Week 8 trough concentration (19.5 [1.33, 285, p=0.030]; per doubling of concentration) were retained as statistically significant predictors of Week 48 HIV RNA ≥50 c/mL.

However, it should be noted that the low number of subjects with HIV-1 RNA >50 c/mL limits the reliability of the multivariable logistic modeling and backwards selection procedure. In addition, the dichotomization of subtype into A1 vs. others was made post hoc, which may have introduced selection bias, and not all relevant factors could be measured and included in the multivariable analysis, such as Baseline phenotypic

susceptibility. For these reasons, the predictors identified from these analyses should be interpreted with caution and considered as exploratory findings.

Pharmacokinetic/Safety Relationships

No clinically significant relationships between CAB concentrations and the following parameters of interest were identified: QTc changes, ALT changes from Baseline, or changes in bilirubin [Data Source: GSK Doc. # 2017N345267_00 Week 48 Section 8.5].

Conclusions:

- Given the low incidence of CVF in subjects receiving CAB + RPV, relationships between drug concentrations and CVF are difficult to establish. Multiple factors, including plasma concentrations, may be associated with the occurrence of virologic failure.

- No relationship was identified between PK concentrations and safety findings.

2.1.4.3. Study 207966 (ATLAS-2M): Maintenance of Virologic Suppression with CAB + RPV Q8W or CAB + RPV Q4W in Treatment Experienced Subjects (Phase IIIb)

Study Title: A Phase IIIb, randomized, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety, and tolerability of long-acting cabotegravir plus long-acting rilpivirine administered every 8 weeks or every 4 weeks in HIV-1-infected adults who are virologically suppressed

Location of Report: m5.3.5.1, 207966 Week 48

The objectives, study design, methods, and PK results are described in Section 2.1.2.3.

Results:

Pharmacokinetic/Efficacy Relationships

Exposure-response relationships for efficacy endpoints are discussed in Section 3.1.1.

The CAB + RPV Q8W dosing regimen demonstrated noninferiority to the CAB + RPV Q4W dosing regimen. Of the 1045 subjects included in the CAB + RPV ITT-E population, a total of 14 (1.3%) subjects (9 [1.7%] on Q8W and 5 [1.0%] on Q4W) were identified as having HIV-1 RNA ≥50 c/mL at the Week 48 analysis, based on the Snapshot algorithm [Data Source: GSK Doc. # 2019N406358_01 Table 16, Section 6.1.1].

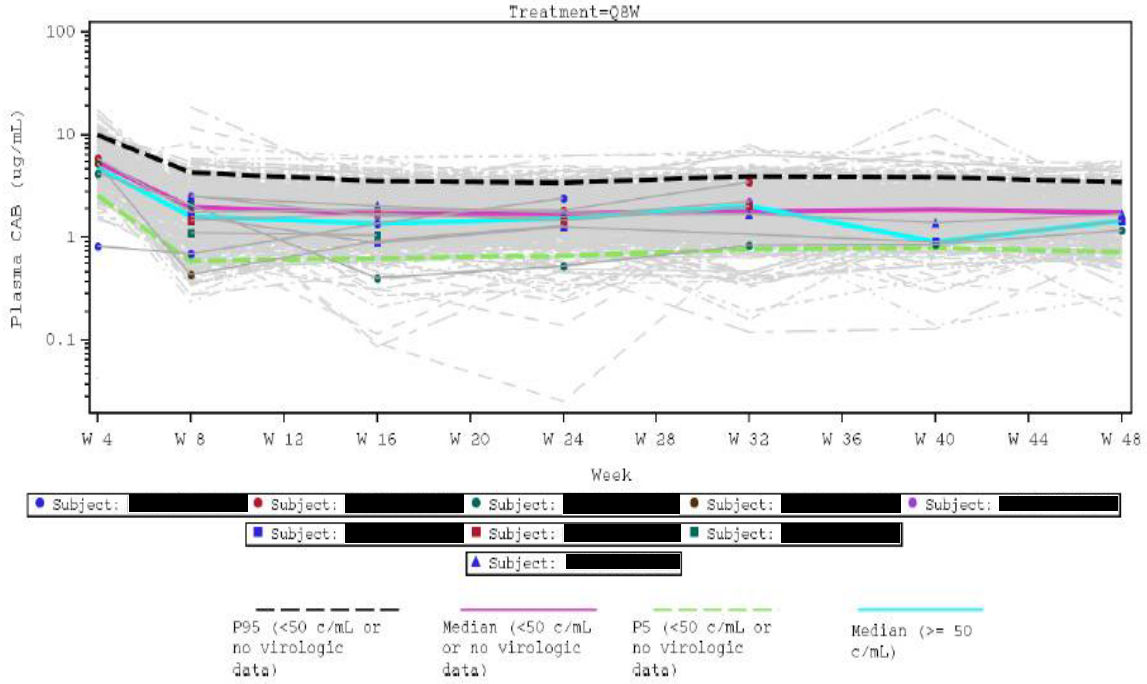
Individual and median plasma CAB and RPV concentration-time data for subjects with HIV-1 RNA ≥50 c/mL at Week 48 were plotted against the median (5th, 95th percentiles) plasma CAB and RPV concentration-time data for subjects with HIV-1 RNA <50 c/mL at Week 48, identified as virologic successes (i.e., those in the category of HIV-1

<50 c/mL or No Virologic Data, per the Snapshot algorithm at Week 48) by regimen and by analyte (Figure 5, Figure 6, Figure 7, and Figure 8). In addition, for subjects with no prior exposure to CAB + RPV, the Week 8 CAB and RPV plasma concentrations (4 weeks after first injection) were summarized descriptively (Table 29) and presented in scatterplots (Figure 9) for subjects with Week 48 HIV-1 RNA ≥ or <50 c/mL. There was no clear relationship between CAB and/or RPV pre-dose concentrations at Week 8 (following initial injection) and having Week 48 HIV RNA ≥50 c/mL in individuals without prior exposure to CAB + RPV.

Ten subjects met criteria for CVF (i.e., 2 consecutive HIV-1 RNA ≥200 c/mL), 8 (5 with Baseline NNRTI RAMs, 1 with Baseline NNRTI + INSTI RAMs) on Q8W and 2 (1 with Q190G in association with RPV resistance) on Q4W. Seven subjects experiencing CVF had no exposure to CAB + RPV prior to Day 1. Three subjects experiencing CVF were categorized as having 1 to 24 weeks of prior exposure to the regimen, receiving CAB + RPV for 8, 9, and 13 weeks (OLI + 1 to 2 Q4W injection visits) in Study 201585 prior to Day 1 in Study 207966, for a cumulative exposure at the SVF visit of 16, 33, and 61 weeks, respectively.

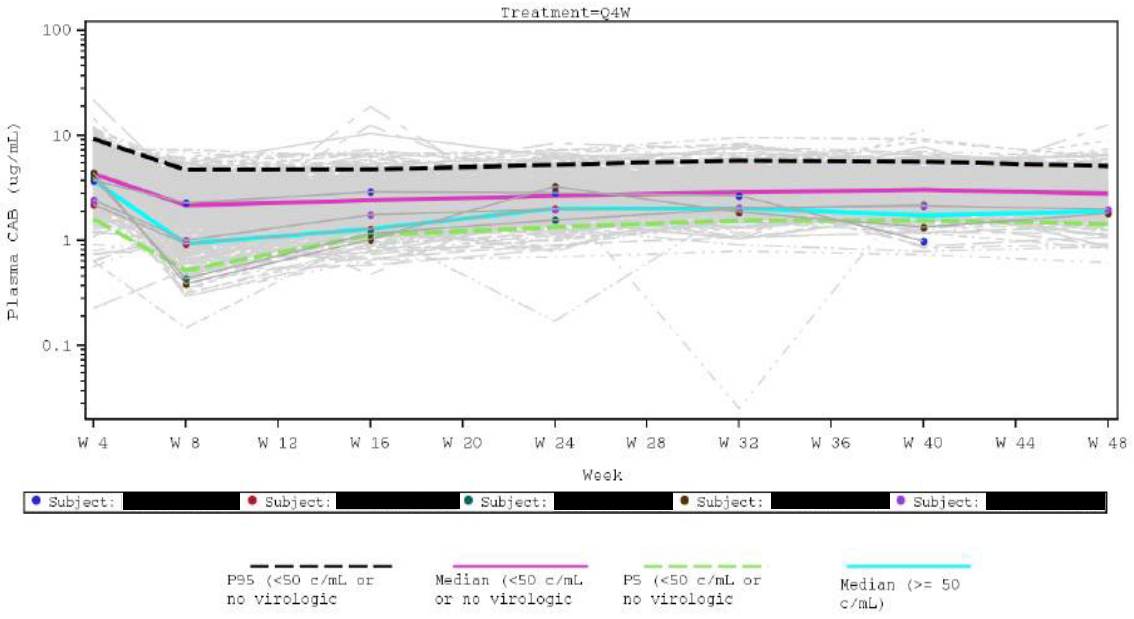
For each subject with CVF, the CAB and RPV plasma concentrations at the SVF visit [Data Source: GSK Doc. # 2019N406358_01 Table 2.23] were compared with the geometric mean [min, max] values for the overall population matched for strata of prior exposure at that same visit (Table 30), which includes also identification of subjects with RAMS). At each visit, there were subjects with virologic success with lower CAB and RPV concentrations than those observed at the SVF visit for subjects with CVF.

Figure 5 **Individual and Median CAB Concentration-time Profiles for Subjects Randomized to the Q8W Regimen with HIV-1 ≥50 c/mL at Week 48 (n=9) and Median (5th, 95th percentile) Profile for Other Subjects (n=512) (Semi-Log) (PK Population)**



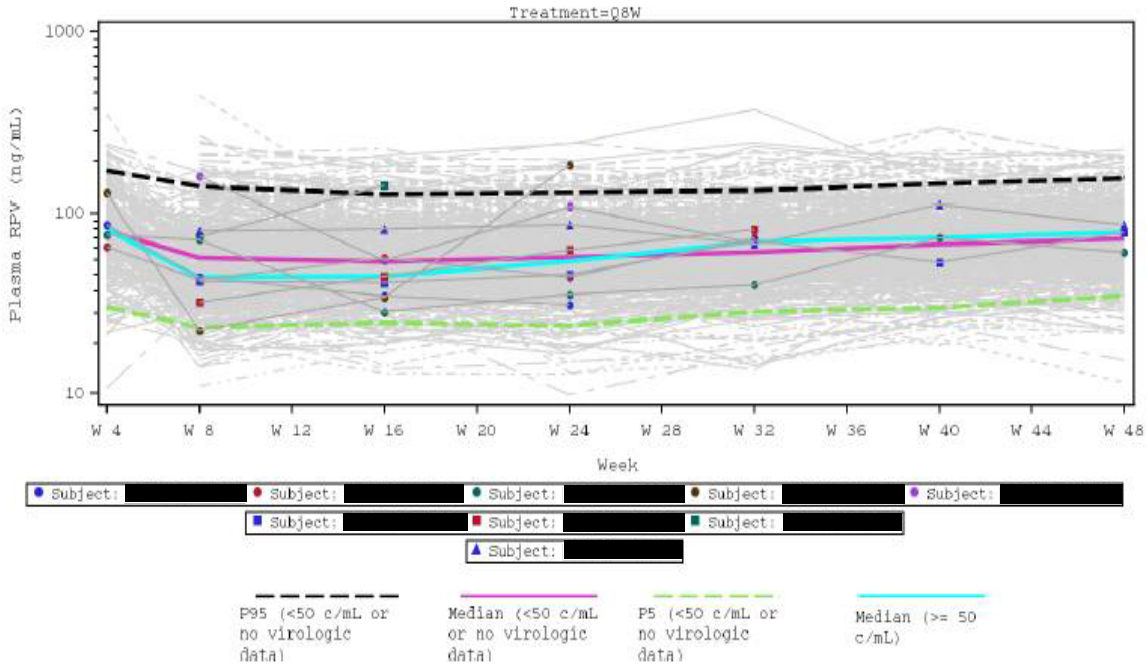
Data Source: GSK Doc. # 2019N406358_01 Figure 5.3.

Figure 6 **Individual and Median CAB Concentration-time Profiles for Subjects Randomized to the Q4W Regimen with HIV-1 ≥50 c/mL at Week 48 (n=5) and Median (5th, 95th percentile) Profile for Other Subjects(n=516) (Semi-Log)**



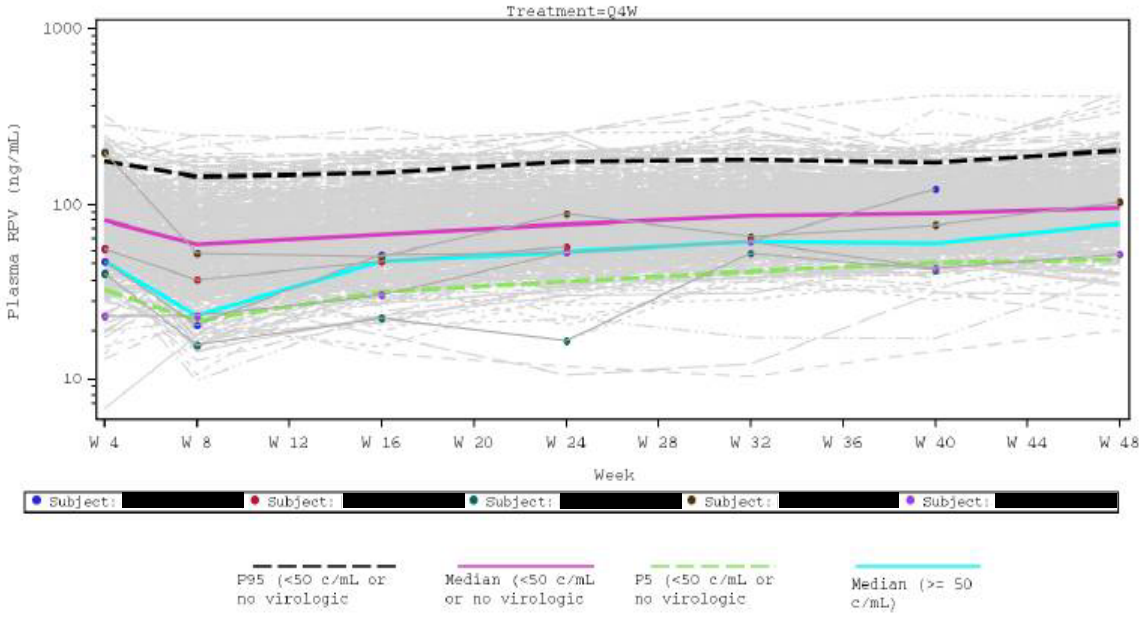
Data Source: GSK Doc. # 2019N406358_01 Figure 5.3.

Figure 7 **Individual and Median RPV Concentration-time Profiles for Subjects Randomized to the Q8W Regimen with HIV-1 ≥50 c/mL at Week 48 (n=9) and Median (5th, 95th percentile) Profile for Other Subjects(n=512) (Semi-Log) (PK Population)**



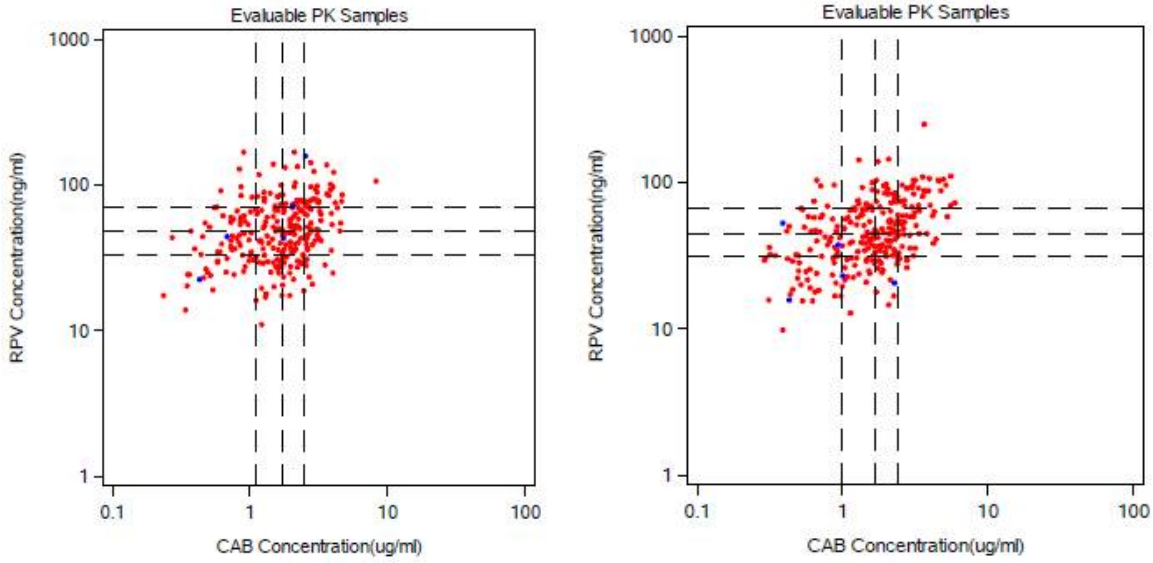
Data Source: GSK Doc. # 2019N406358_01 Figure 5.4.

Figure 8 **Individual and Median RPV Concentration-time Profiles for Subjects Randomized to the Q4W Regimen with HIV-1 ≥50 c/mL at Week 48 (n=5) and Median (5th, 95th percentile) Profile for Other Subjects(n=516) (Semi-Log) (PK Population)**



Data Source: GSK Doc. # 2019N406358_01 Figure 5.4.

Figure 9 **RPV vs. CAB Week 8 Pre-dose Concentration in Relation to HIV RNA ≥50 c/mL at Week 48 for Subjects with No Prior Exposure to CAB + RPV (Q8W left panel, Q4W right panel) (PK Population)**



Data Source: GSK Doc. # 2019N406358_01 Figure 5.5.
The reference lines are quartiles of Week 8 CAB and RPV pre-dose concentrations. Blue = Subjects with Week 48 Snapshot HIV-1 RNA ≥50 c/mL; Red = Other.

Table 29 Summary of Week 8 Pre-dose Concentrations by Snapshot HIV-1 RNA ≥50 c/mL at Week 48 (Yes vs. No) for Subjects with No Prior Exposure to CAB + RPV

Regimen	CAB[a] (μg/mL)		RPV[a] (ng/mL)	
	HIV RNA ≥50 c/mL = YES[b]	HIV RNA ≥50 c/mL = NO[c]	HIV RNA ≥50 c/mL = YES[b]	HIV RNA ≥50 c/mL = NO[d]
Q8W	1.75 (0.43, 2.52)	1.75 (0.24, 8.22)	44.2 (22.4, 157)	48.8 (11.0, 168)
Q4W	0.930 (0.39, 2.27)	1.70 (0.29, 5.94)	23.1 (15.7, 52.9)	45.8 (9.83, 248)

Data Source: GSK Doc. # 2019N406358_01 Table 5.3, Table 5.4

a. Median (min, max)
b. n=5 each for Q8W and Q4W
c. n=316 for Q8W and n=314 for Q4W
d. n=315 for Q8W and n=314 for Q4W

Table 30 Summary of CAB and RPV Plasma Concentrations at the SVF Visit for Subjects with CVF Compared with the Overall Population at the Corresponding Study Visit

Regimen	CVF Subject Number	SVF Visit	Strata of Prior exposure to CAB + RPV	CAB (µg/mL)		RPV (ng/mL)	
				CVF Subject at SVF Visit	Population[a,b]	CVF Subject at SVF Visit	Population[a,b]
Q8W	[redacted][c]	8	1-24 wk	1.1	1.65 (63) [0.272, 11.7]	74	51.3 (42) [15.4, 148]
	[redacted][d]	16	0	0.65	1.41 (58) [0.085, 4.12]	14.2	45.6 (40) [13.6, 172]
	[redacted][c, e]	16	0	1.35	1.41 (58) [0.085, 4.12]	34.8	45.6 (40) [13.6, 172]
	[redacted]	16	0	0.921	1.41 (58) [0.085, 4.12]	34.2	45.6 (40) [13.6, 172]
	[redacted][c]	24	0	1.57	1.44 (62) [0.025, 4.45]	108	49.1 (43) [13.0, 145]
	[redacted][c]	24	0	1.82	1.44 (62) [0.025, 4.45]	44.3	49.1 (43) [13.0, 145]
	[redacted][c]	24	1-24 wk	1.45	1.62 (54) [0.565, 6.20]	62.6	57.1 (47) [21.5, 163]
	[redacted]	48	1-24 wk	1.44	1.77 (63) [0.239, 4.95]	78.5	77.6 (50) [22.2, 196]
Q4W	[redacted][f]	16	0	1.28	2.13 (46) [0.602, 12.4]	47.4	56.4 (46) [17.9, 208]
	[redacted]	32	0	1.99	2.69 (51) [0.025, 8.46]	52.9	75.8 (44) [12.2, 341]

Data Source: GSK Doc. # 2019N406358_01 Listing 29, Listing 30, Table 4.5, Table 4.6.

a. Matched for strata of CVF.
b. Geometric mean (CVb%) [min, max].
c. Major NNRTI RAMs at Baseline.
d. CVF but not Snapshot failure, achieved <50 c/mL at the Week 20 Visit.
e. Major INSTI RAMs at Baseline.
f. G190Q at Baseline associated with high level resistance to RPV, not defined as RAM.

Univariable and Multivariable Logistic Regression Analyses

Univariable and multivariable logistic regression analyses (using backwards covariate selection of predictors that were significant in the univariable analysis with $p < 0.15$) were conducted for the population without prior exposure to CAB + RPV and for the overall population. The following factors were evaluated: Treatment (dosing regimen), age, race, sex, Baseline CD4+ cell count, Baseline HIV-1 RNA, derived Baseline CDC Stage, Baseline BMI, Baseline third agent class, Week 8 RPV pre-dose concentration, Week 8 CAB pre-dose concentration, length of first RPV injection needle, and length of first CAB injection needle.

The univariable logistic regression analyses provided similar results as the multivariable analyses [Data Source: GSK Doc. # 2019N406358_01 Table 5.1 and Table 5.5].

Both in the univariable and the multivariable regression analyses for the overall population, Baseline CDC stage of disease, Baseline BMI, and Week 8 CAB plasma concentration at the end of the dosing interval following the first injection were identified as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL [Data Source: GSK Doc. # 2019N406358_01 Table 5.5 and Data Source: GSK Doc. # 2019N406358_01 Table 5.6].

In the univariable regression analysis for subjects without prior exposure, Baseline BMI, and Week 8 CAB plasma concentration (at the end of the dosing interval following the first injection) were identified as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL [Data Source: GSK Doc. # 2019N406358_01 Table 5.1]. For subjects without prior exposure, in the multivariable analysis only BMI (>30 kg/m^2) was retained as a statistically significant predictor of Week 48 HIV RNA ≥50 c/mL (Odds Ratio [95% CI; (p-value)] 5.626 [1.48, 21.4 (0.011)] [Data Source: GSK Doc. # 2019N406358_01 Table 5.2], without accounting for multiplicity.

Given the few subjects with Week 48 HIV RNA ≥50 c/mL, and even fewer with CVF on CAB + RPV and the fact that there is a high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF or HIV RNA ≥50 c/mL, it is difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. In addition, other factors like viral phenotype were not included in this analysis. Multiple factors, including PK and viral phenotype, may be associated with the occurrence of virologic failure. Virology results are presented in m2.7.2.4.

Pharmacokinetic/Safety Relationships

No relationships between CAB concentrations and the following parameters of interest were identified: QTcF change from Baseline [Data Source: GSK Doc. # 2019N406358_01 CAB, Figure 5.13], ALT maximum change from Baseline [Data Source: GSK Doc. # 2019N406358_01 CAB, Figure 5.6], or total bilirubin maximum change from Baseline [Data Source: GSK Doc. # 2019N406358_01 CAB, Figure 5.8].

Conclusions:

- There was no clear relationship between Week 48 HIV RNA ≥50 c/mL and CAB exposures. Given the low incidence of CVF in subjects receiving CAB + RPV, relationships between drug concentrations and CVF are difficult to establish. Multiple factors, including PK and viral phenotype, may be associated with the occurrence of virologic failure.
- No clear relationships were identified between CAB concentrations and safety parameters of interest including ALT, total bilirubin, and change in QTcF.

2.1.4.4. Study 200056 (LATTE-2): Switching to CAB + RPV Q8W or Q4W After Induction of Virologic Suppression in Treatment Naïve Subjects (Phase IIb)

Study Title: A Phase IIb study evaluating a long-acting intramuscular regimen of CAB plus RPV for the maintenance of virologic suppression following an induction of virologic suppression on an oral regimen of CAB plus abacavir/lamivudine in HIV-1-infected, antiretroviral therapy-naive adult subjects.

Location of Report(s): m5.3.4.2, 200056 Week 48, Week 96, and Week 160

The objectives, study design, methods, and PK results are described in Section 2.1.2.4.

Injection Period Pharmacokinetic/Pharmacodynamic Relationships

Table 31 Summary of Study Outcomes at Weeks 48 and 96 – Snapshot (MSDF) Analysis Following Repeat Dose Administration of CAB LA + RPV LA Q4W and Q8W (ITT-ME Population)

Endpoint (Week)	Outcome	Q8W IM n=115 n (%)	Q4W IM n=115 n (%)	CAB 30 mg+ ABC/3TC n=56 n (%)	Subtotal IM N=230 n (%)
Week 48	HIV RNA <50 c/mL, n (%)	106 (92)	105 (91)	50 (89)	211 (92)
	HIV RNA >50 c/mL, n (%)	8 (7)	1 (<1)	1 (2)	9 (4)
Week 96	HIV RNA <50 c/mL, n (%)	108 (94)	100 (87)	47 (84)	208 (90)
	HIV RNA >50 c/mL, n (%)	5 (4)	0	1 (2)	5 (2)

Data Source: GSK Doc. # 2016N273084_00 Week 48 Table 7.1002; GSK Doc. # 2017N337118_00 Week 96 Table 7.1002

In the Q8W IM dosing arm, 8 subjects (7%) had HIV RNA >50 c/mL, including 5 who re-suppressed at visits subsequent to Week 48, 1 who was withdrawn for injection intolerability, 1 who experienced PDVF at Week 48, and 1 who discontinued for lack of efficacy at Week 8 due to apparent maladministration of RPV LA, leading to unmeasurable RPV concentrations, alongside CAB concentrations within the expected range, and virologic rebound without resistance.

In the Q4W IM arm, 1 subject (<1%) failed Snapshot for virologic reasons at Week 48 but re-suppressed at subsequent study visits (Weeks 56 and 64).

In the oral comparator arm (CAB 30 mg + 2 NRTIs), 1 subject failed Snapshot for virologic reasons.

Logistic regression was used to examine the association between Snapshot HIV RNA >50 c/mL at Week 48 with CAB and RPV PK trough concentrations. In a post-hoc multivariable analysis, 3 covariates were identified as statistical predictors of Week 48 HIV RNA >50 c/mL:

- Day 1 plasma HIV RNA >50 c/mL,

- time to achieve viral suppression to <50 c/mL of greater than 4 weeks of ART induction (after the Week -16 visit), and
- last RPV trough concentration prior to the Week 48 visit.

Several other factors were considered. Baseline viral load, while associated in the univariate model, was not retained in the multivariate model. There was no apparent association with last CAB trough concentration, age, gender, country, or CD4 cell count category.

PK/PD assessments were not repeated at Week 96. However, at Week 160, 90% (Q8W IM arm) and 83% (Q4W IM) of subjects randomized to receive injectable dosing from Day 1 maintained virologic suppression (HIV-1 RNA <50 c/mL). At Week 160, 97% (Optimized Q8W IM arm) and 100% (Optimized Q4W IM) of subjects who were randomized to receive oral CAB + 2 NRTIs on Day 1 and switched to an optimized injectable dosing regimen of their choice on Week 100 maintained virologic suppression (HIV-1 RNA <50 c/mL) [Data Source: GSK Doc. # 2018N380094_00 Week 160].

Conclusion:

- Due to the limited number of PDVFs, relationships between drug concentrations and PDVFs are difficult to establish. Multiple factors, including plasma concentrations, may be associated with the occurrence of PDVFs.

2.2. Cabotegravir PopPK Modeling and Simulations

CAB PopPK Modeling and Simulations for CAB LA Monthly Regimen

Study Title: Population Pharmacokinetic Analysis of Cabotegravir

Location of Report: m5.3.3.5, Q4W CAB LA PopPK

PopPK Simulations for CAB LA Every Two Months Regimen

Study Title: Population Pharmacokinetic Evaluation of Cabotegravir Q8W Regimen

Location of Report: m5.3.3.5, Q8W CAB LA PopPK

2.2.1. CAB PopPK Model

2.2.1.1. Objectives

- To further characterize CAB PK based on data from healthy subjects and HIV-1 infected patients following administration as oral tablet and LA IM injection
- To evaluate the association between intrinsic and extrinsic factors and the variability of CAB PK parameters and exposure.

- To summarize post-hoc PK parameter estimates, including exposure metrics (AUCtau, Cmax and Ctau) for the overall population and subgroups of various patient characteristics.
- To perform simulations that guide dosing strategies under various scenarios (e.g., dosage errors, unplanned and planned dosing delays, concomitant medications, and treatment discontinuation).

2.2.1.2. Modeling Steps and Data

Rich and sparse plasma CAB concentration data obtained from 10 clinical studies with oral CAB (9 Phase I and 1 Phase II) and 6 clinical studies with CAB LA (1 Phase I, 3 Phase II, and 2 Phase III [CAB LA + RPV LA monthly regimen]) were pooled for the PopPK analysis using a non-linear mixed effect modelling approach (NONMEM).

Table 32 Summary of PopPK Modelling Dataset (All Subjects)

	Number of Subjects	Percentage of Subjects (%)	Number of PK Samples	Percentage of PK Samples (%)
Total	1650 [a]	100	24,039 [a]	100
Oral CAB (10, 30, and 60 mg once daily)	1631	98.8 [b]	6500	27
CAB LA (200, 400, 600, and 800 mg IM)	1258	76.2[b]	17,539	73

Data Source: GSK Doc. # 2018N384611_01 Q4W Table 9
a. After exclusions, 23,926 plasma CAB concentrations in 1647 subjects remained in the analysis.
b. 98.8% of subjects provided oral CAB data and 76.2% of subjects provided CAB LA data

When data for the Phase IIIb study supporting the safety and efficacy of the CAB + RPV every 2 months regimen (Study 207996) became available, the PopPK model was evaluated through external validation using data from Study 207966 as the validation data set. Study 207966 contains both newly enrolled subjects and transition subjects from Study 201585. The transition subjects were included in the original PopPK analysis; therefore, the external validation dataset included newly enrolled subjects. The number of Study 207966 subjects and PK samples in the external validation population are summarized in Table 33.

Table 33 Summary of External Validation Dataset (n=647)

	Number of PK Samples	Percentage of PK Samples (%)
Total	**5137**	**100**
30 mg (oral CAB)	637	12.4
400 mg (CAB LA)	1617	31.5
600 mg (CAB LA)	2883	56.1

Data Source: GSK Doc. # 2019N421460_00 Q8W Table 10.
External validation population: 647 subjects who were not included in the previous CAB PopPK analysis [GSK Doc. # 2018N384611_01]

Table 34 Summary of Covariates

Covariate		Subjects Included in PopPK Modelling (N = 1647)	Subjects Included in External Validation (N = 647)
		Median (range)	**Median (range)**
Age (year)		36 (18-74)	42 (19-83)
Age ≥65 years, n (%)		20 (1.2)	
Baseline body weight (kg)		76.6 (41.2-168.3)	77.1 (41.8-138.9)
Baseline BMI (kg/m^2)		25.37 (15.3-69.51)	25.26 (16.57-54.02)
		Number of subjects (%)	**Number of Subjects (%)**
Female [a]		424 (25.7)	140 (21.64)
HIV-1-infected patients		1189 (72.2)	647 (100)
Race	White [b]	1102 (66.9)	491 (75.89)
	Black / African American	394 (23.9)	100 (15.46)
	Asian [c]	56 (3.4)	27 (4.17)
	Other [d]	93 (5.6)	29 (4.48)
	Unknown	2 (0.12)	0
Smoker status	Never smoked	590 (35.8)	340 (52.55)
	Former smoker	210 (12.8)	103 (15.92)
	Current smoker	447 (27.1)	204 (31.53)
	Not current smoker [e]	120 (7.3)	0
	Unknown	280 (17.0)	0

		Injections Included in the PopPK Modeling (n=12,169)	Injections Included in External Validation (n=5367)
		Number of injections (%)	Number of Injections (%) [g]
Injection type	Unsplit	11,443 (94.0)	5367 (100)
	Split [f]	726 (6.0)	0
Injection needle length (inch) [h]	1	151 (1.2)	50 (0.93)
	1.5	10,766 (88.5)	5042 (93.94)
	2	766 (6.3)	275 (5.12) [f]
	2.5	1 (<1)	0 [f]
	Unknown	485 (4.0)	0 [f]

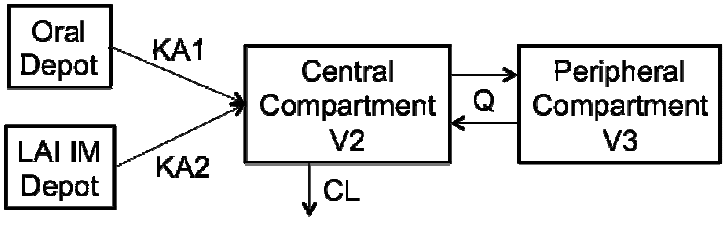
Data Source: GSK Doc. # 2018N384611_01 Table 11; GSK Doc. # 2019N421460_00 Table 11

a. Refers to biological gender (i.e., male versus female only). No transgender was observed in the data.
b. Subjects included in External Validation included 2 subcategories: White / Caucasian / European Heritage and Arabic / North African Heritage.
c. Subjects included in External Validation included all subjects with Asian Heritage including but not limited to the subjects enrolled in Asia.
d. Other Race includes Mixed, American Indian/Alaskan Native, Other, Native Hawaiian/other Pacific Islander, Latino/Hispanic.
e. Subjects included in External Validation: "Not current smoker" could be "Never smoked" or "Former smoker", which was not specified in the source data.
f. Injections Included in the PopPK Modeling: Split injections were used in some Phase I and Phase II studies. The CAB LA dose volumes (2 to 3 mL) used in Phase III were accommodated by a single (unsplit) injection.
g. Injections Included in External Validation: Values of these 2 covariates were unique for each injection (one record per dosing event) but not unique in each subject because each subject may have multiple injections. Therefore, each subject could have multiple injection types or needle lengths for different injections.
h. Injections Included in the PopPK Modeling: Phase IIb and Phase III protocols recommended a 1.5-inch needle length for most subjects and stated that longer needle lengths may be required for participants with higher BMIs (example >30 kg/m^2) to ensure that injections were administered IM as opposed to subcutaneously

2.2.1.3. CAB PopPK Model Results

The base model was a two-compartment model with first-order oral and IM absorption and elimination (Figure 10). There were two depot compartments, one for oral and one for LA. The NONMEM subroutine ADVAN5 TRANS1 was used for estimation.

Figure 10 CAB PK Model: Two-compartment Model with First-order Oral and IM Absorption and Elimination



Data Source: GSK Doc. # 2018N384611_01 Figure 1

The structural model parameters for the base model included apparent clearance (CL/F), apparent central volume of distribution (V2/F), apparent inter-compartmental clearance (Q/F), apparent peripheral compartment volume of distribution (V3/F), and distinct absorption rate constants for oral tablet (KA1) and LA IM (KA2) formulations. F represents the bioavailability from the LA IM depot compartment. Bioavailability of the oral formulation relative to the LA IM formulation (F1) was estimated. Various dual absorption models were evaluated for the LA formulation.

Body weight was included as part of the base model ($p < 0.01$), and used to scale CL/F, V2/F, Q/F and V3/F using a power function. The exponent was estimated and was the same for CL/F and Q/F and for V2/F and V3/F.

An overview of the stepwise covariate model building procedure is presented in Table 35. The covariate model that resulted from the stepwise forward addition and backward elimination procedure was defined as the full model. During model refinement, covariates with minimal impact were excluded from the full model for parsimony. A covariate was dropped from the model if the CI of its coefficient included zero (e.g., based on the standard errors obtained from model bootstrapping). After statistically significant covariates had been included in the model, the model was then reduced. The effect of a covariate was considered removable if the PK parameter estimate of a typical person differed by less than 15% from a person with an extreme covariate value (10th and 90th percentiles for a continuous covariate).

Table 35 Covariate Analysis

Steps	Covariates
Added during forward inclusion	KA2: BMI, needle length, gender, split
	CL/F: albumin, bilirubin, race, gender, smoke
	V2/F: albumin, gender, smoke
	F1: HIV status, race
Dropped during backward elimination	None
Full model	KA2: BMI, needle length, gender, split
	CL/F: albumin, bilirubin, race, gender, smoke
	V2/F: albumin, gender, smoke
	F1: HIV status, race
Retained in the final model	KA2: BMI, needle length, gender, split
	CL/F: smoke

Data Source: GSK Doc. # 2018N384611_01 Section 5.2.2
Race was categorized as Caucasian (66.9%), Black/African American (23.9%), Asian (3.4%), and Other (and Unknown; 5.7%).
Not current smoker was modelled as fraction of never smoked. Unknown smoker status was considered as a separate category.
Unknown needle length was imputed as 1.5-inch (most common category).
Needle length was modelled as a continuous variable.

CAB PK after Oral and IM Administration:

The parameter estimates of the final PopPK model, including the covariate effects, are presented in Table 36. All parameters could be estimated with adequate precision, as measured by a RSE <20% for fixed effects (except for needle length on KA2, with an RSE of 36.2%) and a RSE <25% for random effects.

Table 36 Parameter Estimates and Standard Errors from the Final PK Model with M3 Method Applied (final110), Including Covariate Effects

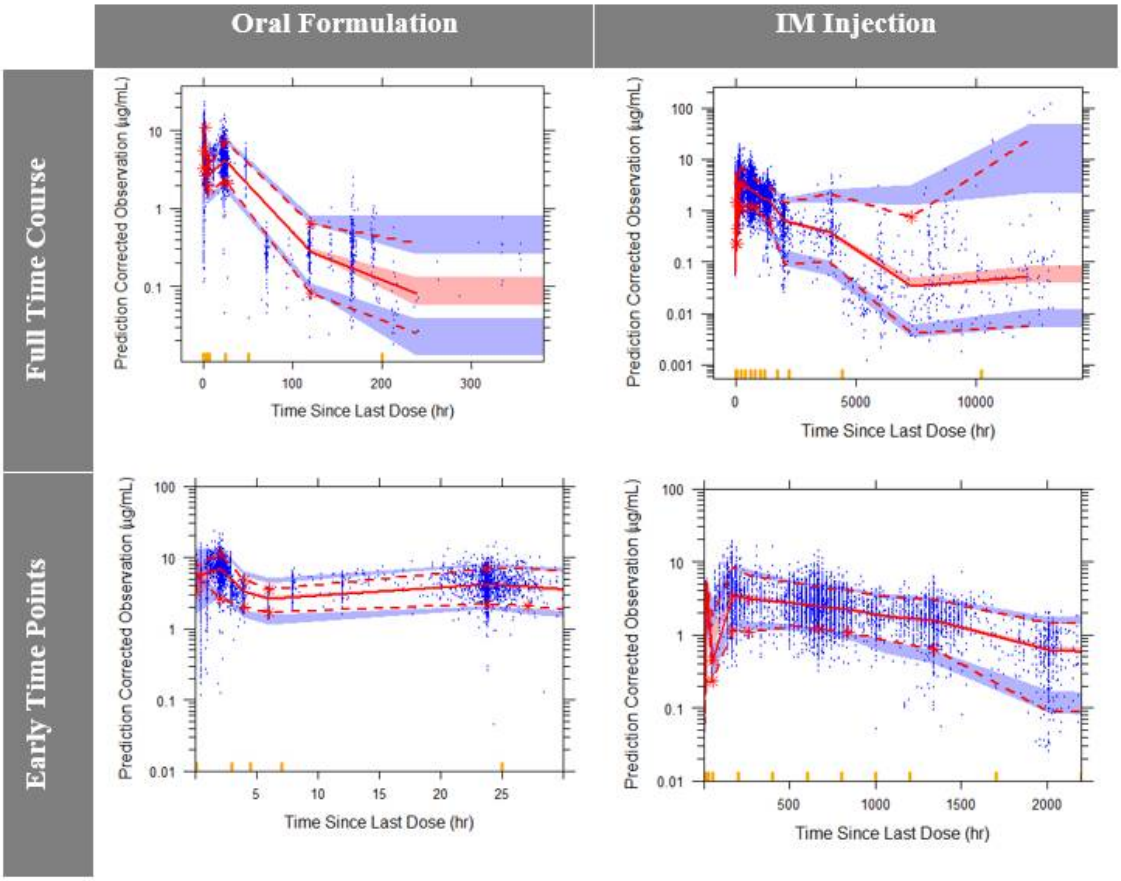
Parameter	Estimate	RSE (%)	90% CI (Bootstrap) 5th, 95th Percentile	IIV (%)	RSE of IIV (%)	Shrinkage (%)	Equation Expression
KA1 (/hour)	1.41	4	1.23,1.52	89.4	4.34	69.1	
KA2 (/hour)	0.000733	2.3	0.000705, 0.000761	57.9	2.46	17.9	$KA2 = 0.00073 \times (1 - 50.9\% \text{ if female})) \times (1 + 47.8\% \text{ if split}) \times \left(\frac{BMI \text{ in } \frac{kg}{m^2}}{25.4}\right)^{-0.766} \times \left(\frac{NDL \text{ in inch}}{1.5}\right)^{0.479}$
CL/F (L/hr)	0.151	0.9	0.148, 0.153	23.3	2.58	10.3	$CL/F = 0.151 \times \left(\frac{BWT}{76.6}\right)^{0.618} \times (1 + 17.4\% \text{ if current smoker})$
V2/F (L)	5.27	2	5.07, 5.45	20.3	9.38	31.1	$V2/F = 5.27 \times \left(\frac{BWT}{76.6}\right)^{0.702}$
Q/F (L/hr)	0.507	6.6	0.455, 0.579				$Q/F = 0.507 \times \left(\frac{BWT}{76.6}\right)^{0.618}$
V3/F (L)	2.43	4.8	2.26, 2.66				$V3/F = 2.43 \times \left(\frac{BWT}{76.6}\right)^{0.702}$
F1	0.756	0.9	0.744, 0.768	17.4	5.70	40	
Add Err (μg/mL)	0.0319	19.4	0.0202, 0.0496				
Prop Err	27.3%	1.1	26.7%, 27.8%				
BWT on CL/F and	0.618	5.6	0.562, 0.68				

Parameter	Estimate	RSE (%)	90% CI (Bootstrap) 5th, 95th Percentile	IIV (%)	RSE of IIV (%)	Shrinkage (%)	Equation Expression
Q/F							
BWT on V2/F and V3/F	0.702	7.1	0.622, 0.79				
Smoke on CL/F	17.4%	9.3	14.7%, 20%				
BMI on KA2	-0.766	13	-0.922, -0.611				
Needle length on KA2	0.478	36.2	0.184, 0.747				
Gender (Female) on KA2	-50.9%	4.4	-54.1%, -47.1%				
Split on KA2	47.8%	14.2	36.9%, 60.2%				

Data Source: GSK Doc. # 2018N384611_01 Table 15

The pcVPC demonstrated that the final model adequately described the time course of plasma CAB concentration and its associated variability after oral and IM dosing overall (Figure 11) and by covariates [Data Source: GSK Doc. # 2018N384611_01 Figure 12].

Figure 11 Prediction-corrected VPC of the Final Model (final110)



Data Source: GSK Doc. # 2018N384611_01 Figure 10

Notes: Solid line corresponds to observed median; dashed lines correspond to the 5th and 95th percentiles of prediction-corrected observations; shaded regions correspond to 95% of the simulated (n = 500) values of the predicted median (pink), 5th, and 95th percentiles (blue). Red asterisks highlight where prediction-corrected observation lines were not contained within the shaded region. Blue dots correspond to prediction-corrected observed data. Yellow bars on the x axis indicate the boundaries between bins.

CAB is rapidly absorbed following oral administration, the bioavailability of oral CAB relative to CAB LA (F1) was 76% and the half-life was estimated as 36.5 hours (non-smoker, body weight 76.6 kg; GSK Doc. # 2018N384611_01 Section 5.2.3.1).

The model characterized the 'flip-flop' (absorption-rate limited) nature of CAB PK following IM injection because CAB is slowly absorbed into the systemic circulation following IM injection into the gluteus medius muscle. The rate of absorption following IM administration of CAB LA (KA2 = 0.000733 h^{-1}) is much slower than the rate of CAB elimination from plasma. The PopPK estimate of plasma CAB half-life after IM dosing was 6.4 weeks in the studied population of 74.3% male and 25.7% female [Data

Source: GSK Doc. # 2018N384611_01 Section 5.2.1]. Separate plasma CAB half-life estimates by gender were 5.6 weeks for males and 11.5 weeks for females [Data Source: GSK Doc. # 2018N384611_01 Section 5.2.3.1]. The absorption profile contributed to time to steady state taking approximately 44 weeks (based on observed data in Phase III studies). The time to achieve steady-state is prolonged with CAB LA with efficacious concentrations achieved following the initial IM injection.

The estimate of plasma CAB Vc/F was 5.27 L and Vp/F was 2.43 L; these volume estimates, along with the assumption of high F, suggest some distribution of CAB to the extracellular space. CAB is a low clearance drug based on the estimated CL/F of 0.151 L/h.

CAB PK variability was explained by gender, BMI, needle length, and split injection, which were statistically significant covariates of CAB LA absorption rate (KA2), and current smoker status, which was a statistically significant covariate of CAB CL/F (body weight scaling on CL/F, V2/F, Q/F, and V3/F was also implemented) in the final CAB PopPK model (Table 36). Females had 50.9% lower KA2 compared with males and split injection had 47.8% higher KA2 compared with unsplit injections. BMI was inversely correlated with KA2 and needle length was positively correlated with KA2, but the effect sizes were relatively small (<20% difference at 5^{th} and 95^{th} percentiles compared with median covariate values) [Data Source: GSK Doc. # 2018N384611_01 Table 14]. Being a smoker (UGT1A1 inducer) was associated with a 17.4% increase in plasma CAB CL/F.

Age, race, Baseline clinical laboratory parameters, HIV status, and HIV viral load had no effect on CAB PK [Data Source: GSK Doc. # 2018N384611_01 Figure 5, Figure 6, Appendix Figure 2]. CAB PK data in subjects of ≥65 years old and some racial groups are limited.

Impact of Covariates on Exposure:

The exposure predictions were made spanning the covariate ranges observed in the Phase III studies and then categorized according to binary covariate distinctions. In this manner the influence of a covariate can be observed within the population whilst maintaining the physiologically relevant spread of the other covariates. Thus, the categorization reflected not only the effect of the covariate of choice but also the influence of any co-varying covariates.

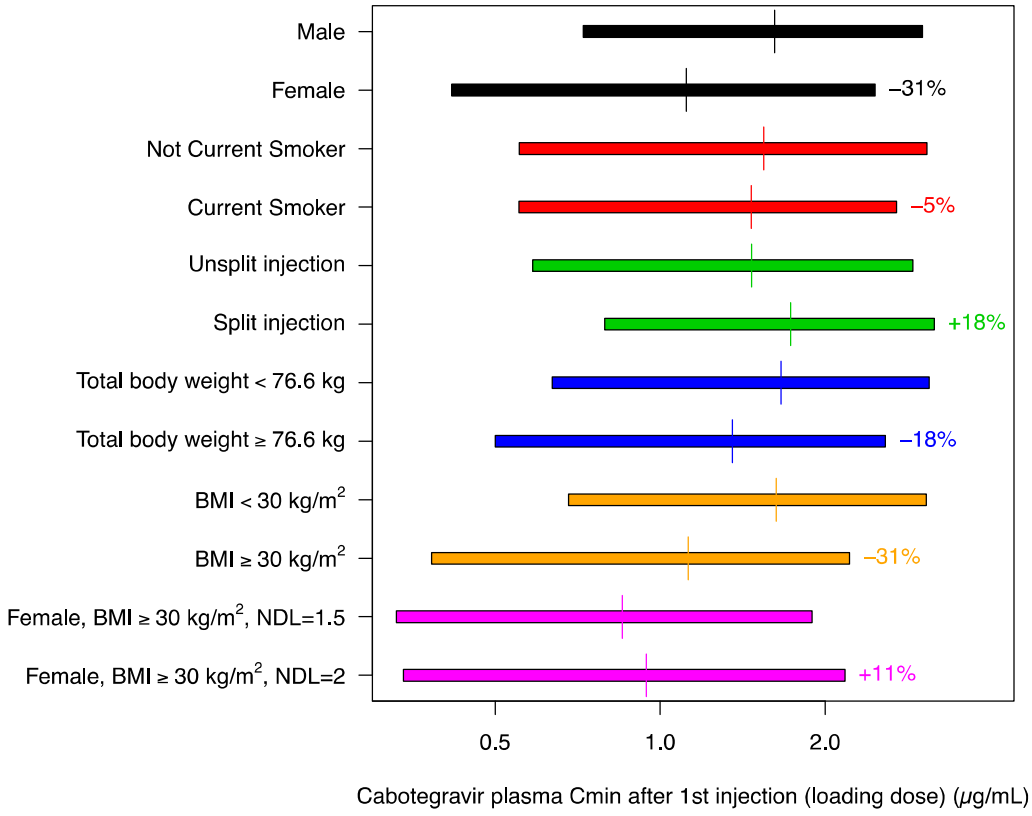
Based on the simulations, the covariates leading to the greatest differential upon initial IM dose Cmin were gender and BMI. Smoker status, split injection, WT, and needle length led to a relatively small differential of <20% upon initial IM dose Cmin. Categorization of initial IM dose Cmin by gender showed that the median was lower in females than males by 31% (Figure 12a). Similarly, a categorization by BMI showed that subjects with BMI ≥30 kg/m^2 had 31% lower median initial IM dose Cmin than those with BMI<30 kg/m^2.

Although covariate analysis identified females with high BMI as having initial IM dose Cmin in the lower overall population range, the proposed dosing regimen is sufficient for such patients. Females with high BMI were successfully treated in the 2 Phase III studies. Thus, no dose adjustment is required for these or other covariate effects.

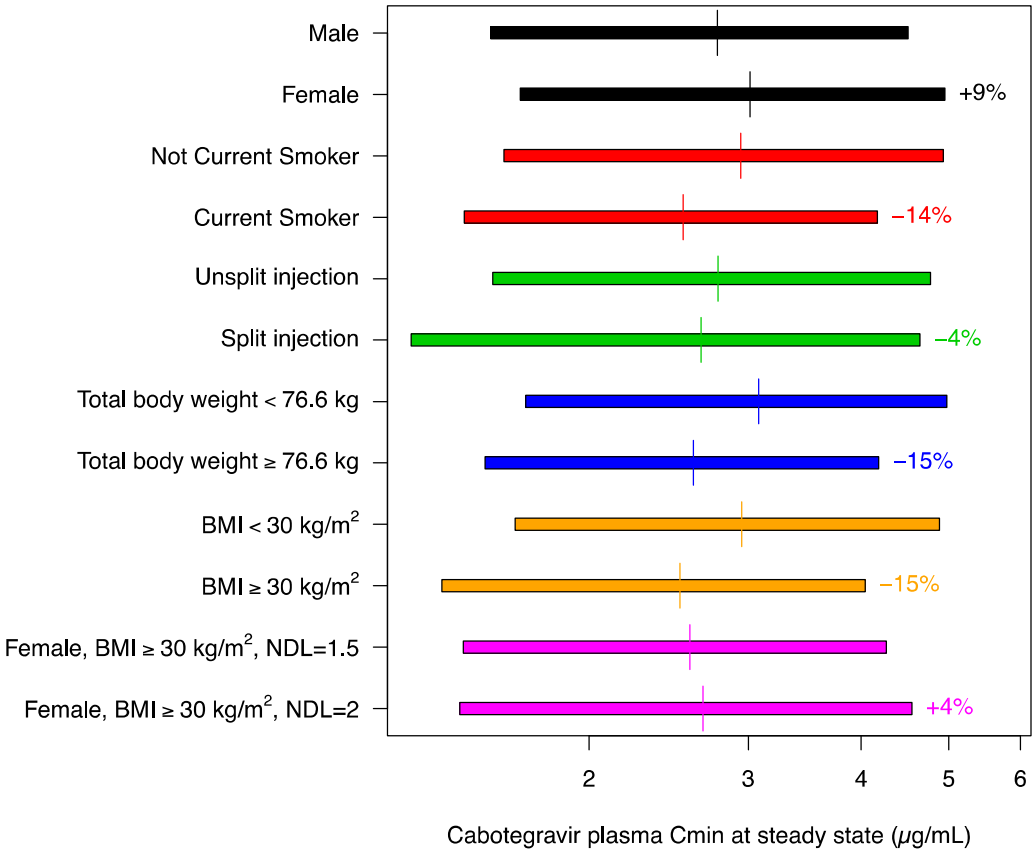
The impact of all covariates on plasma CAB steady-state Cmin following IM administration was predicted to be relatively small (≤15%, Figure 12b). Unlike the initial IM dose Cmin, which was lower in females than males, steady-state Cmin was higher in females than males. The impact of all covariates on plasma CAB steady-state Cmax were also predicted to be relatively small (≤21%, Figure 12c).

Figure 12 Impact of Covariates on Plasma CAB Cmin after the First Injection (a), Cmin at Steady State (b), and Cmax at Steady State (c)

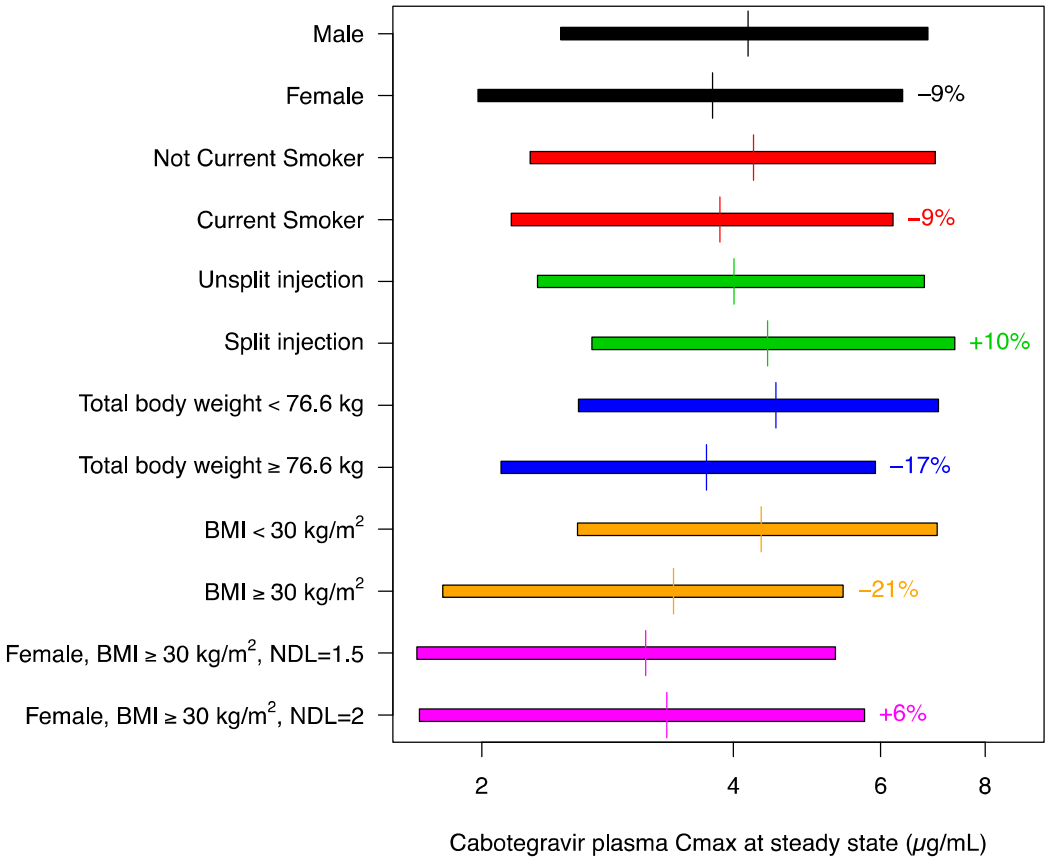
a. Impact of Covariates on Cmin after the First IM Injection



b. Impact of Covariates on Cmin at Steady State Following IM Injection



c. Impact of Covariates on Cmax at Steady State following IM Injection



Data Source: GSK Doc. # 2018N384611_01 Figure 13, Figure 14

Each bar represents 5th to 95th percentile with median in each subgroup within the covariate (or covariate combination). Percentage numbers on the right side of each bar represent the percentage change in median versus the median of the reference subgroup within the same covariate or covariate combination (i.e. versus the other bar of the same color).

2.2.2. External Validation of the CAB PopPK Model

2.2.2.1. External Validation Methods

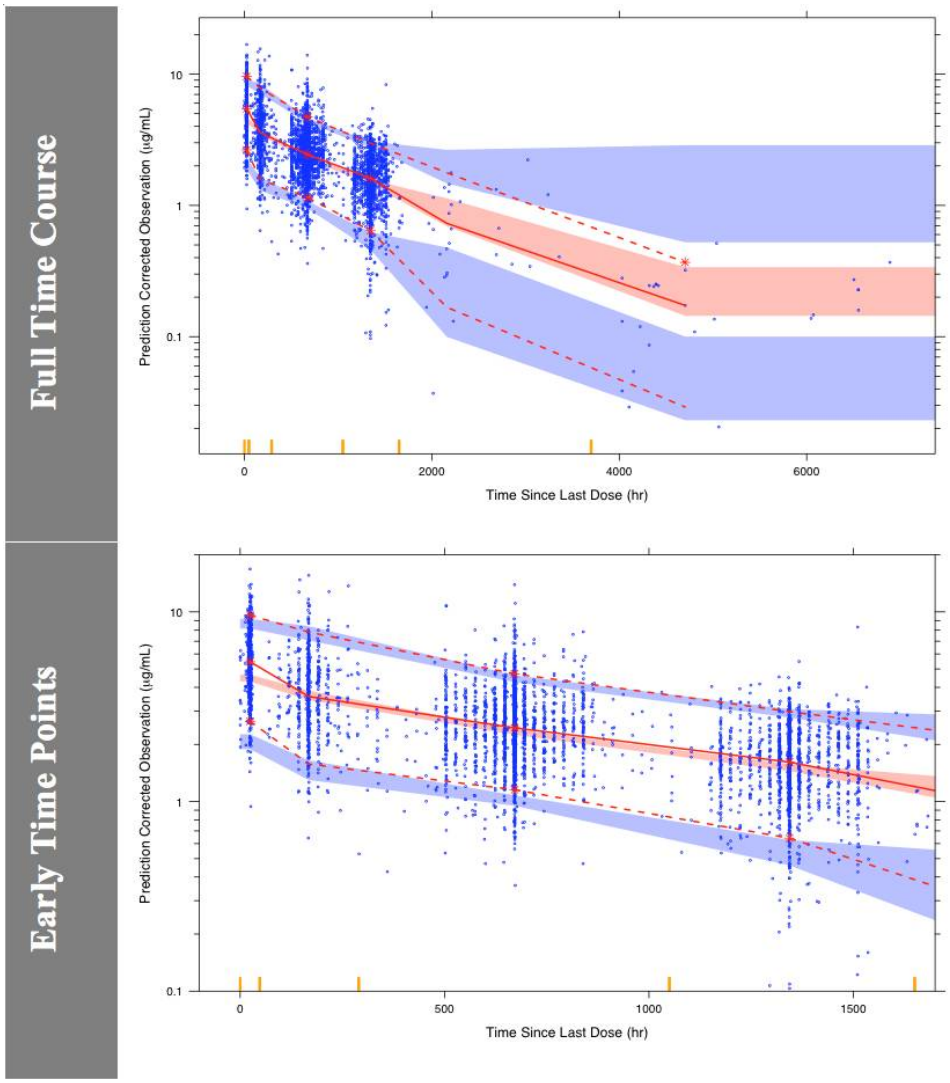
CAB plasma concentrations in the external validation population were predicted using the final CAB PopPK model parameter estimates and the covariates from the external validation population that were statistically significant (body weight, gender, BMI, split injection, needle length, and smoking status). Predicted CAB concentrations in the external validation population were then compared to the observed data. Prediction corrected VPC with 500 replications was performed with the final CAB PopPK model parameters [Data Source: GSK Doc. # 2018N384611_01, Section 3.4.5.2] to compare PIs for the 5th percentile, median, and 95th percentiles of the simulated PK data in the external validation population with the corresponding values computed for the observed data in the external validation population. The observed concentration vs. time data was overlaid on the PI to visually assess the concordance between the simulated and observed data. The pcVPCs were stratified by gender, BMI, and smoker status. Model

performance was evaluated based upon the extent to which the observed median values fell within the associated 90% PIs. Percentages of observed concentrations above and below PI were calculated. Post-hoc PK parameters were obtained by fitting the final Q8W CAB PopPK model (final110) [Data Source: GSK Doc. # 2019N421460_00, Section 3.5.1] to the 647 new subjects from Study 207966 with the estimation option MAXEVALS set to 0. Once deemed adequate to describe the new 207966 study data, the final CAB PopPK model was used for all subsequent analyses.

2.2.2.2. External Validation Results

The pcVPC of the external validation population using the final CAB PopPK model is shown in Figure 13. In general, the model predictions adequately captured the observed concentration vs. time points and trends within the 90% PI (5th and 95th percentiles) of the simulated values. Overall, the final CAB PopPK model adequately described CAB exposure in new subjects from Study 207966.

Figure 13 Prediction-corrected VPC of External Validation



Data Source: GSK Doc. # 2019N421460_00 Q8W Figure 3.
Notes: Solid line corresponds to observed median; dashed lines correspond to the 5th and 95th percentiles of prediction corrected observations; shaded regions correspond to 95% CI of the simulated (n = 500) values of the predicted median (pink), 5th, and 95th percentiles (blue). Red asterisks highlight where prediction corrected observation lines were not contained within the shaded region. Blue dots correspond to prediction corrected observed data. Yellow bars on the x axis indicate the boundaries between bins.

2.2.3. Simulation Results

CAB LA Treatment Simulations:

The final PopPK model was used to simulate plasma PK profiles of CAB in virologically suppressed, HIV-1 infected patients. The objectives of these simulations were to provide a visual representation of CAB PK during permitted dosing windows, dosing errors (underdosing and higher than planned doses), missed doses, oral therapy for planned missed injections, and concomitant administration of enzyme inducers and inhibitors during and following CAB LA discontinuation. Simulations supporting

recommendations for resuming injection dosing after missed injections are presented in Section 3.1.4. Results of all simulations for the CAB LA monthly regimen are described in GSK Doc. # 2018N384611_01 Section 5.3 and simulation results for the CAB LA every 2 months regimen are described in GSK Doc. # 2019N421460_00 Section 4.3.

Conclusions:

- The PK of CAB following PO and IM administration was adequately characterized based on data from healthy subjects and HIV-1-infected subjects. A 2-compartment model with first-order oral and IM absorption and elimination best described the plasma CAB PK profile.
- The model characterized the 'flip-flop' (absorption-rate limited) nature of CAB PK following IM injection. The PopPK estimate of plasma CAB half-life after oral dosing was 36.5 hours and after IM dosing was 6.4 weeks for the overall population (5.6 weeks for males and 11.5 weeks for females).
- CAB PK variability was explained by gender, BMI, needle length, split injection, current smoker status, and body weight; however, the effects of these covariates are not considered clinically relevant. Age and race had no effect on CAB PK. No CAB dose adjustment is necessary for the covariates evaluated.
- The final CAB PopPK model adequately described CAB exposure in new subjects from Study 207966.
- Simulations support an injection window of ±1 week for CAB LA regimens (Section 3.1.4).
- Simulations support recommendations for resumption of dosing following interruptions of CAB LA with or without oral therapy (see Section 3.1.4).

2.3. Cabotegravir LA

Table 37 Listing of Studies of CAB LA

Study	Population	Regimens	Study Design	Section
201120 (ECLAIR)	Healthy Subjects	CAB LA quarterly	Phase IIa repeat dose PK and safety	2.3.1.1
LAI115428 (Cohort 4)	Healthy Subjects	CAB LA quarterly	Phase I repeat dose escalation	2.3.1.2
LAI114433	Healthy Subjects	Single dose CAB LA	Phase I single dose escalation	2.3.1.3
			Distribution into genital tract tissues	2.3.1.4

2.3.1. Pharmacokinetics in Healthy Subjects

2.3.1.1. Study 201120 (ECLAIR): Repeat Dose PK of CAB LA 800 mg IM Q12 Weeks (Phase IIb)

Study Title: A Phase IIa study to evaluate the safety, tolerability and acceptability of long acting injections of the HIV integrase inhibitor, GSK1265744, in HIV uninfected men (ÉCLAIR)

Only PK data from this study is presented in this module.

Location of Reports: m5.3.3.1, 201120 Week 81

Objectives: The primary objective of the study was to evaluate the safety and tolerability of CAB LA 800 mg IM administered at 12-week intervals for 3 doses through Week 41 in HIV-uninfected men. Secondary objectives included evaluation of CAB PK following IM injection through the 41-week Injection Phase and following discontinuation during the 52-week Long-term Follow-up Phase.

Study Design and Methods: This was a Phase IIa, randomized, multi-site, 2-arm, double-blinded study to evaluate the safety, tolerability, and acceptability of CAB in adult male subjects at low risk for sexual acquisition of HIV infection. A total of 127 subjects were randomized (5:1) to CAB or placebo through 41 weeks. Subjects received oral CAB 30 mg once daily or placebo without regard to meals for 4 weeks followed by a 1-week washout period followed by CAB LA 800 mg (2 x 400 mg split) IM or saline placebo injections administered every 12 weeks at 3 time points (Week 5, Week 17, and Week 29). All subjects were followed for 52 weeks following the last injection to Week 81.

Results: Geometric mean AUC(0-tau) increased by 19% for Injection 3 compared with Injection 1 (Table 38). Estimation of t1/2 following Injection 1 was limited by the short sampling period of 12 weeks prior to administration of Injection 2, likely biasing reportable t1/2 values to those of shorter duration. There were not sufficient data to estimate t1/2 for Injection 2. A majority of subjects (~60) had no or 1 measurable PK concentration in the Follow-up Period. For these subjects, estimation of t1/2 was limited by the sparse sampling collection during the Follow-up Period. Fourteen subjects, however, still had measurable concentrations at Week 81, 52 weeks after the final injection at Week 29.

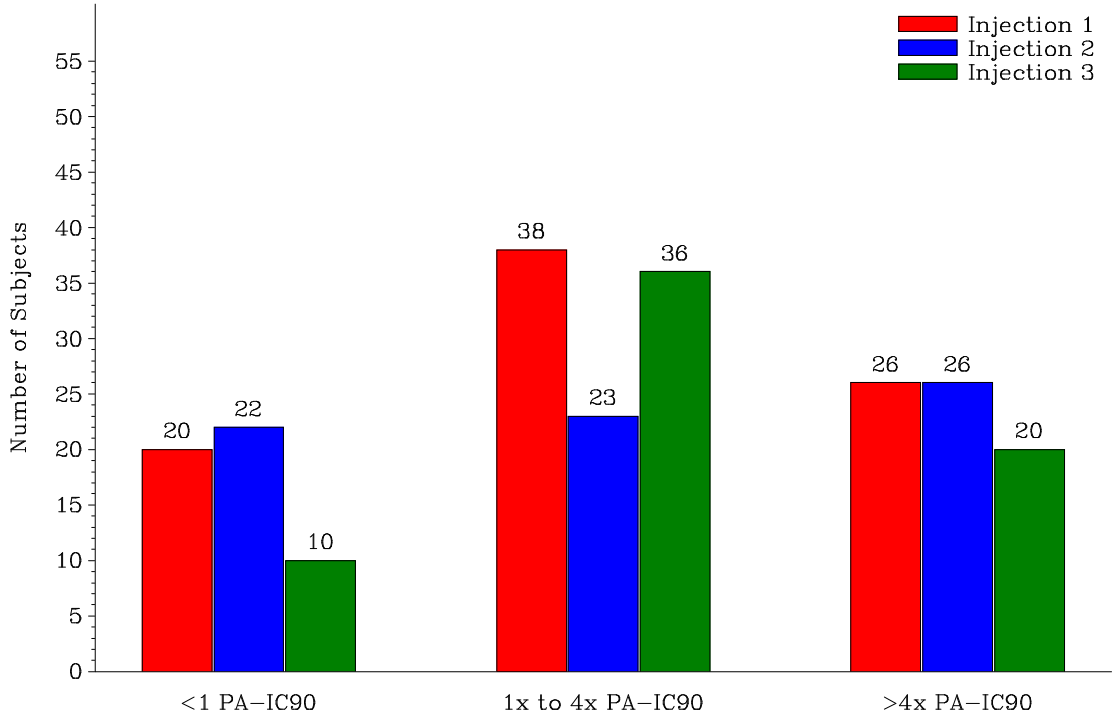
Table 38 Summary of Plasma CAB PK Parameters Following CAB LA 800 mg Q12W (PK Parameter Population)

Plasma CAB Parameter	Geometric Mean [95% CI] (CVb%)		
	Injection 1	Injection 2	Injection 3
Cmax (µg/mL) (Injection 1 n=93; Injection 2 n=89; Injection 3 n=85)	4.26 [3.64, 4.98] (88.6)	5.22 [4.52, 6.04] (78.0)	4.91 [4.31, 5.60] (66.6)
Ctau (µg/mL) (Injection 1 n=84; Injection 2 n=71; Injection 3 n=66)	0.302 [0.237, 0.385] (157)	0.331 [0.253, 0.435] (165)	0.387 [0.296, 0.505] (150)
AUC(0-tau) (h•µg/mL) (Injection 1 n=93; Injection 2 n=89; Injection 3 n=85)	3415 [3140, 3714] (42.5)	3873 [3543, 4235] (44.3)	4047 [3758, 4357] (35.3)

Data Source: GSK Doc. # 2016N269422_00 Week 81 Table 9.2
Ctau was evaluable only if the actual sampling time fell within ±4 days of the scheduled sampling time.

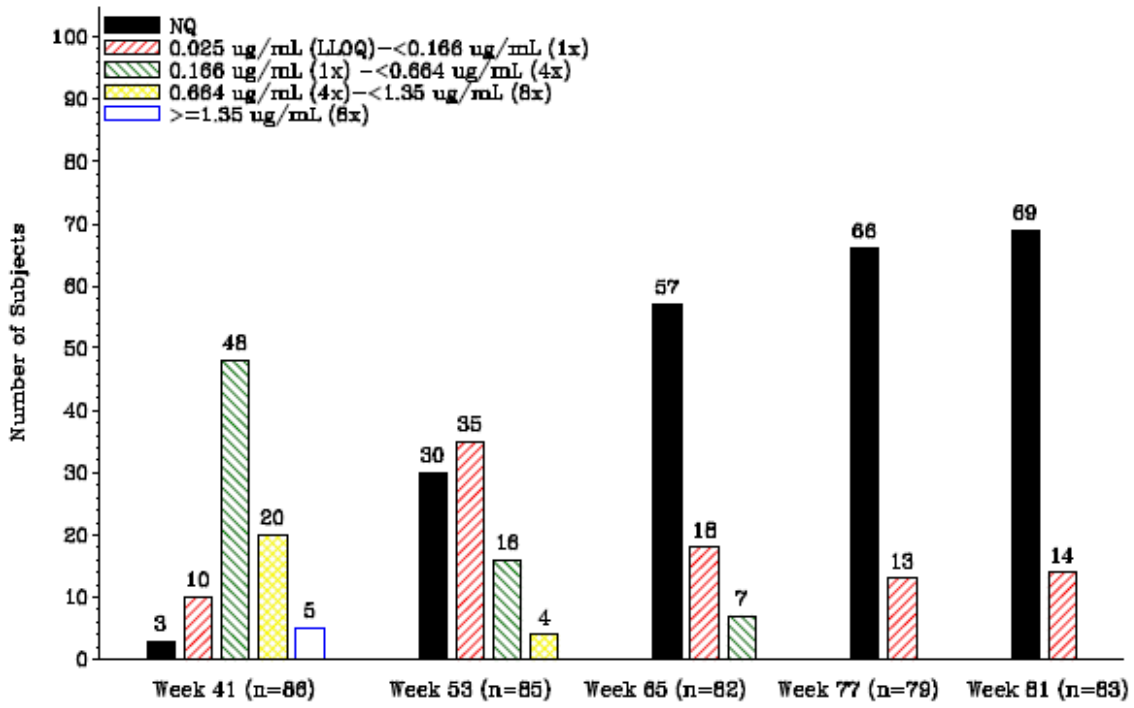
Figure 14 presents bar graphs showing the number of subjects with Ctau within various intervals relative to the PA-IC90 value of 0.166 µg/mL. Approximately 75% of the reportable Ctau values exceeded the PA-IC90 value, and one-third of the values exceeded 4 times the PA-IC90 value. Thus, approximately two thirds of Ctau values were below the target value of 4 times PA-IC90.

Figure 14 Number of Subjects in CAB Ctau Ranges by Injection Visit Following CAB LA 800 mg Q12W (PK Parameter Population)



Data Source: GSK Doc. # 2016N269422_00 Week 81 Figure 9.8

Figure 15 Numbers of Subjects with Plasma CAB within Concentration Ranges Versus Time (Weeks) Following Injection 3 (Weeks 41 to 81) Following CAB LA 800 mg Q12W Administration (PK Parameter Population)



Data Source: GSK Doc. # 2016N269422_00 Week 81 Figure 9.9
Third and final injection of CAB LA occurred at Week 29

Conclusions:

- Q12W injections of CAB LA 800 mg IM did not achieve the desired proportion of subjects above the target concentrations in this large study of uninfected male subjects.
- Approximately one-sixth of the PK subjects still had measurable concentrations at 52 weeks after the third injection; these subjects generally had BMI values above the median, suggesting an inverse relationship between BMI and the rate of drug absorption.

2.3.1.2. Study LAI115428: Repeat Dose PK of CAB LA Quarterly IM Injections (Cohort 4)

Study Title: A randomized, open label study to investigate the safety, tolerability and pharmacokinetics of repeat dose administration of long acting GSK1265744 and long-acting TMC278 intramuscular and subcutaneous injections in healthy adult subjects

Location of Report: m5.3.3.1, LAI115428

Objectives Study Design, and Methods: Refer to Section 2.1.1.1.

Table 39 CAB LA Quarterly Dosing Regimen

Cohort	Lead-in Period Day -21 to -8	Quarter 1 and 2
4	Oral CAB 30mg q24h x 14 days	CAB LA 800mg IM (2 × 400mg split)

Table 40 Summary of Select Plasma CAB PK Parameters Following CAB LA Quarterly Dosing (Cohort 4)

Treatment	n	AUC(0-tau) [a] (μg.h/mL)	Cmax [a] (μg/mL)	Ctau [a] (μg/mL)	tmax [b] (Day)
CAB LA 800mg IM Q1	10	2917 (53)	2.70 (99)	0.74 (97)	16.5 (2.0-83.0)
CAB LA 800mg IM Q2	9	4468 (52)	3.31 (59)	1.10 (140)	15.0 (6.0-42.0)
CAB LA 800mg IM Q1, Q2 Overall	19	3570 (57)	2.97 (79)	0.89 (116)	15.0 (2.0-83.0)

Data Source: GSK Doc. # 2013N159813_01 Table 3.4
a. Geometric mean (CV%)
b. Median (range)

Conclusions:

- Q12W injections of CAB LA 800 mg IM achieved geometric mean Ctau values above the 4-times PA-IC90 clinical target in this small number of subjects, supporting further investigation of quarterly dosing for pre-exposure prophylaxis.

2.3.1.3. Study LAI114433: PK of CAB LA Following Single Dose IM or SC Administration

Study Title: An observer- and subject-blinded, randomized, placebo-controlled, single dose escalation study to investigate the safety, tolerability and pharmacokinetics of intramuscular and subcutaneous long acting GSK1265744 in healthy subjects

Location of Report: m5.3.3.1, LAI114433

Objectives: The primary objective was to investigate the safety, tolerability, and PK of CAB LA following single dose IM or SC administration in healthy subjects. An additional objective was to investigate CAB PK in cervicovaginal fluid, vaginal tissue, cervical tissue, and rectal tissue and relate it to CAB PK in plasma (see Section 2.3.1.4).

Study Design and Methods: LAI114433 was a Phase I, observer- and subject-blind, randomized, placebo-controlled, single-dose escalation study to determine the safety,

tolerability, and PK profile of IM and SC injections of CAB LA in healthy subjects. Within each of Cohorts 1 to 7, 8 subjects were randomized to CAB LA or placebo in a ratio of 3:1 (Table 41). In addition, 16 subjects, balanced for gender, were randomized to CAB 400 mg IM as a single 400 mg injection (Cohort 8) or divided into two 200 mg injections (Cohort 9). Serial plasma PK samples for CAB analysis were collected through ≥12 weeks following single dose administration on Day 1 (Table 42). Female subjects in Cohorts 8 and 9 had CV fluid, cervical tissue, and vaginal tissue samples collected at 2 visits, and male subjects in these cohorts had rectal tissue samples collected at 2 visits. Subjects were followed minimally through 12 weeks after drug administration, with follow-up extended until plasma CAB concentrations reached <0.10 μ/mL or until the subject completed Week 24 and any AEs had resolved or stabilized.

Table 41 CAB LA Single Ascending Dose Study Design

Cohort	Randomized (n)	CAB LA/ placebo (n/n)	Route	CAB LA Dose (mg)
1	8	6/2	IM	100
2	8	6/2	IM	200
3	8	6/2	IM	400
4	8	6/2	IM	800 (400 x 2)
5	8	6/2	SC	100
6	8	6/2	SC	200
7	8	6/2	SC	400 (200 x 2)
8	16 (Male/Female: 8/8)	8/0 (Male/Female: 4/4)	IM	400
9		8/0 (Male/Female: 4/4)	IM	400 (200 x 2)

Data Source: GSK Doc. # 2013N159605_00 Section 3.3 and Section 3.6
Cohorts 1 & 5: 4 subjects (3 active & 1 placebo) were initially dosed; the next 4 subjects (3 active & 1 placebo) were dosed 1 week later following review of safety and tolerability data from the first 4 subjects.
Dosing between cohorts was separated by ≥3 weeks to allow review of safety and PK data from previous cohorts.
Cohorts 1-3 & 5-7 (CAB LA Batch [redacted]): To maintain human study subject exposure of zirconium and yttrium below qualified dose levels, a minimum study subject body weight of 60 kg (vs. 45 kg for the overall protocol) was required for CAB LA doses >200mg (i.e. Cohorts 3 and 7)
Cohorts 4, 8, 9 (CAB LA Batch [redacted]): Drug product met all appropriate specifications such that a body weight cut-off was not required.

Table 42 CAB LA Single Ascending Dose PK Sampling Schedule

Time of Plasma PK Sample Relative to Single Dose on Day 1 All Cohorts																									
Hour	0	4	8	12	24	48	72	96	120	144	168	192	216	240	264	288	312	480	648	816	984	1320	1656	1992	
Day	1	1	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	21	28	35	42	56	70	84	
Week	1	1	1	1	1	1	1	1	1	1	2	2	2	2	2	2	2	3	4	5	6	8	10	12	Q4W
Time of Cervical and Vaginal (Female), and Rectal (Male) Tissue PK Sample Relative to Single Dose on Day 1																									
400 mg IM Cohort 8																		**400 mg (200 mg x 2) IM Cohort 9**							
Week 2								Week 8										Week 4				Week 12			

Data Source: GSK Doc. # 2013N159605_00 Table 1, Table 2, and Section 3.7.2

After Week 12, subjects continued plasma PK sampling Q4W until plasma CAB concentration was <0.10 μg/mL or the subject reached Week 24 and any AEs were resolved/stabilized.

At each visit, one cervicovaginal fluid, one cervical tissue, and two vaginal tissue samples were collected in female subjects, and two rectal tissue samples were collected in male subjects.

Results: Absorption of CAB from depot injection sites began within 4 h, the first sampling time, following LA administration as no lagtime was observed in any subject (Table 43). Plasma concentration-time profiles were consistent with LA administration, with low Cmax values, prolonged median tmax values ranging from 6 to 69 days, and measurable concentrations in 2/40 subjects receiving IM injections to ~1-year post-dose. In addition, the apparent terminal phase t1/2, which reflects the rate limiting step of absorption from the depot site rather than elimination from plasma, was prolonged, with geometric mean values ranging from 25 to 54 days. Split LA administered dosing – 400 mg (200 mg x 2) IM and SC as well as 800 mg (400 mg x 2) IM – achieved geometric mean C28d above 4*PA-IC90.

Table 43 Summary of Selected Plasma CAB PK Parameters Following Single-Dose CAB LA IM Administration [a]

PK parameter	Treatment				
	100mg Cohort 1	200mg Cohort 2	400mg Cohorts 3 & 8	400mg (200x2) Cohort 9	800mg (400x2) Cohort 4
n	6	6	14	8	6
AUC(0-28d) [a] (μg.h/mL)	118 (74.9)	136 (26.0)	290 (46.2)	644 (61.7)	1497 (79.2)
AUC(0-inf) [a] (μg.h/mL)	920 [b] (12.3)	1234 (34.6)	2652 [c] (29.8)	2687 (53.0)	5872 (12.6)
Cmax [a] (μg/mL)	0.2 (58.6)	0.3 (28.9)	0.7 (55.2)	1.4 (53.4)	3.3 (75.1)
tmax [d] (day)	9.00 (4.0-83.0)	44.50 (27.0-170.1)	69.00 (2.0-213.0)	13.00 (4.0-84.2)	7.58 (5.0-147.0)
C28d [a] (μg/mL	0.1 (82.7)	0.2 (37.0)	0.4 (54.6)	1.1 (49.3)	2.0 (76.9)
t1/2 [a] (day)	33.3 [e] (66.8)	53.9 (32.2)	38.3 [f] (57.3)	31.7 [g] (61.8)	25.4 (51.7)

Data Source: GSK Doc. # 2013N159605_00 Table 11.4
a. Geometric mean (CV%)
b. n=4
c. n=10
d. Median (range)
e. n=3
f. n=10
g. n=7

The results of the dose proportionality assessment using the Power model showed that plasma CAB exposures following a single IM injection increased less than dose proportional in the dose range of 100 mg to 400 mg. Plasma CAB exposures following split IM injections (400 mg and 800 mg IM) increased slightly more than dose proportional.

Conclusions:

- LA administration of CAB produced prolonged plasma concentrations in healthy subjects for up to ~1 year in 2/40 subjects receiving single IM injections.
- Variability in PK parameters was moderate to high, particularly in parameters associated with absorption (Cmax, AUC0-28d, t1/2).
- CAB apparent terminal half-lives following LA administration ranged from 25 to 54 days, reflecting rate limiting absorption rather than the terminal phase elimination t1/2 of ~40 h observed following oral administration.
- Results support investigation of doses of 400 mg IM to 800 mg IM for use in treatment studies.

2.3.1.4. Study LAI114433: PK of CAB in Cervicovaginal Fluid, Cervical Tissue, Vaginal Tissue, and Rectal Tissue

Study Title: An observer- and subject-blinded, randomized, placebo-controlled, single dose escalation study to investigate the safety, tolerability and pharmacokinetics of intramuscular and subcutaneous long acting GSK1265744 in healthy subjects

Location of Report: m5.3.3.1, LAI114433

Methods: Genital tract samples in females or rectal compartment samples in males were collected at 2 visits per subject following dosing: Cohort 8 at Week 2 and 8 following CAB LA 400 mg IM (unsplit dose administration) and Cohort 9 at Week 4 and 12 following CAB LA 400 mg IM (split dose administration). Each biopsy visit was completed within ±7 days of the scheduled (nominal) visit.

The objectives, study design, and methods are described in Section 2.3.1.3.

Results: Females provided CVT biopsies but attempts to obtain cervicovaginal fluid were not successful. CAB tissue concentrations were low (Table 44). Assuming a density of 1 g of tissue/mL of homogenate, median cervical and vaginal tissue concentrations were approximately equivalent to the in vitro PA-IC90 (0.166 μg/mL) at some visits.

Table 44 Summary of CAB Tissue Concentrations by Visit Following Single-Dose CAB LA IM Administration

Tissue Type	Tissue Concentration [a](μg/g) (n=4/visit)			
	400mg IM unsplit (Cohort 8)		400mg IM split (2x 200mg IM, Cohort 9)	
	Week 2	Week 8	Week 4	Week 12
Cervical	0.081 (NQ- 0.17)	0.096 (0.06 - 0.19)	0.177 (0.07- 0.50)	0.133 (NQ - 0.21) [c]
Vaginal [b]	0.121 (NQ - 0.18)	0.184 (0.09 - 0.44)	0.155 (NQ - 0.90)	0.181 (NQ - 0.35)
Rectal [b]	NQ (NQ - 0.10)	NQ (NQ - 0.05)	0.079 (NQ - 0.20)	0.063 (NQ - 0.08)

Data Source: GSK Doc. # 2013N159605_00 Table 11.9

a. Median (range)
b. n=8 samples
c. n=3 samples

Across visits, median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28. Median rectal tissue:plasma ratios were ≤0.08 (Table 45).

Table 45 Summary of CAB Tissue:Plasma Ratios by Tissue Type Following Single-Dose CAB LA IM Administration

Tissue Type	400mg IM unsplit (Cohort 8) [a]	400mg IM split (2x 200mg IM, Cohort 9) [a]
Cervical [b]	0.20 (0.0 - 0.40)	0.16 (0.0 - 0.4)
Vaginal [c]	0.28 (0.0 - 0.7)	0.19 (0.0 - 0.7)
Rectal [c]	0.00 (0.0 - 0.1)	0.08 (0.0 - 0.2)

Data Source: GSK Doc. # 2013N159605_00 Table 11.10

a. Median (range)
b. n=8 unsplit; n=7 split
c. n=24

Conclusions:

- Tissue concentrations were low with median tissue:plasma ratios ranging from 16 to 28% in cervicovaginal tissue and ≤8% in rectal tissue following CAB 400 mg IM. Median cervical and vaginal tissue concentrations were approximately equivalent to the in vitro PA-IC90 (0.166 μg/mL) at some visits; rectal tissue was below the in vitro PA-IC90.

2.4. Oral Cabotegravir + Oral Rilpivirine

Table 46 Listing of Studies of Oral CAB + Oral RPV

Study	Population	Regimens	Study Design	PK Section	PK/PD Section
200056 (LATTE-2)	HIV-infected subjects	Oral CAB + Oral RPV once daily	Phase IIb maintenance of virologic suppression following induction	2.4.1.1	-
LAI116482 (LATTE)	HIV-infected subjects	Oral CAB + Oral RPV once daily	Phase IIb maintenance of virologic suppression following induction	2.4.1.2	2.5.1

2.4.1. Pharmacokinetics in HIV-infected Subjects

2.4.1.1. Study 200056 (LATTE-2): Switching to CAB + RPV Q8W or Q4W After Induction of Virologic Suppression in Treatment Naïve Subjects (Phase IIb) (Induction Period)

Study Title: A Phase IIb study evaluating a long-acting intramuscular regimen of GSK1265744 plus TMC278 for the maintenance of virologic suppression following an induction of virologic suppression on an oral regimen of GSK1265744 plus abacavir/lamivudine in HIV-1-infected, antiretroviral therapy-naive adult subjects

Location of Report: m5.3.4.2, 200056 Week 32

Objectives, Study Design, and Methods: Refer to Section 2.1.2.4.

Results: All subjects received oral CAB 30 mg once daily + 2 NRTIs for 20 weeks with oral RPV 25 mg once daily added for the last 4 weeks prior to randomization at Day 1 to either an LA regimen or the oral comparator group. Prior to the final oral dosing on Day 1, CAB pre-dose plasma concentrations were determined. Geometric mean values were consistent with previous data for oral CAB (Table 47).

Table 47 Summary of Induction Period Steady State Plasma CAB Trough Concentrations (Day 1 Pre-dose) Following Oral Once Daily Administration in HIV-infected Subjects (PK Summary Population)

Regimen (Oral) (N=286)	Geometric Mean [95% CI] (CVb%) (n=246)
	Plasma CAB C0 (μg/mL)
CAB 30 mg once daily + RPV 25 mg once daily	4.22 [4.0, 4.4] (43)

Data Source: GSK Doc. # 2015N246053_00 Week 32 Table 10.1014

Conclusion:

- Geometric mean trough values were consistent with previous data for oral CAB in healthy and HIV-1 infected subjects.

2.4.1.2. Study LAI116482 (LATTE): Oral CAB Dose Ranging Study (10-60mg once daily)–Maintenance Period (+ RPV)

Study Title: A Phase IIb, dose ranging study of oral GSK1265744 in combination with nucleoside reverse transcriptase inhibitors for induction of HIV-1 virologic suppression followed by an evaluation of maintenance of virologic suppression when oral GSK1265744 is combined with oral rilpivirine in HIV-1-infected, antiretroviral therapy naive adult subjects

Location of Reports: m5.3.4.2, LAI116482 Week 24, Week 48, and Week 96

Objectives: The primary objective was to select a dose of CAB for further evaluation as part of a 2-drug combination ART regimen with RPV for 24 weeks, following a 24-week Induction Period of CAB with two NRTIs, in HIV-1-infected, antiretroviral naïve subjects. In the Induction Period, a secondary objective was to characterize the PK parameters of CAB and to explore exposure-response relationships (e.g., the relationship between CAB plasma exposure at Weeks 2 and 12 and virologic response or occurrence of AEs through Week 24) (Section 2.6.4.1). In the Maintenance Period, a secondary objective was to characterize the PK parameters of CAB and RPV and to explore exposure-response relationships (e.g., the relationship between CAB and RPV plasma exposure at Weeks 26 and 36 and virologic response or occurrence of AEs from Week 24 through Week 96). Individual Average C0 was calculated from multiple trough concentrations during the Induction Phase and Maintenance Phase to provide a single representative value for each individual for each phase prior to summarization.

Study Design and Methods: This Phase IIb study in HIV-1-infected, ART-naive adult subjects consisted of 2 parts, an Induction Period and a Maintenance Period.

The Induction Period consisted of a 24-week dose ranging evaluation of CAB at blinded oral doses of 10 mg, 30 mg, and 60 mg once-daily tablets and a contemporary control arm of open-label EFV 600 mg once daily. The background dual NRTI for all arms was either ABC/3TC or TDF/FTC FDC tablets, as chosen by the Investigator. CAB once daily blinded doses in combination with background NRTIs were evaluated on the basis of antiviral activity, safety, and PK over 24 weeks. Subjects randomized to a CAB containing arm, who successfully completed 24 weeks on study and demonstrated virologic suppression (defined as having a plasma HIV-1 RNA <50 c/mL before Week 24, with no signs of virologic rebound) were eligible for the Maintenance Period of this study.

During the Maintenance Period, subjects continued their oral CAB dose; however, the background NRTIs were discontinued and replaced with RPV 25 mg once daily for an additional 72 weeks. The Maintenance Period evaluated the ability of this 2-drug ART

regimen to maintain virologic suppression through Week 48, Week 72, and Week 96. Subjects randomized to the EFV arm continued their randomized regimen through Week 96.

Results:

Table 48 Summary of Maintenance Period Steady-State Plasma CAB Pre-dose Concentrations (Combined Week 26 and Week 36) Following Oral Once Daily Administration in HIV-infected Subjects (PK Summary Population)

PK/Statistical Parameter	Treatment Group		
	CAB 10 mg	CAB 30 mg	CAB 60 mg
CAB			
Individual Average C0 [a, b] (µg/mL)	1.34 [1.1, 1.6] (58)	3.93 [3.5, 4.4] (44)	8.22 [7.4, 9.1] (37)
GLS Mean Ratio [90 CI] (%CVw) Maintenance: Induction	0.992 [0.849, 1.16] (51.4)	0.938 [0.823, 1.07] [c]	1.04 [0.919, 1.17] [c]

Data Source: GSK Doc. # 2013N180642_00 Week 48 Table 9.4 and Table 9.9; GSK Doc. # 2014N216014_00 Week 96 Table 9.4, Table 9.5, and Table 9.9

a. Geometric mean [95% CI] (CVb%)
b. CAB: 10 mg, n=50; 30 mg, n=51; 60 mg, n=49
c. %CVw was not reported

Oral CAB (10 mg, 30 mg, and 60 mg) was administered with oral RPV 25 mg.

Conclusions:

- Geometric mean CAB Individual Average C0 was 8.1-, 24-, and 50-fold above the in vitro PA-IC90 following 10 mg, 30 mg, and 60 mg once daily, respectively, during the Maintenance Period when co-administered with RPV 25 mg once daily.
- CAB exposures during RPV co-administration confirm selection of the 30 mg CAB dose for future oral CAB short term use.

2.5. Pharmacokinetic-Pharmacodynamic Relationships in HIV-infected Subjects

2.5.1. Study LAI116482 (LATTE): Oral CAB Dose Ranging Study (10 to 60 mg once daily) –Maintenance Period (+ RPV)

Study Title: A Phase IIb, dose ranging study of oral GSK1265744 in combination with nucleoside reverse transcriptase inhibitors for induction of HIV-1 virologic suppression followed by an evaluation of maintenance of virologic suppression when oral GSK1265744 is combined with oral rilpivirine in HIV-1-infected, antiretroviral therapy naive adult subjects

Location of Reports: m5.3.4.2, LAI116482 Week 24 and Week 96

The objectives, study design, methods, and PK results for the Induction and Maintenance Periods are described in Section 2.4.1.2.

Maintenance Period PK in Virologic Failure Subjects

All 3 CAB doses showed rapid and sustained virologic response and no apparent dose-response relationship was observed. An overall response rate of 87% of subjects achieving the primary endpoint of plasma HIV-1 RNA <50 c/mL through Week 24 was observed in subjects receiving CAB + 2 NRTIs and sustained during CAB + RPV through Week 96 (overall response rate of 76% with CAB + RPV for 72 weeks).

Three subjects experienced virologic failure at the Week 48 primary endpoint of the Maintenance Period. One subject randomized to CAB 30 mg with RPV 25 mg once daily met PDVF criteria at Week 36 and had plasma CAB concentrations consistent with study averages. One subject randomized to CAB 10 mg with RPV 25 mg once daily met PDVF criteria at Week 48 and had plasma CAB concentrations below study averages. One subject randomized to CAB 10 mg with RPV 25 mg once daily had HIV-1 RNA >50 c/mL at Week 48 (Snapshot failure) but was lost to follow-up prior to confirmation of virologic failure; this subject had plasma CAB concentrations below study averages consistent with noncompliance.

Conclusion:

- No relationship was identified between CAB PK and virologic outcomes.

2.6. Oral Cabotegravir

Table 49 Listing of Studies of Oral CAB

Study	Population	Regimens	Study Design	PK Section	PK/PD Section
ITZ111451 Parts A and B	Healthy Subjects	Single dose oral CAB 5, 10, 25, and 50 mg and repeat dose 5, 10, and 25 mg once daily	Phase I single and repeat-dose escalation PK	2.6.1.1	-
LAI117008	Healthy Subjects	Oral [^{14}C]-CAB 30 mg single dose Oral CAB 150 mg single dose	Single dose mass balance PK and single supratherapeutic dose PK	2.6.1.2	-
LAI115428	Healthy Subjects	Oral CAB 30 mg once daily x 14 days	Repeat dose	2.6.1.3	
LAI117009	Healthy Subjects	Oral CAB 150 mg q12h x 3 doses	Repeat dose (supratherapeutic dose) Thorough QTc study	-	2.6.2.1
LAI116482 (LATTE)	HIV-infected Subjects	Oral CAB 10, 30, 60 mg once daily with 2 NRTIs	Phase IIb dose ranging Induction with 2 NRTIs	2.6.3.1	2.6.4.1
ITZ112929	HIV-infected Subjects	Oral CAB 5 mg once daily	Phase IIa monotherapy PK	2.6.3.2	2.6.4.2
ITZ111451 Part C	HIV-infected Subjects	Oral CAB 30 mg once daily	Phase IIa monotherapy PK	2.6.3.3	2.6.4.2
201479	Moderate Hepatic Impaired Subjects Healthy Subjects	Oral CAB 30 mg single dose	Phase I HI PK	2.6.5.1	-
201480	Severely Impaired Renal Function Subjects Healthy Subjects	Oral CAB 30 mg single dose	Phase I renal impairment PK	2.6.5.2	-
LAI116181	Healthy Subjects	Oral CAB 30 mg + Oral RPV 25 mg repeat dose	Phase I RPV DDI PK	2.6.6.1	-
205712	Healthy Subjects	Oral CAB 30 mg + Oral RBT 300 mg repeat dose	Phase I RBT DDI PK	2.6.6.2	-
LAI117010	Healthy Subjects	Oral CAB 30 mg + Oral RIF 600 mg repeat dose	Phase I RIF DDI PK	2.6.6.3	-
LAI117011	Healthy Female Subjects	Oral CAB 30 mg + Oral LNG 0.15 mg and EE 0.03 mg repeat dose	Phase I oral contraceptives DDI PK	2.6.6.4	-
LAI116815	Healthy Subjects	Oral CAB 30 mg repeat dose + Oral MDZ 3 mg single dose	Cytochrome P450 3A (CYP3A) enzymes study	2.6.6.5	-
ITZ111839	Healthy	Oral CAB 30 mg + Oral	Phase I ETV DDI PK	2.6.6.6	-

Study	Population	Regimens	Study Design	PK Section	PK/PD Section
	Subjects	ETV 200 mg BID repeat dose			
205162	Healthy Subjects (Phase I) HIV-infected Subjects (Phase II)	Oral CAB 30 mg once daily repeat dose	PGx meta-analysis in 4 Phase I and 4 Phase II studies	-	2.6.7.1

2.6.1. Pharmacokinetics in Healthy Subjects

2.6.1.1. Study ITZ111451: Single Dose, Suspension, 5 to 50 mg and Repeat-Dose, Suspension, 5 to 25 mg

Study Title: A double-blind, parallel, randomized, placebo-controlled, single and repeat dose escalation first time in human study to investigate the safety, tolerability and pharmacokinetics of GSK1265744 in healthy male and female subjects and subjects infected with HIV

Location of Report: m5.3.3.1, ITZ111451

Objectives: The primary objectives were to investigate the safety, tolerability, and PK of CAB following single and repeat oral administration in healthy subjects and to investigate the safety, tolerability, PK, antiviral activity of CAB during 10-day monotherapy in HIV-infected adults at the highest tolerated exposure in healthy subjects.

Study Design and Methods: This was a 3-part Phase I, double-blind, randomized, placebo-controlled, single and repeat-dose escalation study of CAB in healthy subjects and a single repeat dose cohort in HIV-1-infected subjects. Two cohorts of 9 subjects (7 active, 2 placebo) received single suspension doses of 5, 10, 25, and 50 mg in an alternating panel design (Part A). Three cohorts of 10 subjects (8 active, 2 placebo) received repeat suspension doses of 5, 10, and 25 mg once daily for 14 days (Part B). One cohort of 8 HIV-infected subjects (6 active, 2 placebo) received repeat tablet doses of 30 mg (6 x 5 mg) once daily for 10 days (Part C). Results for Parts A and B are presented. Part C is discussed in Section 2.6.3.3. Study treatments are described in Table 50.

Table 50 Study Treatments

Drug	Dose/Form/Route	Frequency/Duration
CAB	5, 10, 25, 50 mg/ suspension/ oral 5, 10, 25 mg/ suspension/oral	Single Dose Repeat Doses, once daily, for 14 days
CAB	6 x 5 mg / tablet / oral	Repeat Doses, once daily, for 10 days
Placebo	6 x 5 mg / tablet / oral	Repeat Doses, once daily, for 10 days

Results:

Part A:

CAB was readily absorbed following single-dose administration with no lag time for all treatment regimens (Table 51). Median CAB tmax was 0.5 to 1.5 h across doses. Extrapolation of CAB AUC from Clast to infinity (%AUCex) was >20% for more than 20% of the single dose profiles, indicating that the lambda z and related parameters were not well estimated; therefore, AUC(0-inf) and t1/2 values were not reported. Inter-subject variability was low to moderate following single-dose administration of CAB with %CVb ranging from 13% to 53%. CAB PK parameters increased slightly less than proportionally to dose following single-dose administration of 5 mg to 50 mg using a power model approach.

Table 51 Summary of Selected Plasma CAB PK Parameters Following Single-dose Administration (Part A, Suspension)

Treatment	Geometric mean [95%CI] (CVb%)			
	AUC(0-t) [a] (μg.h/mL)	Cmax (μg/mL)	C24 (μg/mL)	tmax [b] (h)
5 mg (n=7)	26.6 [23.4, 30.1] (14)	1.15 [0.99, 1.33] (16)	0.42 [0.37, 0.48] (13)	0.50 (0.50 – 1.00)
10 mg (n=7)	51.7 [42.4, 63.0] (22)	2.15 [1.84, 2.51] (17)	0.83 [0.68, 1.02] (22)	1.00 (0.50 – 1.50)
25 mg (n=7)	117 [104, 132] (13)	4.38 [3.54, 5.41] (23)	1.93 [1.67, 2.23] (16)	1.50 (0.50 – 3.00)
50 mg (n=7)	231 [170, 313] (34)	8.57 [6.89, 10.7] (24)	3.82 [2.81, 5.18] (34)	1.50 (0.50 – 3.00)

Data Source: GSK Doc. # RM2008/00633/00 Table 11.4
a. AUC(0-t) = AUC(0-72h)
b. Median (range)

Part B:

Since only 24 h sampling was performed on Day 1, AUC(0-inf) and terminal half-life could not be estimated directly from the data. Inter-subject variability was low with %CVb ranging from 9% to 14% on Day 1 and from 15% to 23% on Day 14. Day 14 geometric mean C24 values were 6.4-, 14-, and 33-fold above the target PA-IC90 of 0.166 μg/mL.

Following single-dose administration in Part B, Day 1 AUC(0-tau) and C24 increased proportionally to dose and Cmax increased less than proportionally to dose over the range of 5 to 25 mg (Table 52). Following repeat-dose administration in Part B, Day 14

AUC(0-tau), Cmax, Ctau, and Cmin increased proportionally to dose using the power model.

Following 14-day repeat-dose administration of CAB in healthy subjects, the mean accumulation ratios for AUC(0-tau) were 2.38 to 2.52 across dose levels. Since Day 1 AUC(0-inf) could not be estimated, time invariance was not evaluated. Assuming time invariant PK, however, the effective half-life was estimated to be 30.5 to 33 h based on mathematical derivation from the accumulation ratio.

CAB steady state was reached by Day 12 for all doses in Part B (see Data Source: GSK Doc. # RM2008/00633/00).

Table 52 Summary of Selected Plasma CAB PK Parameters Following Single- and Repeat-dose Administration for 14 Days (Part B, Suspension)

Treatment Day	Treatment	AUC(0-24) [a] (µg.h/mL)	Cmax [a] (µg/mL)	C24 or Ctau [a] (µg/mL)	tmax [b] (h)	Accumulation Ratio (AUC) [a,c]
Day 1	5mg (n=8)	13.7 [12.7, 14.7] (9)	1.17 [1.04, 1.31] (14)	0.41 [0.38, 0.44] (9)	0.75 (0.50-1.00)	-----
	10mg (n=8)	27.5 [24.7, 30.6] (13)	2.30 [2.07, 2.56] (13)	0.84 [0.75, 0.94] (14)	0.75 (0.50-1.50)	-----
	25mg (n=8)	63.6 [58.5, 69.2] (10)	4.73 [4.31, 5.19] (11)	2.02 [1.87, 2.18] (9)	1.00 (0.50-2.00)	-----
Day 14	5mg (n=8)	32.5 [28.6, 37.0] (16)	2.08 [1.78, 2.42] (19)	1.06 [0.90, 1.25] (20)	0.63 (0.25-1.50)	2.38 [2.21, 2.57] (9)
	10mg (n=8)	69.2 [59.6, 80.3] (18)	4.29 [3.80, 4.84] (15)	2.39 [1.98, 2.88] (23)	0.88 (0.50-1.50)	2.52 [2.28, 2.78] (12)
	25mg (n=8)	160 [136, 188] (20)	9.47 [8.12, 11.1] (19)	5.40 [4.51, 6.47] (22)	1.25 (0.50-4.00)	2.51 [2.17, 2.92] (18)

Data Source: GSK Doc. # RM2008/00633/00 Table 11.10 and Table 11.12

a. Geometric mean [95%CI] (CVb%)
b. Median (range)
c. Accumulation ratio = Day 14 AUC(0-24)/Day 1 AUC(0-24)

Conclusions:

- CAB PK exposure increased less than proportionally to dose following single-dose oral (5 to 50 mg) administration in Part A and increased proportionally to dose following repeat-dose (5 to 25 mg) administration in Part B.
- After repeat-dose administration, plasma concentrations of CAB reached steady state after 12 days of dosing of oral solution in healthy subjects.
- The accumulation ratio for AUC ranged from 2.38 to 2.52 across dose levels and populations, and effective half-life was estimated to be 30.5 to 33 h.

- Following repeat-dose administration of the oral solution formulation in healthy subjects in Part B, Day 14 geometric mean Ctau values were 6.4-, 14-, and 33-fold above the in vitro PA-IC90 (0.166 μg/mL) for the 5 mg, 10 mg, and 25 mg once daily doses, respectively, supporting evaluation of once daily doses in HIV-infected subjects.

2.6.1.2. Study LAI117008: Single Dose Mass Balance

Study Title: An open label, non-randomized, mass balance study to investigate the recovery, excretion, and pharmacokinetics of ^{14}C-GSK1265744 administered as a single oral dose and a placebo-controlled, randomized study to describe the pharmacokinetics of a supratherapeutic dose of GSK1265744 in healthy adult subjects

Location of Report: m5.3.3.1, LAI117008

Objectives: The primary objectives in Part A (single, oral solution dose of [^{14}C]-CAB) were to 1) describe CAB and metabolite PK in plasma and total radioactivity PK in blood and plasma, 2) determine the total recovery and relative excretion of total radioactivity in urine and feces, and 3) determine the metabolic profile of CAB by quantifying CAB and metabolites in urine, feces, and bile. One of the primary objectives in Part B was to evaluate the plasma CAB PK following administration of a single supratherapeutic dose of CAB 150 mg. This evaluation was conducted to inform selection of a supratherapeutic dose for a TQT study (Study LAI117009).

Study Design and Methods: This was a 2-part study in healthy adults.

Part A was a Phase I, non-randomized, open-label, single-dose, single-center mass balance study in healthy adult male subjects. Subjects in Part A (n=6) received a target CAB dose of 30 mg (actual mean dose of 26.7 mg) as an oral solution containing [^{14}C]-CAB of approximately 70 μCi (0.96 MBq) of radioactivity under fasted conditions. Blood, urine, and fecal samples were collected for a minimum of 336 h (14 days) to a maximum of 504 h (21 days) following study drug administration. The Entero-Test capsule was swallowed 2 h post-dose; at 5 h post-dose gall bladder emptying was stimulated using food cues and the string was retrieved 1 h later (at 6 h post-dose).

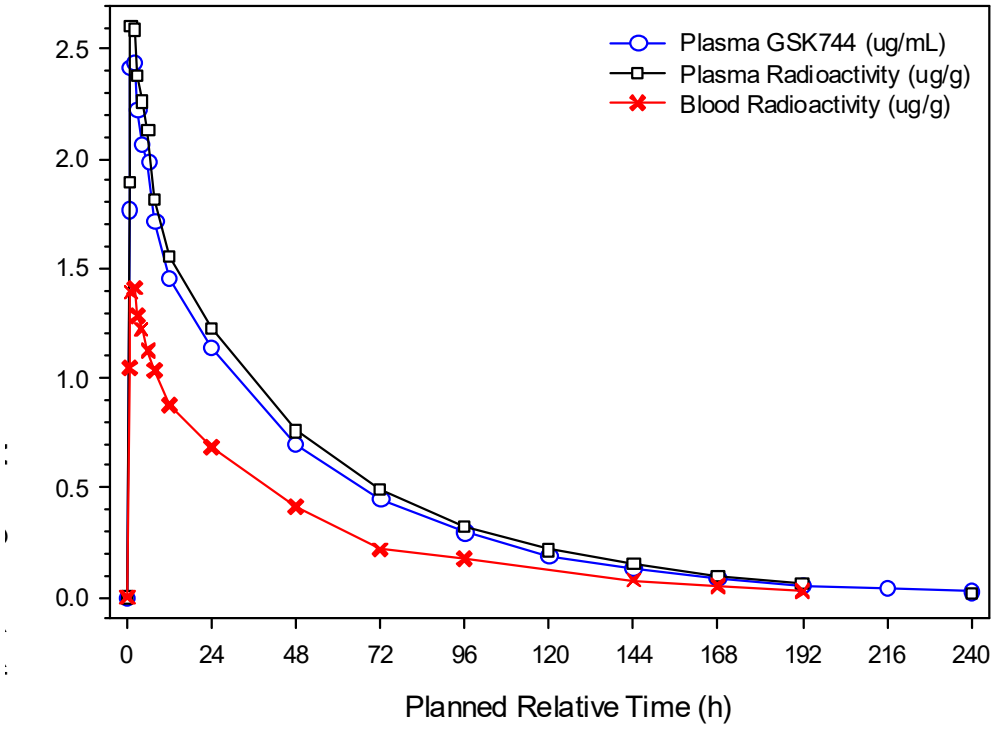
In Part B, subjects received a single supratherapeutic dose of CAB 150 mg (5 x 30mg tablets) (n=8) or placebo (n=2). Subjects enrolled in Part B were not the same subjects enrolled in Part A of the study. Serial plasma PK samples for analysis of CAB were collected for a minimum of 336 hours (14 days) after dosing.

Results:

Plasma and Whole Blood PK

CAB was the predominant circulating compound in plasma, representing 80.5 to 100% of plasma total radiocarbon in pooled plasma samples collected 2 to 24 h post-dose (Table 53, Figure 16, Data Source: GSK Doc. # 2013N167401_01) and the majority of the plasma radiocarbon AUC(0-inf) (Table 54); no metabolites were quantified in pooled plasma samples.

Figure 16 Mean Concentration-Time Profiles for Plasma CAB, Plasma Radioactivity, and Blood Radioactivity



Data Source: GSK Doc. # 2013N167401_01 Figure 1

Table 53 CAB and Metabolite Profiling in Pooled Plasma and Percent (%) of Plasma Radiocarbon that Each Represented Following Single Dose Administration of [^{14}C]-CAB 30 mg Oral Solution

Metabolite ID	% Radioactivity in Human Plasma (Concentration [nmol/g])				
	2 h	6 h	12 h	24 h	168 h
CAB	80.5 (5.2)	100 (5.4)	95.6 (3.7)	94.3 (2.9)	<LLQ (<LLQ)
Total Quantified	80.5 (5.2)	100 (5.4)	95.6 (3.7)	94.3 (2.9)	<LLQ (<LLQ)

Data Source: GSK Doc. # 2013N167401_01 Table 2
Overall recovery of radioactivity in plasma was 91.6% (at 168 h) to 100% (at all other time points) [recoveries of >100% were set to 100% for calculation purposes]
Equal volumes of plasma samples from each subject were pooled at each time point.

Mean blood:plasma total radiocarbon ratios ranged from 0.437 to 0.571 between 2 and 216 hours post-dose [Data Source: GSK Doc. # 2013N179556_00, Table 3.2]. Blood total radiocarbon was approximately 52% of plasma radiocarbon AUC(0-inf) (Table 54, Figure 16). The low radiocarbon concentrations in blood (versus plasma) suggest minimal association of CAB with red blood cells.

Table 54 Summary of Plasma CAB PK Parameters and Radioactivity PK Parameters in Blood and Plasma Following Single Dose Administration of [^{14}C]-CAB 30 mg Oral Solution

PK Parameter	Plasma CAB [a]	Plasma Radioactivity [a]	Blood Radioactivity [a]
Cmax [b] (μg/mL or μg eq/g)	2.48 (21)	2.65 (21)	1.43 (21)
AUC(0-inf) [b] (μg.h/mL or μg eq/g)	96.5 (25)	107 (24)	56.1 (26)
t1/2 [b] (h)	38.8 (10)	41.2 (16)	39.4 (14)
tmax [c] (h)	2.00 (0.98-3.00)	1.52 (0.98-2.00)	1.52 (0.98-4.00)

Data Source: GSK Doc. # 2013N179556_00 Table 3.3 Part A, Table 3.4 Part A, Table 3.5 Part A
a. N = 6
b. Geometric mean (CV%)
c. Median (range)

Recovery in Urine and Feces, and Bile

The overall mean recovery of radioactivity in urine and feces samples was 85.3%. On average, fecal excretion accounted for 58.5% and urinary excretion accounted for 26.8% of the administered dose (Table 55).

Table 55 Summary of Percent Radioactivity Recovered in Feces and Urine Following a Single Oral Dose Administration of [^{14}C]-CAB-Part A

	Percent of Administered Dose Recovered [a]		
	Feces	Urine	Total
Mean	58.5	26.8	85.3
SD	9.8	8.4	7.9

Data Source: GSK Doc. # 2013N179556_00 Table 8
a. N = 6

CAB accounted for 46.8% of the administered dose in feces and was not detected in urine (Table 56). Based on metabolic profiling in urine, feces, and bile, glucuronidation leading to formation of GSK3388352 (M1) is the primary metabolic pathway, accounting for 20% of the administered dose (Table 56) [Data Source: GSK Doc. # 2013N167401_01]. Glucose conjugation leading to formation of M2 is a minor pathway for CAB metabolism; M2 was detected, but not quantifiable, in urine.

Table 56 CAB and Metabolite Profiling in Urine and Feces and Percent (%) of Radiocarbon that Each Represented Following Single Dose Administration of [^{14}C]-CAB 30 mg Oral Solution

Metabolite ID	Mean % Radioactivity (% of Administered Dose)	
	Urine	Feces
CAB	-	83.4 (46.8)
M1 (GSK3388352)	75.0 (20.0)	-
M2	<LLQ (<LLQ)	-
Total Quantified	75.0 (20.0)	83.4 (46.8)

Data Source: GSK Doc. # 2013N167401_01 Table 3 and Table 4.

For each subject, feces and urine were pooled proportionally by sample weight to obtain pools containing >90% of the radioactivity excreted via that route. Mean recovery of radioactivity was 94% in urine and 95.3% in feces.

Unchanged CAB was confirmed in all duodenal bile samples collected using the Entero-Test. The glucuronic acid metabolite GSK3388352 (M1) was also confirmed in some, but not all, duodenal bile samples [Data Source: GSK Doc. # 2013N167401_01, Section 6.4].

Supratherapeutic Dose

Table 57 Summary of Plasma CAB PK Parameters Following CAB 150 mg (5 x 30mg tablet) Single Dose Administration

Treatment	n	Cmax [a] (μg/mL)	AUC(0-inf) [a] (μg.h/mL)	t1/2 [a] (hr)	tmax [b] (hr)
CAB 150 mg	8	10.4 (26)	418 (32)	38.1 (16)	2.50 (1.00-4.03)

Data Source GSK Doc. # 2013N167401_01 Table 3.2 Part B
a. Geometric mean (CV%)
b. Median (range)

Conclusions:

- CAB was the predominant circulating compound in plasma.
- Low radiocarbon concentrations in blood (versus plasma) suggest minimal association of CAB with red blood cells.
- The overall mean recovery of radioactivity in excreta was 85.3%; 58.5% of the dose was recovered in feces and 26.8% was recovered in urine.
- CAB accounted for 46.8% of the administered dose in feces and was not detected in urine.
- Glucuronidation is the primary metabolic pathway for CAB.
- CAB and the glucuronide metabolite GSK3388352 (M1) were detected in duodenal bile samples.
- Single dose CAB 150 mg did not achieve maximum concentrations significantly higher than the steady-state Cmax observed following administration of the clinical dose of 30 mg once daily, suggesting that a repeat-dose strategy would be required to achieve supratherapeutic doses for evaluation of effect of CAB on QTc.

2.6.1.3. Study LAI115428 – Repeat Dose, Tablet, 30 mg (OLI)

Study Title: A randomized, open label study to investigate the safety, tolerability and pharmacokinetics of repeat dose administration of long acting GSK1265744 and long-acting TMC278 intramuscular and subcutaneous injections in healthy adult subjects

Location of Report: m5.3.3.1, LAI115428

Objectives, Study Design, and Methods: See Section 2.1.1.1.

Results:

Table 58 Summary of Steady-State PK Parameters Following Repeat Oral Administration of CAB Tablets for 14 Days to Healthy Subjects (LAI115428)

Treatment [a]	Plasma CAB PK Parameter [b]			
	AUC(0-tau) (μg.h/mL)	Cmax (μg/mL)	Ctau (μg/mL)	tmax [c] (h)
CAB 30 mg tablets once daily for 14 days	147 [135, 159] (27)	8.30 [7.67, 8.99] (26)	4.87 [4.46, 5.33] (30)	2.0 (1.0-8.0)

Data Source: GSK Doc. # 2013N159813_01 Table 3.4
a. N = 43
b. Geometric mean [95% CI] (CVb%)
c. Median (range)

Conclusion:

- Steady-state CAB PK parameters following CAB 30 mg once daily in this study were similar to those observed in other studies of healthy and HIV infected subjects.

2.6.2. Pharmacodynamics in Healthy Subjects

2.6.2.1. Study LAI117009: Thorough QTc Study

Study Title: A study to evaluate the effect of GSK1265744 150 mg administered orally every 12h x 3 doses on cardiac conduction as assessed by 12-lead electrocardiogram compared to placebo and a single oral dose of moxifloxacin

Location of Report: m5.3.4.1, LAI117009

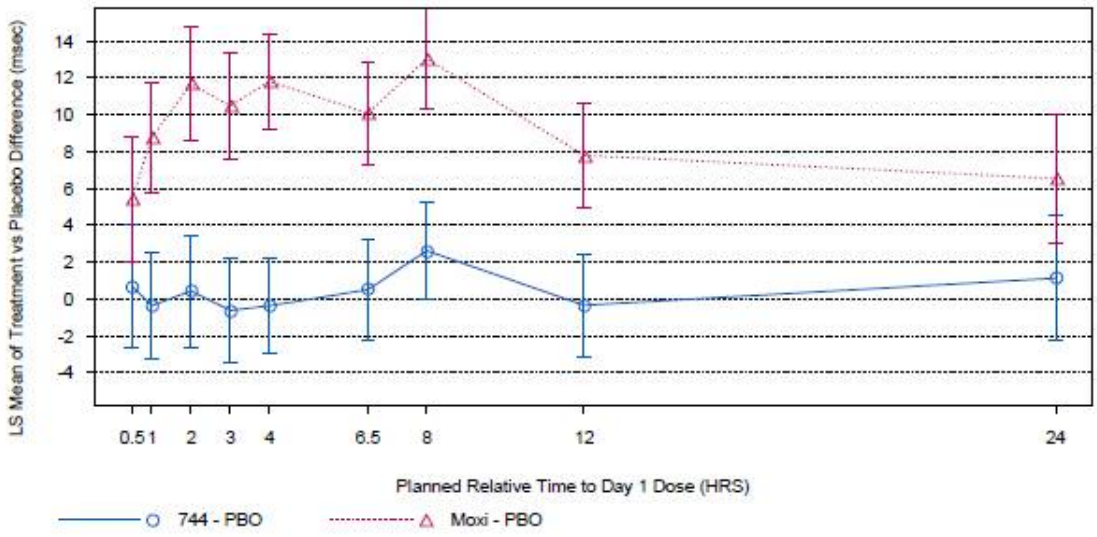
Objective: The primary objective was to demonstrate a lack of effect of repeat oral doses of CAB (150 mg) (supratherapeutic dose) as determined by the Baseline-adjusted, maximum time-matched QTcF effect when compared with placebo (ddQTcF).

Study Design and Methods: This was a randomized partial-blind, repeat dose, 3-period, balanced crossover study. Subjects (n=42) were randomized to receive CAB 150 mg (5 x 30 mg tablets) q12 h x 3 doses, CAB placebo (5 tablets) q12 h x 3 doses, or a single dose of moxifloxacin 400 mg (1 x 400 mg tablet) (positive control). Subjects received each of the three treatments in a randomized fashion, with a washout period of at least 21 days between doses. Subjects and the investigator were blinded only for CAB/placebo treatments, and moxifloxacin was administered open-label.

Results: CAB had no significant effect on cardiac repolarization. For the primary endpoint, QTcF, all time-matched values, and their corresponding upper bounds of the 90% CI were below 10 msec for CAB (Figure 17). The maximum observed time-matched change from Baseline in QTcF for CAB 150 mg was at 8 h (2.62 msec, 90% CI:

-0.02, 5.26 msec). The maximum observed time-matched change from Baseline in QTcF for moxifloxacin was at 8 h (13.03 msec, 90% CI: 10.32, 15.74 msec).

Figure 17 Plot of Least Squares Mean of Treatment Difference (CAB or Moxifloxacin) from Placebo for QTcF Change from Baseline (90% CIs) Following Oral CAB or Placebo Q12h (PD Population)



Data Source: GSK Doc. # 2014N208600_00 Figure 2.1
Note: Three subjects were excluded from analysis due to missing time points
Treatments:
CAB = 3 doses of CAB 150mg (5 x 30 mg tablets) q12 h.
PBO = 3 doses of CAB placebo (5 tablets) q12 h.
Moxifloxacin = A single dose of moxifloxacin 400 mg (1 x 400 mg tablet).

A geometric mean Cmax of 22.5 µg/mL following CAB 150 mg q12 h x 3 doses is 3-fold above the Cmax,ss of 7.5 µg/mL observed following a therapeutic dose of 30 mg once daily in LAI116482, demonstrating that supratherapeutic CAB concentrations were achieved (Table 59). All subjects exceeded the therapeutic Cmax by ≥2-fold, and no individual subject exceeded the NOAEL in monkeys (AUC 901 µg.h/mL, Cmax 58.1 µg/mL). Exposures were similar in males and females receiving the supratherapeutic regimen. Overall variability was low with CV% ranging from 15 to 22% across PK parameters.

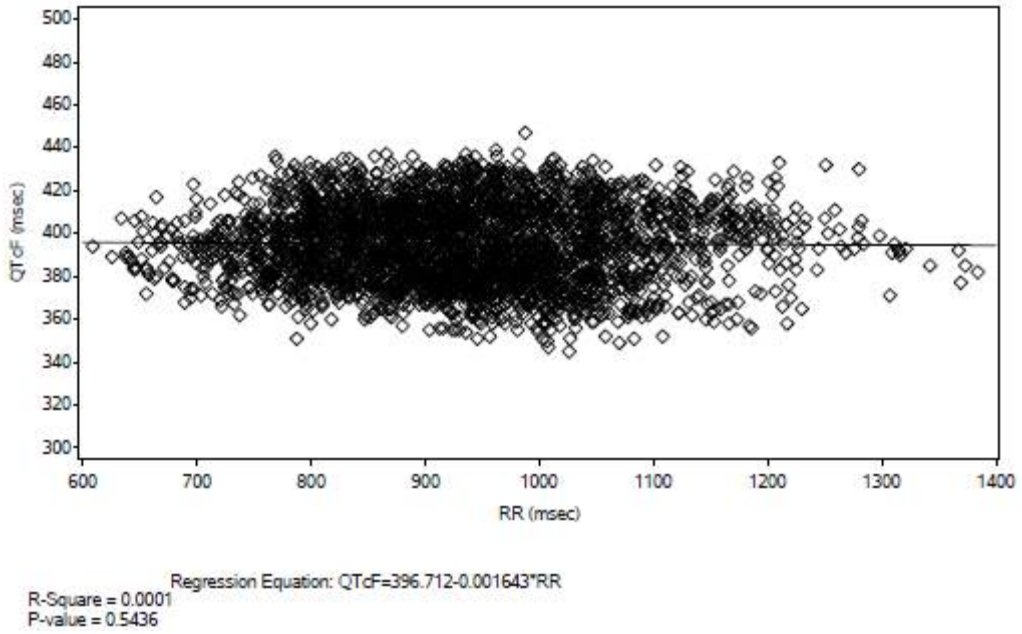
AUC(0-inf), CL/F, Vz/F, t1/2, and λz were not estimated due to limitations of the study design.

Table 59 Summary of Plasma CAB PK Parameters Following Oral CAB Q12h (PK Summary Population)

Treatment	Sex	n	Cmax [a] (µg/mL)	AUC(0-12h) [a] (µg.h/mL)	AUC(0-24h) [a] (µg.h/mL)	tmax [b] (h)
CAB [c] 150 mg	Female	9	25.1 [21.2, 29.6] (22)	234 [198, 277] (22)	409 [345, 484] (22)	2.0 (1.0 – 4.0)
	Male	31	21.9 [20.4, 23.4] (19)	213 [202, 225] (15)	380 [359, 402] (15)	2.0 (1.0 – 4.0)
	Overall	40	22.5 [21.1, 24.0] (20)	217 [206, 229] (17)	386 [366, 408] (17)	2.0 (1.0 – 4.0)

Data Source: GSK Doc. # 2014N208600_00 Table 3.2
a. Geometric mean [90%CI] (CVb%)
b. Median (range)
c. Three doses of CAB 150 mg (5 x 30 mg tablets) q12 h

Figure 18 Plot of Individual Subject Pre-dose QTcF vs. Pre-dose RR (PD Population)



Data Source: GSK Doc. # 2014N208600_00 Figure 2.3

Relationship between PK and PD parameters

As 95% CI of parameter estimates contain zero, it can be concluded that there is no relationship between CAB plasma concentration and ddQTcF [Data Source: GSK Doc. # 2014N208600_00 Table 4.1].

Based on the PK/PD model, ddQTcF at the highest predicted clinically relevant Cmax was predicted. The mean Cmax at 150 mg once daily was 23.01 μg/mL, and geometric mean Cmax is 22.5 μg/mL which achieved supratherapeutic CAB concentrations. The results of the predicted mean and 90% CI of ddQTcF given at mean Cmax of 23.01 μg/mL for 150 mg of CAB suggest that CAB will not have an effect on ddQTcF at the expected highest Cmax in a clinical setting [Data Source: GSK Doc. # 2014N208600_00 Table 4.2].

Conclusions:

- CAB had no effect on cardiac repolarization at a supratherapeutic dose of 150 mg q 12 h x 3 doses.
- The geometric mean CAB Cmax achieved in this study was approximately 3-fold higher than that of the standard clinical dose of 30 mg once daily at steady-state and approximately 6-fold higher than that of the Q4W regimen at steady-state.
- The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QTcF confirming the validity of the results.

2.6.3. Pharmacokinetics in HIV-1-infected Subjects

2.6.3.1. Study LAI116482: Oral CAB Dose Ranging Study (10 to 60mg once daily) – Induction Period (+ 2 NRTIs)

Study Title: A Phase IIb, dose ranging study of oral GSK1265744 in combination with nucleoside reverse transcriptase inhibitors for induction of HIV-1 virologic suppression followed by an evaluation of maintenance of virologic suppression when oral GSK1265744 is combined with oral rilpivirine in HIV-1-infected, antiretroviral therapy naive adult subjects

Location of Report: m5.3.4.2, LAI116482 Week 24 and Week 96

Objectives, Study Design, and Methods: Refer to Section 2.4.1.2.

Results:

Table 60 Summary of Induction Period Steady State Plasma CAB PK Parameters at Week 2 and Week 12 Following Oral Once Daily Administration with 2 NRTIs in HIV-infected Subjects [a] (PK Summary Population)

Plasma CAB Parameter	CAB 10 mg n=14	CAB 30 mg n=12	CAB 60 mg n=9
AUC(0-τ) [a] (µg•h/mL)	45.69 [38.2, 54.6] (32)	134 [110, 163] (32)	227.58 [159.4, 325.0] (57)
Cmax [a] (µg/mL)	2.77 [2.3, 3.3] (33)	7.49 [6.3, 8.9] (28)	13.12 [9.9, 17.5] (44)
Individual Average C0 [a,b] (µg/mL)	1.35 [1.2, 1.5] (45)	4.20 [3.8, 4.7] (40)	7.93 [7.2, 8.8] (39)
tmax [c] (h)	1.0 (0.9 – 8.0)	2.0 (1.0 – 8.0)	2.0 (1.0 – 8.0)
CL/F [a] (L/h)	0.22 [0.2, 0.3] (32)	0.22 [0.2, 0.3] (32)	0.26 [0.2, 0.4] (57)

Data Source: GSK Doc. # 2014N216014_00 Week 96 Table 9.4
a. Geometric mean [95% CI] (CVb%)
b. Individual Average C0: n=57, 10 mg; n=53, 30 mg; n=55, 60 mg
c. tmax shown as median (range)

Exposure increased proportionally to dose from 10 mg to 30 mg and slightly less than proportional to dose from 30 mg to 60 mg.

Conclusions:

- CAB Individual Average C0 was 8.1-, 25-, and 48-fold above the in vitro PA-IC90 following 10 mg, 30 mg, and 60 mg once daily, respectively, during the Induction Period.
- CAB PK parameters estimated during the Induction Period increased in proportion to slightly less than proportional to dose from 10 mg to 60 mg (Table 105).
- Variability in PK parameters following CAB 30 mg once daily in the Induction Period was moderate (28 to 40%) (Table 104).

2.6.3.2. Study ITZ112929: 10-day Monotherapy, CAB 5 mg Once Daily

Study Title: A Phase IIa study to compare antiviral effect, safety, tolerability and pharmacokinetics of GSK1265744 monotherapy versus placebo in HIV-1-infected adults (ITZ112929)

Location of Report: m5.3.3.2, ITZ112929

Objectives: The primary objectives were; 1) to evaluate the antiviral activity of CAB vs. placebo in ART-naïve and experienced (IN naïve) HIV-1-infected patients during 10 days of monotherapy; 2) characterize the PK of CAB in HIV-1-infected patients; 3) assess the safety and tolerability of CAB vs. placebo; and 4) explore the relationship between CAB exposure and change in plasma HIV-1 RNA (see Section 2.6.4.2).

Study Design and Methods: This was a Phase IIa, double-blind, randomized, placebo-controlled study. Utilizing a blinded adaptive design, a cohort of 8 subjects (6 active, 2 placebo) were randomized to receive 10 days of CAB monotherapy or placebo at the planned tablet dose of 5 mg followed by at least 14 days of investigator chosen optimized therapy. The protocol allowed for evaluation of other dose levels of CAB monotherapy as supported by the results of the 5 mg once daily regimen.

The dose-ranging studies completed with CAB 5-mg (see Section 2.6.1.1) and 30-mg (see Section 2.6.3.3) (Study ITZ111451) doses provided sufficient data to progress into longer-term clinical studies. Therefore, no additional doses were studied, and the study was stopped after Cohort 1.

Results:

Table 61 Summary of Selected Plasma CAB PK Parameters Following Single and Repeat Dose Administration for 10 Days of CAB 5 mg to HIV-infected Subjects

Treatment	AUC(0-24) [a] (μg.h/mL)	AUC(0-tau) [a] (μg.h/mL)	Cmax [a] (μg/mL)	C24 or Ctau [a] (μg/mL)	tmax [b] (h)	Accumulation Ratio [a] RAUC
Day 1 (n=7)	7.53 (23)	-	0.52 (20)	0.23 (28)	2.00 (1.00-4.00)	-
Day 10 (n=7)	-	17.7 (31)	1.02 (25)	0.57 (33)	2.00 (1.50-4.08)	2.35 (17)

Data Source: GSK Doc. # RM2009/00485/00 Table 11.3 and Table 11.5
a. Geometric mean (CVb%)
b. Median (range)
Accumulation ratio RAUC = AUCtau on Day 10/AUC24 on Day 1.
CAB 5 mg = CAB 5 mg once daily x10 days.

Dose proportionality was observed between CAB 30 mg in HIV patients (ITZ111451 Part C HIV cohort) and CAB 5 mg from this study.

Following 10-day repeat-dose administration of CAB, the mean accumulation ratio for AUC(0-tau) was 2.36. Since Day 1 AUC(0-inf) could not be estimated, time invariance was not evaluated.

Table 62 Summary of HIV-1 RNA Change from Baseline to Day 11

	GSK1265744 5 mg (n=7)	Placebo (n=2)
Mean change from Baseline (SD) (Log10 c/mL)	-2.169 (0.2405)	-0.092 (0.1499)
Adjusted mean difference: active vs. placebo	-2.090	NA
95% CI for adjusted mean difference	-2.547, -1.632	NA
p-value for adjusted mean difference	<0.001	NA

Data Source: GSK Doc. # RM2009/00485/00 Table 13.1
CAB 5 mg = CAB 5 mg once daily x10 days.

Conclusions:

- CAB exhibited proportionality in plasma exposures following both single- and repeat-dose administration in HIV-infected patients when comparing CAB 5 mg once daily to CAB 30 mg once daily (ITZ111451).
- Following 5 mg once daily CAB administration for 10 days, there was a statistically significant decrease (mean change - 2.169 for CAB 5 mg vs.- 0.092 for placebo) in plasma HIV-1 RNA from Baseline to Day 11.
- CAB 5 mg steady state was reached by Day 7 following repeat-dose administration in HIV-infected patients.
- The accumulation ratios for AUC, Cmax, and Cτ following repeat-dose administration of CAB at 5 mg were estimated to be 2.36, 1.96, and 2.48, respectively.

2.6.3.3. Study ITZ111451: 10-day Monotherapy, CAB 30 mg Once Daily

Study Title: A double-blind, parallel, randomized, placebo-controlled, single and repeat dose escalation first time in human study to investigate the safety, tolerability and pharmacokinetics of GSK1265744 in healthy male and female subjects and subjects infected with HIV

Location of Report: m5.3.3.1, ITZ111451

The objectives, overall study design, and treatments are presented in Section 2.6.1.1.

Results for Parts A and B are presented in Section 2.6.1.1. Part C results are presented in this section. Data from Study ITZ111451 (CAB 30 mg in HIV patients Part C HIV cohort) were combined with data from Study ITZ112929 for PK/PD analyses (see Section 2.6.4.2).

Results: The Day 10 geometric mean CAB Ctau of 3.28 μg/mL exceeded the PA-IC90 by 20-fold following CAB 30 mg once daily in HIV-infected subjects (Table 63). The effective t1/2 was estimated to be 33 h based on the accumulation ratio of 2.51. CAB steady state was achieved by Day 7 following repeat administration of 30 mg (6 x 5 mg tablets) in HIV-infected subjects in Part C.

Table 63 Summary of Selected Plasma CAB PK Parameters Following Single and Repeat Dose Administration for 10 Days to HIV-infected Subjects (Part C, Tablet Formulation)

Treatment Day	AUC(0-24) [a] (μg.h/mL)	Cmax [a] (μg/mL)	C24 or Ctau [a] (μg/mL)	tmax [b] (h)	Accumulation Ratio [a,c]
Day 1 (n=8)	41.5 [31.2, 55.0] (35)	2.84 [2.18, 3.70] (32)	1.25 [0.91, 1.72] (39)	1.50 (1.00-3.00)	---
Day 10 (n=8)	104 [82.9, 131] (28)	6.37 [5.26, 7.72] (23)	3.28 [2.46, 4.38] (36)	2.50 (1.00-4.00)	2.51 [2.21, 2.86] (15)

Data Source: GSK Doc. # RM2008/00633/00 Table 11.10 and Table 11.12
a. Geometric mean [95%CI] (CVb%)
b. Median (range)
c. Accumulation ratio = Day 10 AUC(0-24)/Day 1 AUC(0-24)

Table 64 Summary of Plasma HIV-1 RNA Change from Baseline for Part C of ITZ111451

Parameter	Treatment	Mean (SD)	Median (Range)	Treatment versus Placebo [a]		
				Geometric LS Mean	Difference (95% CI)	p-value
Plasma HIV-1 RNA Change from Baseline to Day 11 (log_{10} c/mL)	CAB 30mg (N=8)	-2.344 (0.6491)	-2.548 (-2.97, -0.99)	-2.549	-2.865 (-3.249, -2.480)	<0.001
	Placebo (N=3)	-0.232 (0.2247)	-0.273 (-0.43, 0.01)	0.315	--	--
Plasma HIV-1 RNA Change from Baseline to Nadir (log_{10} c/mL)	CAB 30mg (N=8)	-2.449 (0.6739)	-2.727 (-2.97 -0.99)	-2.675	-2.852 (-2.925, -2.779)	<0.001
	Placebo (N=3)	-0.427 (0.2600)	-0.397 (-0.70, -0.18)	0.177	--	--

Data Source: GSK Doc. # RM2008/00633/00 Table 13.1
a. ANCOVA with treatment as fixed effect and Baseline HIV-1 RNA as covariate.

Conclusions:

- In Part C, HIV-infected subjects (IN naïve) received repeat administration of CAB 30 mg for 10 days followed by an optimized background regimen of 3 active ARVs for 14 days. Day 10 geometric mean Cτ for CAB was 20-fold above the in vitro PA-IC90.
- Following 30 mg once daily CAB administration for 10 days, there was a statistically significant decrease (mean change - 2.344 for CAB 30 mg vs. - 0.232 for placebo) in plasma HIV-1 RNA from Baseline to Day 11. All subjects achieved a Day 11 HIV

RNA change from Baseline of -1.9 log_{10} or greater regardless of Day 10 Cτ or inhibitory quotient (Cτ/PA-IC90).

- Following repeat-dose administration, plasma concentrations of CAB reached steady state by Day 7 of dosing of tablets in HIV-infected subjects.
- The accumulation ratio for AUC was 2.51 following 30 mg once daily in HIV-infected subjects.

2.6.4. Pharmacokinetics and Pharmacokinetic-Pharmacodynamic Relationships in HIV-infected Subjects

2.6.4.1. Study LAI116482 (LATTE): Oral CAB Dose Ranging Study (10 to 60mg once daily)– Induction Period (+ 2 NRTIs)

Study Title: A Phase IIb, dose ranging study of oral GSK1265744 in combination with nucleoside reverse transcriptase inhibitors for induction of HIV-1 virologic suppression followed by an evaluation of maintenance of virologic suppression when oral GSK1265744 is combined with oral rilpivirine in HIV-1-infected, antiretroviral therapy naive adult subjects

Location of Report: m5.3.4.2, LAI116482 Week 96

The objectives, study design, methods, and PK results are described in Section 2.4.1.2.

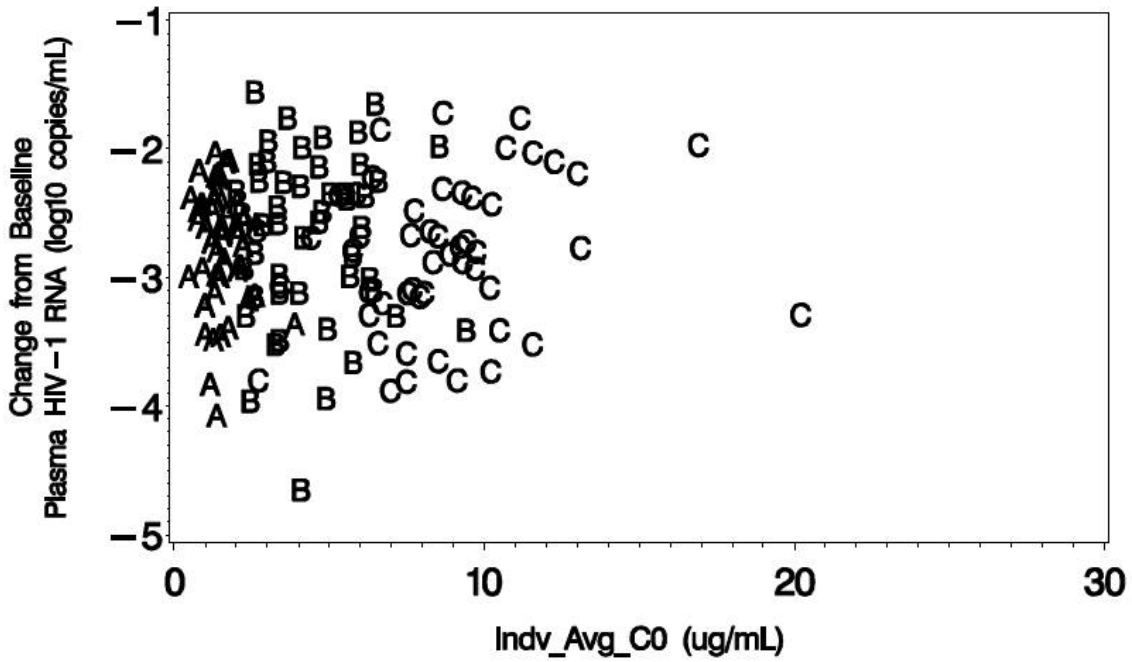
Table 65 Summary of Change from Baseline in Plasma HIV-1 RNA (log_{10} c/mL) at Week 24

	CAB			EFV
	10 mg	30 mg	60 mg	600 mg
Baseline HIV-1 RNA, log_{10} c/mL	**N=60**	**N=60**	**N=61**	**N=62**
Mean (SD)	4.424 (0.5838)	4.271 (0.6359)	4.428 (0.6412)	4.290 (0.6693)
Week 24 HIV-1 RNA Change from Baseline, log_{10} c/mL	**N=56**	**N=53**	**N=56**	**N=48**
Mean (SD)	-2.832 (0.5469)	-2.661 (0.6489)	-2.831 (0.6299)	-2.694 (0.6855)

Data Source GSK Doc. # 2014N216014_00 Week 96 Table 7.18
Note: Baseline values are actual Plasma HIV-1 RNA (log_{10} c/mL) values.

Given that CAB C0 (pre-dose concentrations) exceeded the in vitro PA-IC90 by an average of 8-fold or greater for all CAB doses, no difference in antiviral response at Week 24 was expected and change from Baseline viral load was similar across all CAB doses + 2NRTIs at Week 24. Graphical exploration of the relationship between the Week 24 change in HIV-1 RNA from Baseline vs. Individual Average C0 confirmed that all doses were equally efficacious following 24 weeks of treatment with CAB with 2 NRTIs (Figure 19).

Figure 19 Individual Week 24 Change from Baseline in Plasma HIV RNA vs. Individual Average CAB C0 in HIV-1-infected ART-naïve Subjects (PK/PD Population)



Data Source: GSK Doc. # 2014N216014_00 Week 96 Figure 11.4
A = Oral CAB 10 mg once daily, B = Oral CAB 30 mg once daily, C = Oral CAB 60 mg once daily (CAB was co-administered with 2 NRTIs once daily)

Conclusions:

- Median change in HIV RNA from Baseline was -2.7, -2.6, and -2.8 $\log_{10}$ following 24 weeks of oral CAB 10, 30, and 60 mg once daily, respectively, with 2 NRTIs. All doses produced maximal reduction in viral load, and no relationship was identified between CAB concentrations and virologic response.

2.6.4.2. Combined Data from Study ITZ112929 (10-day Monotherapy, CAB 5 mg Once Daily) + Study ITZ111451 (10-day Monotherapy, CAB 30 mg Once Daily)

Study Title: A Phase IIa study to compare antiviral effect, safety, tolerability and pharmacokinetics of GSK1265744 monotherapy versus placebo in HIV-1-infected adults (ITZ112929)

Location of Report: m5.3.3.2, ITZ112929

The objectives, study design, methods, and PK results are described in Section 2.6.3.2.

Data from CAB 30 mg in HIV patients (Study ITZ111451 Part C HIV cohort) were combined with data from this study for PK/PD analyses.

Scatter plots and Pearson's correlations of plasma HIV-1 RNA change from Baseline to Day 11 vs. plasma CAB PK parameters on Day 10 (AUC(0-tau), Cmax, Cmin, C0, and Ctau) were generated separately for each active treatment.

In addition, relationships between various PK parameters (AUC, Cmax, Cmin, C0, and Ctau) and PD measures (e.g., log10 reduction in plasma HIV-1 RNA to Day 11 from Baseline) were explored with various Emax and linear models using SAS PROC NLMIXED. HIV-RNA results from the SuperLow assay were not explored in PK/PD modeling.

Results:

In the combined analysis overall, there were no significant correlations between CAB exposure and change in plasma HIV-1 RNA from Baseline to Day 11 (Table 66).

Table 66 Summary of Pearson's Correlations (p-values) of Changes in Log10 c/mL Plasma HIV-1 RNA from Baseline to Day 11 and Day 10 CAB Exposures (Overall) in ITZ112929

PK Parameter	Pearson Correlation (p-value) (PK parameter on original scale)	Pearson Correlation (p-value) (PK parameter on log scale)
AUC(0-tau)	-0.201 (0.490)	-0.373 (0.189)
C0	-0.190 (0.516)	-0.330 (0.250)
Cmax	-0.262 (0.366)	-0.412 (0.143)
Cmin	-0.189 (0.518)	-0.330 (0.249)
Ctau	-0.178 (0.543)	-0.352 (0.217)

Data Source: GSK Doc. # RM2009/00485/00 Table 14.1
Treatment: CAB 5 mg once daily x 10 days from Study ITZ112929; CAB 30 mg once daily x 10 days from Study ITZ111451

Table 67 summarizes estimated model parameters of the best model for the relationship between Cmax and reduction in log10 c/mL plasma HIV-1 RNA from Baseline to Day 11 (Model 1) in the combined analysis.

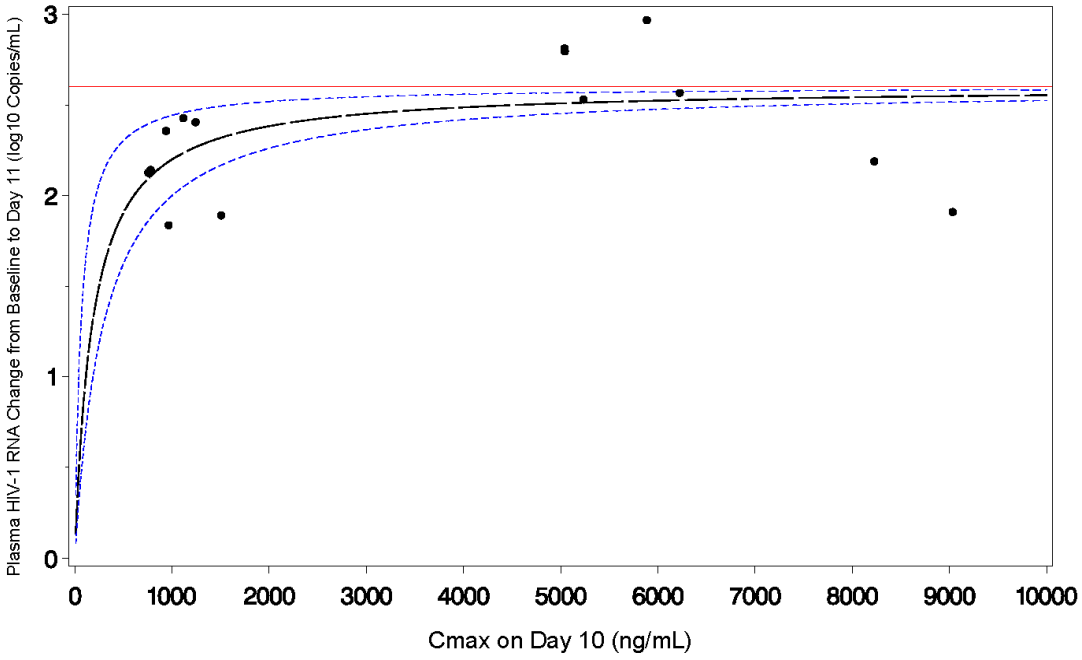
Table 67 Summary of Estimated Model Parameters of Relationship between Reduction in log10 c/mL Plasma HIV-1 RNA from Baseline to Day 11 and Day 10 PK Parameter (Cmax) (Model 1) in ITZ112929

PD Parameter	PK Parameter	Emax	γ	EPK50 (SE)	p-value
Reduction in log10 c/mL Plasma HIV-1 RNA from Baseline to Day 11	Cmax, µg/mL	2.6 (fixed)	1 (fixed)	0.182 (0.060)	0.009

Data Source: GSK Doc. # RM2009/00485/00 Table 14.4
Emax and Linear models include CAB 5 mg once daily x 10 days data from Study ITZ112929 and CAB 30 mg once daily x 10 days data from Study ITZ111451

Figure 20 represents a scatter plot of reduction in $\log_{10}$ c/mL plasma HIV-1 RNA from Baseline to Day 11 vs. Cmax and the fitted curve based on Model 1 in the combined analysis.

Figure 20 Relationship Between Reduction in Log_{10} Plasma HIV-1 RNA from Baseline to Day 11 and CAB Cmax, Best Fit Model (Model 1) for Oral CAB Monotherapy in HIV-1-infected Subjects (ART-naïve or ART-experienced/INI-naïve and Off All ART for Greater than or Equal to 12 weeks)



Data Source: GSK Doc. # RM2009/00485/00 Figure 14.3
Note: Lines represent the best fitted line (dash) and 95% CI (dotted).
Emax and Linear models include CAB 5 mg once daily x 10 days data from Study ITZ112929 and CAB 30 mg once daily x 10 days data from Study ITZ111451

Conclusions:

- A PK/PD analysis did not establish any PK parameters associated with antiviral activity as maximal efficacy was achieved across concentrations of CAB.

2.6.5. Special Populations

2.6.5.1. Study 201479: Moderate Hepatic Impairment

Study Title: A Phase I study to evaluate the pharmacokinetics and safety of GSK1265744 in subjects with hepatic impairment and healthy matched control subjects

Location of Report: m5.3.3.1, 201479

Objective: The primary objective was to compare plasma PK parameters of CAB in subjects with HI to healthy controls matched in gender, age, and BMI.

Study Design and Methods: This was a Phase I, open-label, parallel group, single-dose adaptive study in adults with moderate HI (defined by Child-Pugh score of 7 to 9) and matched, healthy control subjects with normal hepatic function. In Part 1, healthy control subjects (n=8) were matched in gender, age (±10 years), and BMI (±25%) to subjects with moderate (n=8) HI. All subjects received CAB 30 mg tablet as a single oral dose in the fasted state. Since the AUC(0-inf) of CAB did not increase by >2-fold in moderately impaired subjects relative to matched controls, the originally planned Part 2 of the study in adults with mild HI was not conducted.

Results: Unbound plasma CAB concentrations in moderate hepatic impaired subjects were 40% and 55% higher than those in healthy subjects at 2 h and 24 h post-dose, respectively (Table 68).

Table 68 Summary and Comparison of Unbound Plasma CAB Concentrations 2 h and 24 h following Single Dose Oral CAB 30 mg to Moderate Hepatically Impaired Subjects and Healthy Matched Control Subjects (PK Concentration and PK Summary Population)

Unbound CAB Concentration	Statistic	Moderate Hepatic Impaired (n=7) [a]	Healthy Matched (n=7) [a, b]	Hepatic Impaired vs. Healthy (n=7) GLS Mean Ratio (90% CI)
2h Post-dose (μg/mL)	Median (range)	0.00831 (0.00289, 0.0234)	0.00591 (0.00364, 0.00958)	----
	Mean (SD)	0.0094 (0.00661)	0.0058 (0.00227)	----
	GLS Mean	0.0074	0.0053	1.401 (0.798, 2.459)
24h Post-dose (μg/mL)	Median (range)	0.00432 (0.00163, 0.0105)	0.00260 (0.00136, 0.00441)	----
	Mean (SD)	0.0050 (0.00317)	0.0026 (0.00107)	----
	GLS Mean	0.0041	0.0026	1.552 (0.820, 2.938)

Data Source: GSK Doc. # 2016N274024_00 Table 3.2 and Table 3.6

a. For 1 subject with HI and 1 healthy subject, protein binding samples were collected, but due to shipment issues, they were not received and thus not processed.

b. Healthy control subjects are matched to the moderate HI subjects in gender, age (±10 years), and BMI (±25%)

PK Parameters

The results of the statistical comparisons showed that the total plasma exposures of CAB in moderate hepatic impaired subjects were approximately 27% lower than those in healthy subjects, and the Fu of CAB in moderate hepatic impaired subjects was approximately 90% to 114% higher than those in healthy subjects at 2 h and 24 h respectively (Table 69).

Table 69 Summary and Comparison of Selected Plasma CAB PK Parameters Following a Single CAB 30 mg Oral Dose to Moderate Hepatically Impaired Subjects and Healthy Matched Control Subjects (PK Summary Population)

CAB PK Parameter (Units)	Geometric Mean [95% CI] (%CVb)		Ratio of GLS Means (90% CI)
	Moderate Hepatic Impaired (n=8)	Healthy Matched [a] (n=8)	Moderate Hepatic Impaired vs. Healthy Matched (n=8)
AUC(0-inf) (μg.h/mL)	102 [75.2, 138] (37.3)	127 [94.7, 170] (36.2)	0.725 (0.497, 1.058)
AUC(0-t) (μg.h/mL)	98.2 [73.3, 132] (36.2)	121 [91.0, 162] (35.4)	0.731 (0.508, 1.053)
Cmax (μg/mL)	2.70 [1.94, 3.76] (41.1)	3.55 [2.90, 4.33] (24.3)	0.685 (0.505, 0.929)
t1/2 (h)	30.8 [23.7, 40.1] (32.2)	37.2 [33.4 ,41.5] (13.1)	0.822 (0.648, 1.042)
tmax (h) [b]	2.0 (1.0 –4.0)	2.0 (1.0 – 3.0)	NR
FU2h (%) [c]	0.307 [0.202, 0.467] (47.6)	0.157 [0.119, 0.207] (30.5)	2.137 (1.574, 2.902)
FU24h (%) [c]	0.322 [0.184, 0.564] (66.6)	0.166 [0.134, 0.207] (23.9)	1.902 (1.139, 3.175)

Data Source: GSK Doc. # 2016N274024_00 Table 3.3 and Table 3.5

a. Healthy control subjects are matched to the HI subjects in gender, age (±10 years), and BMI (±25%)
b. Data are represented as median (range)
c. n=7 for both moderate hepatic impaired and healthy matched groups

Results from Pearson correlation and regression analyses between CAB PK parameters and hepatic function variables revealed that unbound CAB fractions were statistically higher in subjects with higher albumin score (lower serum albumin concentration) and higher Child-Pugh score. There was no apparent relationship between CAB unbound fraction and total protein concentration.

Conclusions:

- Moderate HI had minimal impact on total plasma CAB PK. The fraction unbound (%) of CAB in moderate HI subjects was ~90% to 114% higher than those in healthy subjects likely due to lower albumin concentrations.
- CAB may be taken without dose adjustment in subjects with mild to moderate HI.

2.6.5.2. Study 201480: Severe Renal Impairment

Study Title: A Phase I, open-label, parallel-group study to evaluate the pharmacokinetics and safety of GSK1265744 in subjects with severe renal impairment and healthy matched control subjects

Location of Report: m5.3.3.1, 201480

Objective: The primary objective was to compare plasma PK parameters of CAB in subjects with severe renal impairment to healthy controls matched for gender, age, and BMI following a single oral dose.

Study Design and Methods: This was a Phase I, open-label, multiple center, single-dose study. The study compared the PK in human subjects with severely impaired renal function (CLCR <30 mL/minute based on 24-hour urine collection), who did not require renal replacement therapy, with matched healthy subjects with normal renal function (≥90 mL/minute). All subjects received a single oral dose of CAB 30 mg tablet.

Results:

Table 70 Summary and Comparison of Selected CAB PK Parameters and Unbound Plasma CAB Concentration-time Data Following Single Dose 30 mg CAB Administration to Severe Renally Impaired Subjects and Healthy Matched Control Subjects (PK Summary Population)

PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI) (Severe Renal Impairment vs. Healthy Match [n=8])
	Severe Renal Impairment (n=8)	Healthy Matched Controls [a] (n=8)	
AUC (0-inf) (μg*h/mL)	143 [b] [115, 177] (23)	140 [116, 170] (23)	0.97 (0.835, 1.14)
AUC (0-t) (μg*h/mL)	143 [115, 178] (27)	133 [110, 160] (23)	1.08 (0.885, 1.32)
Cmax (μg/mL)	3.34 [2.67, 4.17] (27)	3.37 [2.96, 3.83] (15)	1.01 (0.865, 1.17)
t1/2 (h)	39.2 [b] [33.9, 45.4] (16)	40.5 [36.9, 44.5] (11)	0.930 (0.831, 1.04)
tmax [c] (h)	2.00 (1.0 – 4.2)	2.00 (1.0- 4.0)	NA
Fu2h (%)	0.18 [0.14, 0.23] (29)	0.14 [0.08, 0.22] (63)	1.31 (0.843, 2.03)
Fu24h (%)	0.17 [0.15, 0.19] (17)	0.11 [0.09, 0.14] (30)	1.51 (1.19, 1.92)
Concentration of unbound plasma CAB (μg/mL)	**Severe Renal Impairment [c] (n=8)**	**Healthy Matched Controls [c] (n=8)**	**GLS Mean Ratio (90% CI) (Severe Renal Impairment vs. Healthy Match [n=8])**
2 hours	0.0056 (0.0034, 0.0129)	0.0047 (0.0022, 0.0162)	1.32 (0.807, 2.153)
24 hours	0.0030 (0.0022, 0.0050)	0.0020 (0.0013, 0.0025)	1.67 (1.33, 2.09)

Data Source: GSK Doc. # 2016N273991_00 Table 3.2, Table 3.3, and Table 3.5

a. Healthy control subjects are matched to the severe renal impairment subjects in gender, age (±10 years), and BMI (±25%)

b. N=7, for 1 subject, parameters associated with terminal phase such as AUC(0-inf), t1/2, CL/F and Vz/F, were excluded from PK summary population as the coefficient of determination (R2) was <0.85 and percentage of AUC(0-inf) extrapolated was>20%

c. Median (range)

Conclusions:

- CAB AUC(0-∞) and Cmax were similar in subjects with severe renal impairment (CLcr <30 mL/minute) compared with healthy, matched control subjects.
- The unbound fraction was 31% to 51% higher in subjects with severe renal impairment at 2 h and 24 h post-dose, respectively, and the unbound concentrations were 32% and 67% higher in subjects with severe renal impairment at 2 h and 24 h post-dose.
- CAB can be administered without dose adjustment in subjects with mild to severe renal impairment who did not require renal replacement therapy.

2.6.6. Drug-drug Interactions

2.6.6.1. Study LAI116181: Rilpivirine

Study Title: A Phase I, open-label, crossover study to evaluate the pharmacokinetics and safety of GSK1265744 and rilpivirine and dolutegravir and rilpivirine in healthy adult subjects

Location of Report: m5.3.3.1, LAI116181

Objectives: The primary objectives, applicable to this application, were to describe and compare steady-state plasma CAB PK following administration of CAB 30 mg once daily with and without RPV 25 mg once daily and compare steady-state plasma RPV PK following administration of RPV 25 mg once daily with and without CAB 30 mg once daily.

Study Design and Methods: This was a single-center, 2-cohort, open-label, 3-period, fixed-sequence cross over study in healthy adult subjects. In Cohort 2, subjects received CAB 30 mg (5 mg x 6 tablets) once daily for 12 days (Treatment D, Reference) in Period 1, followed by a 14-day washout period. Subjects received a RPV 25 mg tablet once daily for 12 days (Treatment B, Reference) in Period 2 and then CAB 30 mg (5 mg x 6 tablets) once daily in combination with a RPV 25 mg tablet once daily for 12 days (Treatment E, Test) in Period 3. Study drugs were taken with a moderate-fat meal.

Results:

Table 71 Summary of Selected Plasma CAB PK Parameters and Statistical Treatment Comparisons Following Repeat Dose Administration of CAB with and without RPV for 12 Days (CAB PK Summary Population)

Plasma CAB PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
	CAB (n=11)	CAB + RPV (n=11)	CAB + RPV vs. CAB (n=11)
AUC(0-tau) (μg.h/mL)	142 [118, 171] (28)	159 [138, 183] (21)	1.12 (1.05, 1.19)
Cmax (μg/mL)	8.22 [6.83, 9.89] (28)	8.65 [7.69, 9.72] (18)	1.05 (0.963, 1.15)
Ctau (μg/mL)	4.65 [3.73, 5.78] (33)	5.29 [4.49, 6.23] (25)	1.14 (1.04, 1.24)

Data Source: GSK Doc. # 2011N130484_00 Table 11.7 and Table 11.10
CAB = CAB 30 mg once daily x 12 days
CAB + RPV = CAB 30 mg once daily + RPV 25 mg once daily x 12 days

Table 72 Summary of Selected Plasma RPV PK Parameters and Statistical Treatment Comparisons Following Repeat Dose Administration of RPV with and without CAB for 12 Days (RPV PK Summary Population)

Plasma RPV PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
	RPV (n=11)	CAB + RPV (n=11)	CAB + RPV vs. RPV (n=11)
AUC(0-tau) (ng.h/mL)	2473 [2034, 3008] (30)	2441 [1916, 3110] (37)	0.987 (0.890, 1.09)
Cmax (ng/mL)	171 [137, 213] (34)	165 [120, 226] (50)	0.963 (0.849, 1.09)
Ctau (ng/mL)	87.4 [66.8, 114] (42)	80.3 [58.6, 110] (50)	0.919 (0.789, 1.07)

Data Source: GSK Doc. # 2011N130484_00 Table 11.12 and Table 11.15
RPV = RPV 25 mg once daily x 12 days
CAB + RPV = CAB 30 mg once daily + RPV 25 mg once daily x 12 days

Conclusions:

- PK parameters of each drug alone were similar to those when given in combination demonstrating a lack of interaction between RPV and CAB.

2.6.6.2. Study 205712: Rifabutin

Study Title: Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects

Location of Report: m5.3.2.2, 205712

Objective: The primary objective was to compare steady state CAB exposure following CAB 30 mg oral dose once daily with and without RBT 300 mg once daily.

Study Design and Methods: This was a Phase I, single-center, open-label, fixed-sequence, 2-period crossover study conducted in healthy adults. This study took place in 2 treatment periods. In Period 1, 15 subjects received CAB 30 mg once daily for 14 days (treatment A). In Period 2, 14 subjects received RBT 300 mg once daily and CAB 30 mg once daily for 14 days (Treatment B). There was no washout between periods.

Results:

Table 73 Summary of Derived Plasma CAB PK Parameters and Statistical Analysis of CAB AUC (0-tau) and Cmax Following Repeat-dose Administration of CAB with and without RBT for 14 Days (PK Summary Population)

PK Parameter	Geometric Mean [95% CI] (CVb%)		Treatment Comparison: RBT + CAB vs. CAB (n=12) (GLS Mean ratio, 90% CI)
	CAB (n=12)	RBT + CAB (n=12)	
AUC (0-tau) (h*μg/mL)	104 [87.1, 124] (28.3)	81.7 [67.9, 98.4] (29.9)	0.786 (0.743, 0.831)
Cmax (μg/mL)	6.36 [5.45, 7.42] (24.7)	5.25 [4.51, 6.11] (24.3)	0.825 (0.761, 0.895)
Ctau μg/mL)	3.36 [2.72, 4.15] (34.3)	2.48 [1.98, 3.10] (36.3)	0.738 (0.702, 0.776)

Data Source: GSK Doc. # 2017N334381_00 Table 3.3 and Table 3.5
CAB: 30 mg once daily × 14 days
RBT + CAB: RBT 300 mg once daily + CAB 30 mg once daily × 14 days

Conclusions:

- Repeat-dose co-administration of CAB with RBT resulted in decreases in CAB AUC(0-tau), Cmax, and Ctau by 21%, 17%, and 26%, respectively, as compared with CAB alone.
- The moderate reduction in plasma CAB exposure by RBT is not considered clinically relevant following oral CAB administration, as concentrations remained above levels associated with durable suppression of HIV infection in Phase II studies.

2.6.6.3. Study LAI117010: Rifampin

Study Title: Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifampin on the pharmacokinetics of oral cabotegravir in healthy subjects

Location of Report: m5.3.3.1, LAI117010

Objective: The primary objective was to compare the single dose PK of CAB 30 mg when co-administered with RIF 600 mg once daily at steady-state to those of CAB 30 mg administered alone.

Study Design and Methods: This was a Phase I, single-center, open-label, fixed-sequence crossover study in healthy adults. Subjects received treatments as described in Table 74.

Table 74 Study Design for LAI117010

Subjects	Screening Period	Period 1 Day 1 – Day 7	Period 2 Days 8 – 20	Period 3 Days 21 - 28	
N=15	Within 30 Days of Day 1	Single dose CAB 30 mg (Day 1)	RIF 600 mg once daily for 13 days (Days 8 – 20)	Single dose CAB 30 mg on Day 21 + RIF 600 mg once daily for 8 days (Days 21 - 28)	Follow-up Day 38 –42

Treatment A: Single dose CAB 30 mg (Day 1)
Treatment B: RIF 600 mg once daily for 13 days (Days 8 – 20)
Treatment C: CAB 30 mg on Day 21 (single dose) + RIF 600 mg once daily for 8 days (Days 21-28)

Results:

Table 75 Summary of Derived Plasma CAB PK Parameters and Statistical Analysis of CAB AUC(0-tau) and Cmax Following Repeat Dose Administration of CAB with and without RIF (PK Summary Population)

PK Parameter	Geometric Mean [95% CI] (CVb%)		Treatment Comparison: CAB + RIF vs. CAB (n=15) (GLS Mean Ratio, 90% CI)
	CAB (n=15)	RIF + CAB (n=15)	
AUC (0-inf) (h*μg/mL)	146 [128, 167] (23.9)	59.7 [52.8, 67.5] (22.4)	0.41 (0.36, 0.46)
Cmax (μg/mL)	3.61 [3.28, 3.96] (16.9)	3.39 [3.05, 3.76] (19.1)	0.94 (0.87, 1.02)

Data Source: GSK Doc. # 2015N263476_00 Table 3.3 and Table 3.5
CAB: Single dose CAB 30 mg (Day 1)
CAB + RIF: CAB 30 mg on Day 21 (single dose) + steady state RIF 600 mg once daily (Days 8-28)

Conclusions:

- Co-administration of steady-state RIF 600 mg with single dose oral CAB 30 mg decreased CAB AUC(0-inf) by 59% and had no impact on CAB Cmax.
- Co-administration of RIF with CAB is not recommended.

2.6.6.4. Study LAI117011: Oral Contraceptives

Study Title: An open-label study to evaluate the pharmacokinetics of an oral contraceptive containing levonorgestrel and ethinyl estradiol when co-administered with GSK1265744 in healthy adult female subjects

Location of Report: m5.3.3.1, LAI117011

Objective: The primary objective was to demonstrate the lack of an effect of CAB 30 mg on the exposure of LNG and EE in healthy female subjects.

Study Design and Methods: This study was an open-label, fixed-sequence crossover study in healthy adult female subjects. The study consisted of a Screening Period, a Run-in Period (if required for subjects not already stabilized on microgynon), 2 Treatment Periods, and a Follow-up visit. Treatment Periods spanned 1 menstrual cycle for each participant. All subjects first received microgynon alone on Days 1 to 10 (Treatment Period 1), directly followed by concomitant daily dosing of microgynon + CAB on Days 11 to 21 (Treatment Period 2) (Table 76).

Table 76 Study Design for LAI117011

Sample Size	Run-In Period [a]	Treatment Period 1	Treatment Period 2
n	Day 1 to 28-49 Days [b]	Days 1-10	Days 11-21
20	Microgynon once daily	Microgynon once daily	Microgynon once daily+ CAB 30 mg once daily

a. Run-in Period was omitted for subjects stabilized on Microgynon and/or could extend for up to 49 days to synchronize dosing days.
b. No Microgynon was given 7 days prior to Day 1, Treatment Period 1, during which withdrawal menses could occur.

Results:

Table 77 Summary of Steady-state Plasma Levonorgestrel PK Parameters and Treatment Comparisons Following Repeat Dose Administration of Microgynon with and without CAB (PK Summary Population)

Levonorgestrel Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
	Microgynon once daily (n=19)	Microgynon once daily + CAB 30mg once daily (n=19)	Microgynon + CAB 30mg vs. Microgynon (n=19)
AUC(0-tau) (h*ng/mL)	77.4 [64.5, 92.9] (39)	87.0 [72.1, 105] (40)	1.12 (1.07, 1.18)
Cmax (ng/mL)	6.86 [5.84, 8.06] (34)	7.20 [6.28, 8.26] (29)	1.05 (0.959, 1.15)
Ctau (ng/mL)	2.41 [1.98, 2.95] (43)	2.59 [2.09, 3.22] (47)	1.07 (1.01, 1.15)

Data Source: GSK Doc. # 2015N227688_00 Table 3.4 and Table 3.6
Microgynon once daily = LNG 0.15 mg and EE 0.03 mg once daily;
Microgynon once daily + CAB 30 mg = LNG 0.15 mg and EE 0.03 mg once daily + oral CAB 30 mg once daily

Table 78 Summary of Steady-state Plasma Ethinyl Estradiol PK Parameters and Treatment Comparisons Following Repeat Dose Administration of Microgynon with and without CAB (PK Summary Population)

Ethinyl Estradiol Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
	Microgynon Once Daily (n=19)	Microgynon Once Daily + CAB 30mg Once Daily (n=19)	Microgynon + CAB 30mg vs. Microgynon (n=19)
AUC(0-tau) [a] (h*pg/mL)	773 [656, 911] (33)	800 [698, 916] (28)	1.02 (0.968, 1.08)
Cmax (pg/mL)	86.2 [72.4, 103] (38)	79.5 [68.0, 92.8] (33)	0.922 (0.827, 1.03)
Ctau [a] (pg/mL)	16.0 [12.5, 20.4] (51)	15.7 [12.9, 19.0] (40)	1.00 (0.919, 1.10)

Data Source: GSK Doc. # 2015N227688_00 Table 3.8 and Table 3.10
a. n= 17 for Microgynon and n=18 for Microgynon + CAB
Microgynon once daily = LNG 0.15 mg and EE 0.03 mg once daily;
Microgynon once daily + CAB 30 mg = LNG 0.15 mg and EE 0.03 mg once daily + oral CAB 30 mg once daily

Table 79 Summary of Steady-state Plasma CAB PK Parameters Following Repeat Dose Co-administration with Microgynon (PK Summary Population)

CAB Parameter	Geometric Mean [95% CI] (CVb%)
	Microgynon Once Daily + CAB 30mg Once Daily (n=19)
AUC(0-tau) (μg.h/mL)	133 [121, 148] (21)
Cmax (μg/mL)	7.81 [7.13, 8.56] (19)
Ctau (μg/mL)	4.33 [3.87, 4.86] (24)

Data Source: GSK Doc. # 2015N227688_00 Table 3.12
Microgynon once daily + CAB 30 mg = LNG 0.15 mg and EE 0.03 mg once daily + oral CAB 30 mg once daily

Conclusions:

- Co-administration of repeat-dose CAB and the oral contraceptive microgynon had no effect on the PK profile of LNG and EE.

- Steady-state CAB plasma PK parameters in this study were comparable to historical values.

2.6.6.5. Study LAI116815: Midazolam Probe

Study Title: A single-center, randomized, open-label, study to assess the relative bioavailability of new formulations of GSK1265744 LAP in healthy adult subjects

Location of Report: m5.3.1.1, LAI116815

Objective: One of the secondary objectives was to investigate the potential of CAB to inhibit or induce cytochrome P450 3A (CYP3A) enzymes using MDZ as a probe substrate following repeat dose oral administration of CAB.

Study Design and Methods: Refer to m2.7.1, Section 2.2.2 for RBA results. Only the MDZ part of the study is presented in this section.

Twelve subjects received a single oral dose of 3 mg MDZ (Day -29) followed by 24-hr PK sampling. Subjects then received oral CAB 30 mg once daily as tablets x 14 days (Day -28 to -15). PK sampling over 24-hr was repeated following the final oral CAB dose and following a single dose of oral CAB 30mg + MDZ 3 mg (Day -14).

Results:

Table 80 Summary of Plasma MDZ PK Parameters and Treatment Comparisons Following Repeat-Dose Administration of CAB for 14 Days with and without MDZ (PK Summary Population)

PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	MDZ (n=12)	MDZ + CAB (n=12)	MDZ + CAB vs. MDZ (n=12)
AUC(0-t) (ng.h/mL)	25.8 [18.77, 35.35] (53)	28.3 [20.51, 38.95] (54)	1.10 [0.954, 1.26]
AUC(0-inf) (ng.h/mL)	27.5 [20.06, 37.66] (53)	29.7 [21.58, 40.95] (54)	1.08 [0.962, 1.22]
Cmax (ng/mL)	12.3 [9.65, 15.70] (40)	13.4 [10.77, 16.70] (36)	1.09 [0.944, 1.26]

Data Source: GSK Doc. # 2014N208332_00 Table 3.9 and Table 3.11
MDZ = MDZ 3 mg
MDZ + CAB = CAB 30 mg PO + MDZ 3 mg

Conclusion:

- CAB did not affect (induce or inhibit) the activity of CYP3A as evidenced by unchanged MDZ PK with co-administration.

2.6.6.6. Study ITZ111839: Etravirine

Study Title: A Phase I, open label crossover study to evaluate the effect of etravirine on GSK1265744 pharmacokinetics in healthy adult subjects (ITZ111839)

Location of Report: m5.3.3.1, ITZ111839

Objective: The primary objective was to compare steady-state plasma CAB PK following administration of CAB 30 mg once daily as tablets with and without ETV 200 mg BID.

Study Design and Methods: This was a single-center, open-label, 2-period, single-sequence crossover study in healthy adult subjects (Table 81). All doses were administered following a moderate-fat meal. There was no washout between treatment periods.

Table 81 Study Design for ITZ111839

Cohort	Sample Size	Period 1 Days 1-10	Period 2 Days 1-14
1	12	Treatment A	Treatment B

Treatment A = CAB 30 mg once daily x 10 days (Reference Treatment)
Treatment B = Etravirine 200 mg BID + CAB 30 mg once daily x 14 days (Test Treatment)

Results:

Table 82 Summary of Plasma ETV PK Parameters Following Repeat-Dose Oral Administration with Oral CAB Once Daily (PK Summary Population)

Treatment	Geometric Mean (CVb%)			
	AUC(0-tau) (ng.h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Ctau (ng/mL)
CAB + ETV	9176 (25)	975 (24)	557 (26)	597 (28)

Data Source: GSK Doc. # RM2009/00483/00 Table 11.9
CAB + ETV = CAB 30 mg q24h x 14 days + ETV 200 mg q12h

Table 83 Summary of Plasma CAB PK Parameters and Treatment Comparisons Following Repeat-Dose Administration of CAB with and without ETV (PK Summary Population)

PK Parameter	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio [90% CI]
	CAB (n=12)	CAB + ETV (n=12)	CAB + ETV vs. CAB (n=12)
AUC(0-tau) (μg.h/mL)	183 [169.4, 198.5] (13)	184 [173.5, 195.6] (9)	1.01 [0.956, 1.06]
Cmax (μg/mL)	9.47 [8.84, 10.1] (11)	9.83 [9.17, 10.5] (11)	1.04 [0.987, 1.09]

Data Source: GSK Doc. # RM2009/00483/00 Table 11.5 and Table 11.6
CAB = CAB 30 mg q24h x 10 days
CAB + ETV = CAB 30 mg q24h x 14 days + ETV 200 mg q12h

Conclusion:

- Co-administration of CAB and ETV had no effect on the PK of CAB.

2.6.7. Pharmacogenetics

2.6.7.1. Study 205162: Pharmacogenetics Following Oral CAB 30 mg Once Daily

Study Title: PGx7646 meta-analysis results report for 205162: PGx7646: Evaluation of relationships between UGT1A1 and UGT1A9 genotypes and cabotegravir pharmacokinetics and tolerability.

Location of Report: m5.3.5.3, 205162

Objective: A PGx meta-analysis was undertaken to evaluate the effect of UGT1A1 and UGT1A9 genotypes on exposure and tolerability in subjects receiving oral CAB using data from 6 studies.

Study Design: The PGx analysis specifically examined: 1) PK measurements by UGT1A1/1A9 genotype from subjects in Phase I and II studies treated with oral CAB 30 mg once daily for at least 8 days, and 2) selected tolerability endpoints by UGT1A1/1A9 genotype using data from subjects treated with oral CAB from a Phase II study. The known functional genetic variants in *UGT1A1* and *UGT1A9* analyzed included the *UGT1A1* rs4148323 polymorphism (*6 allele), the *UGT1A1* rs8175347 TA5/6/7/8 repeat polymorphism (*1, *28, *36 and *37 alleles), and the *UGT1A9* rs3832043 polymorphism (*1B).

CAB parameters of interest, including AUC(0-tau), Cmax, and Ctau, were pooled across studies. Additional independent variables were evaluated as covariates in the model including: study, gender, age, self-reported race and ethnicity, BMI, weight, and Baseline TBL and/or ALT.

Results:

CAB has been generally well tolerated, with few AE-related withdrawals or discernible trends of AEs relative to dose. However, in a Phase II study (LAI116482), a relationship between increases in ALT concentrations and treatment could not be ruled out, although overall rates of more serious (Grade 3 and 4) increases in ALT were similar between the CAB and EFV groups. In addition, it has been hypothesized that mild (Grade 1 to 2), nonprogressive TBL increases observed in a small subset of patients might be a consequence of CAB acting as a substrate of UGT1A1 [Margolis, 2015]. The UGT1A1*28 polymorphism has been reported to be associated with hyperbilirunemia induced by several drugs and is known to cause reduced UGT1A1 expression and predisposes individuals to Gilbert's syndrome, a benign form of episodic jaundice [Bosma, 1995; Raijmakers, 2000; Danoff, 2004; per VOTRIENT labeling; per TASIGNA labeling]. Therefore, ALT and TBL were selected as safety parameters in this study.

A total of 591 subjects provided PGx samples. Genetically predicted UGT1A1 activity was significantly associated with steady-state oral CAB 30 mg PK parameters with mean values of Ctau, AUC(0-tau), and Cmax of ~1.5, 1.4, and 1.3-fold, respectively, higher in subjects with low rather than normal predicted activity (Table 84, Figure 21, Figure 22). Based on the cumulative CAB PK and safety data collected to date, this magnitude of increase in CAB exposure is not anticipated to have a clinically relevant impact and does not change the understood benefit-risk profile of 30 mg oral CAB.

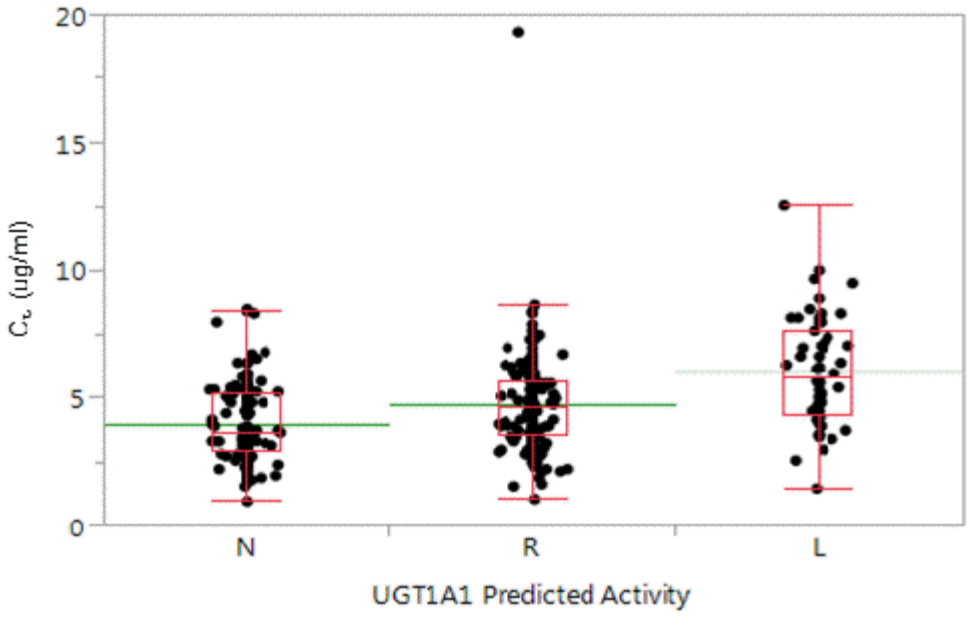
Table 84 Summary of Pharmacogenetic Analysis Results

Gene	Endpoint	Analysis Population, N	P value	Parameter Estimate for Genetically Predicted Activity (Standard Error)	Final Model
UGT1A1	Ctau	346	4.89×10^{-11}	0.19 (0.03)	log(Ctau) ~ UGT1A1 predicted activity + study + age + weight
	AUCtau	59	0.0013	20.03 (5.89)	AUCtau ~ UGT1A1 predicted activity + study + weight
	Cmax	59	0.0213	0.78 (0.33)	Cmax ~ UGT1A1 predicted activity + study + weight
	ALT change from baseline	163	0.6674	-0.03 (0.06)	log(max ALT) – log(Baseline ALT) ~ UGT1A1 predicted activity
	TBL Change from Baseline	163	7.97×10^{-6}	0.13 (0.03)	max TBL – Baseline TBL ~ UGT1A1 predicted activity
UGT1A9	Ctau	347	0.6374	0.01 (0.03)	log(Ctau) ~ UGT1A9 predicted activity + study + age + weight
	AUCtau	60	0.9108	-0.77 (6.80)	AUCtau ~ UGT1A9 predicted activity + study + weight
	Cmax	60	0.8060	-0.09 (0.36)	Cmax ~ UGT1A9 predicted activity + study + weight
	ALT change from Baseline	163	0.3823	-0.05 (0.06)	log(max ALT) – log(Baseline ALT) ~ UGT1A9 predicted activity
	TBL change from Baseline	163	0.0412 [a]	0.06 (0.03)	max TBL – Baseline TBL ~ UGT1A9 predicted activity

Data Source: GSK Doc. # 2016N297524_00 Table 8.41

a. After accounting for UGT1A1 genetic variation within the model, UGT1A9 was no longer significantly associated with change from Baseline TBL (p=0.4481).

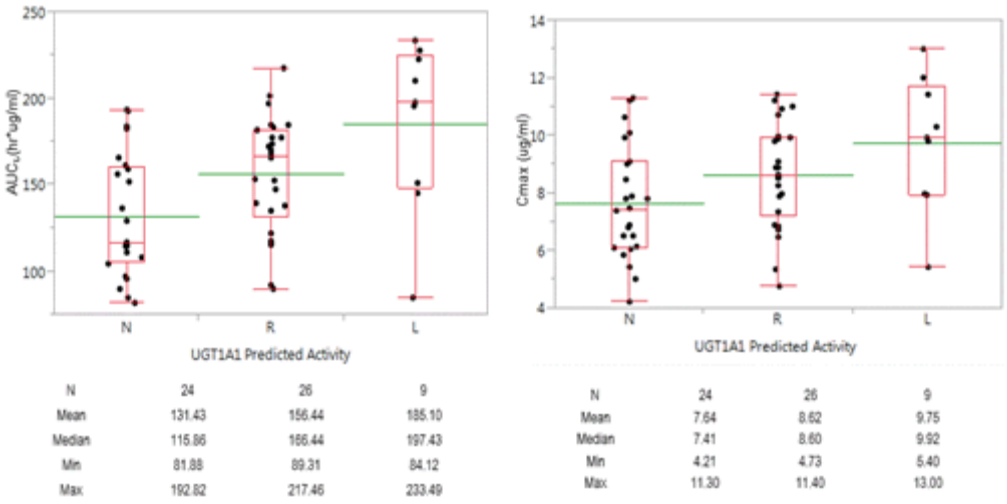
Figure 21 Genetic Effects of UGT1A1 Genotypes on 30 mg Oral CAB Ctau in Subjects with Predicted Normal (N), Reduced (R), and Low (L) Activity



N	128	162	56
Mean	4.03	4.72	6.06
Median	3.71	4.66	5.86
Min	1.02	1.06	1.49
Max	8.51	19.3	12.6

Data Source: GSK Doc. # 2016N297524_00 Figure 18.11

Figure 22 Effects of UGT1A1 Genotypes on 30 mg Oral CAB AUCtau and Cmax in Subjects with Predicted Normal (N), Reduced (R), and Low (L) Activity



	N	R	L
N	24	26	9
Mean	131.43	156.44	185.10
Median	115.86	166.44	197.43
Min	81.88	89.31	84.12
Max	192.82	217.46	233.49

	N	R	L
N	24	26	9
Mean	7.64	8.62	9.75
Median	7.41	8.60	9.92
Min	4.21	4.73	5.40
Max	11.30	11.40	13.00

Data Source: GSK Doc. # 2016N297524_00 Figure 18.12 and Figure 18.13

Genetically predicted UGT1A1 activity was significantly associated with change from Baseline TBL, but not ALT. The maximum individual on-treatment TBL observed in this dataset was 2.27 x ULN (0.91 x ULN increase from Baseline level of 1.36 x ULN) in a subject with low genetically predicted UGT1A1 activity. None of the 5 subjects who had maximum on-treatment TBL ≥1.5 x ULN in this dataset had genetically predicted normal UGT1A1 activity; all carried one or more reduced function UGT1A1 alleles.

The UGT1A9 genetic variant (*1B) was not associated with any PK endpoints analyzed or with maximum on-treatment ALT but was moderately associated with maximum on-treatment TBL. After accounting for genetically predicted UGT1A1 activity within the same model, UGT1A9 *1B is no longer significantly associated with change from Baseline TBL, which suggests that the observed univariate association between UGT1A9 and TBL may be due to the correlation between UGT1A1 and UGT1A9.

The impact of reduced UGT1A1 function on observed CAB parameters following CAB LA are described in Section 2.1.3.1. In Study 200056, *UGT1A1*-reduced function polymorphisms modestly increased CAB PK parameters in HIV-infected patients who received CAB by oral or IM injection administration. There was approximately a 1.2-fold difference in mean CAB LA PK parameter values between patients with low vs. normal predicted UGT1A1 activity, which is lower than that observed with oral CAB (1.38-fold). The impact of reduced clearance on the simulated CAB LA profile is described in Section 3.2.9.1.

Given the overall good tolerability and safety profile of CAB, any increase in concentrations due to low UGT1A1 activity is unlikely to produce AEs and no adjustment in dose is recommended for either formulation.

Conclusion(s)

- Genetically predicted UGT1A1 activity was significantly associated with steady-state oral CAB 30 mg PK parameters with mean values of Ctau, AUC(0-tau), and Cmax of ~1.5-, 1.4-, and 1.3-fold, respectively, higher in subjects with low rather than normal predicted activity. These increases are not considered clinically relevant.
- Genetically predicted reduced UGT1A1 function was associated with increased change from Baseline TBL and was not considered clinically relevant.
- UGT1A9*1B was not associated with oral CAB PK parameters or change from Baseline TBL after including UGT1A1 in the model.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Cabotegravir + Rilpivirine

3.1.1. Exposure-Response Relationship for Efficacy Endpoints

Oral CAB 30 mg once daily + oral RPV 25 mg once daily is proposed as OLI to evaluate the potential in each subject for ADRs, which would preclude IM dosing with CAB LA + RPV LA, and for oral therapy when a patient plans to miss a scheduled injection by more than 7 days. Strong and rapid antiviral responses were observed for the three oral CAB once daily regimens of 10 mg, 30 mg, and 60 mg in combination with 2 NRTIs (Induction Phase of Study LAI116482). Furthermore, all three oral CAB (10 mg, 30 mg, and 60 mg) once daily + oral RPV 25 mg once daily regimens demonstrated similar efficacy at the primary endpoint Week 48 (Maintenance Phase Week 24 of Study LAI116482) (Table 86). Selection of the middle dose (30 mg) was pre-specified if comparable efficacy and safety were observed. Oral CAB 30 mg is sufficiently high for use as a short OLI prior to IM administration. Oral RPV 25 mg once daily is approved for use in combination therapy. Oral CAB 30 mg once daily + oral RPV 25 mg once daily was evaluated as OLI and oral therapy in Phase III Studies 201584, 201585, 207966 and in Phase IIb Study 200056.

The Phase IIb dose selection strategy for CAB LA + RPV LA was based on maintaining efficacious plasma CAB and RPV concentrations beginning with the first injections and throughout the course of therapy. Efficacious concentrations were defined as maintaining plasma Ctau at or above exposures following oral CAB 10 mg once daily and oral RPV 25 mg once daily. Initial and steady-state exposures of CAB and RPV following IM injection were predicted based on PopPK modeling of healthy and HIV-infected subject data. For the Phase III studies, the CAB LA and RPV LA initial injection doses were modified from those used in the maintenance phase of Study 200056 to align number of injections and dose volumes for both products; these initial injection doses were also used for the extension phase of the Phase IIb Study 200056.

The primary efficacy endpoint of the Phase III studies was the proportion of subjects with plasma HIV-1 RNA 50 c/mL at Week 48 (Snapshot Algorithm, ITT-E). In Phase III Studies 201584 and 201585, CAB + RPV Q4W was non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects (Table 89 and Section 2.1.2.3). In Phase IIIb Study 207966, CAB + RPV Q8W was non-inferior to CAB + RPV Q4W in maintaining virologic suppression in HIV-1 infected subjects (Table 13, Table 14, Section 2.1.2.3). Across the Phase III studies and arms, there were few cases of plasma HIV-1 RNA ≥50 c/mL per the Snapshot Algorithm at Week 48.

Across the Phase III studies (201584, 201585, 207966), the overall rate of CVF in subjects receiving Q4W or Q8W regimens was low. Plasma CAB concentrations at the SVF visit for subjects with CVF overlapped with plasma concentrations of subjects with HIV-RNA <50 c/mL at the corresponding visit, making it difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure (Section 2.1.4.1, 2.1.4.2, 2.1.4.3). In addition, some subjects with CVF were found to have pre-existing NNRTI RAMs or INSTI mutations at Baseline (m2.7.2.4), which was further evaluated in a MVA (Section 3.1.1.3). Multiple factors, including PK and viral phenotype, may be associated with the occurrence of virologic failure.

3.1.1.1. CAB

Oral CAB Short-term (10-day) Monotherapy Exposure-Response

In HIV-1-infected ART-naïve and ART-experienced/INI-naïve subjects who were off all ART for at least 12 weeks, oral CAB monotherapy regimens of 5 mg once daily and 30 mg once daily achieved mean decreases in plasma HIV-1 RNA of >2.1 log10 c/mL on Day 11 (Table 85). There was no clear relationship between plasma CAB PK parameters and reduction in plasma HIV-1 RNA concentrations due to the strong antiviral response observed for the two oral CAB monotherapy regimens of 5 mg once daily and 30 mg once daily [Data Source: GSK Doc. # RM2009/00485/00 Figure 14.1, Figure 14.3].

Table 85 Short-term Antiviral Activity of Oral CAB Monotherapy in HIV-1-infected Subjects (ART-naïve or ART-experienced/INI-naïve and Off All ART for ≥12 weeks)

Virologic Response or PK Parameter	Oral CAB Once Daily x 10 days	
	5 mg (n=7) ITZ112929	30 mg (n=8) ITZ111451
Baseline Plasma HIV-1 RNA (c/mL) mean (SD)	4.48 (0.49)	4.140 (0.2672)
Plasma HIV-1 RNA CFB (log10 c/mL) Day 11 mean (SD)	-2.169 (0.2405)	-2.344 (0.6491)
Plasma CAB Ctau (μg/mL) geometric mean (min-max)	0.57 (0.38-0.91)	3.28 (1.72-4.81)
Plasma CAB Ctau/PA-IC90 geometric mean (min-max) [a]	3.43 (2.29-5.48)	19.8 (10.4-29.0)

Data Source: GSK Doc. # RM2009/00485/00 Table 3, Table 16, Table 11.5; GSK Doc. # RM2008/00633/00Table 8, Table 29, Table 11.12

a. CAB PA-IC90 = 0.166 μg/mL

Oral CAB Induction Phase (24 weeks) Combination Therapy Exposure-Response

In HIV-1-infected ART-naïve subjects, oral CAB once daily regimens of 10 mg, 30 mg, and 60 mg, in combination with 2 NRTIs, achieved mean decreases in plasma HIV-1 RNA of >2.6-log10 c/mL at Week 20/24 (Table 86). A higher proportion of subjects receiving CAB regimens achieved plasma HIV-1 RNA <50 c/mL compared with EFV + 2 NRTIs at Week 24.

Table 86 Antiviral Activity of Oral CAB + 2NRTIs in HIV-1-infected ART-Naïve Subjects

Virologic Response or PK Parameter Study LAI116482 Week 24 Study 200056 Day 1 (20 weeks)	200056	LAI116482			
	Oral CAB Once Daily + 2 NRTIs Once Daily x 20-24 weeks [a]				Comparator x 24 weeks
	30 mg (n=309)	10 mg (n=60)	30 mg (n=60)	60 mg (n=61)	EFV + 2 NRTIs [a] (n=62)
Baseline Plasma HIV-1 RNA (c/mL) mean (SD)	4.43 (0.672)	4.424 (0.5838)	4.271 (0.6359)	4.428 (0.6412)	4.29 (0.6693)
Plasma HIV-1 RNA CFB (log10 c/mL) [b] mean (SD)	-2.82 (0.645) [n=291]	-2.832 (0.5469) [n=56]	-2.661 (0.6489) [n=53]	-2.831 (0.6299) [n=56]	-2.694 (0.6855) [n=48]
Plasma HIV-1 RNA <50 c/mL n (%) [b,c]	282 (91%)	52 (87%)	51 (85%)	53 (87%)	46 (74%)
Plasma CAB C0 (μg/mL) geometric mean (min-max)[d]	4.22 (1.0-19.3) [n=246]	1.35 (0.5-3.9) [n=57]	4.20 (2.0-9.4) [n=52]	7.93 (2.6-20.2) [n=55]	-
Plasma CAB C0/PA-IC90 geometric mean (min-max) [d,e]	25.4 (6.02-116)	8.13 (3.01-23.5)	25.3 (12.0-56.6)	47.8 (15.7-122)	-

Data Source: GSK Doc. # 2014N216014_00 Table 13, Table 27, Table 52, Table 9.4; GSK Doc. # 2015N246053_00 Table 19, Table 25, Table 10.1014

a. 2 NRTIs were either ABC/3TC or TDF/FTC; In Study 200056, Oral RPV 25 mg once daily was added for the last 4 weeks.
b. Efficacy population = ITT-E
c. The proportion of subjects achieving plasma HIV-1 RNA <50 c/mL is per the Snapshot (MSDF) Analysis (ITT-E Population).
d. Plasma CAB C0 = individual average of Week 2 and Week 12 values for Study LAI116482 and Day 1 [20 weeks] value for Study 200056.
e. CAB PA-IC90 = 0.166 μg/mL

There was not a relationship between plasma CAB PK parameters and reduction in plasma HIV-1 RNA concentrations given the strong and rapid antiviral response observed for the three oral CAB once daily regimens of 10 mg, 30 mg, and 60 mg in combination with 2 NRTIs [Data Source: GSK Doc. # 2014N216014_00 Figure 7.3, Figure 11.4].

3.1.1.2. CAB + RPV

Oral CAB + Oral RPV Once Daily Regimen: Maintenance Phase CAB Exposure-Response

In the Phase IIb Study LAI116482, all three oral CAB (10 mg, 30 mg, and 60 mg) once daily + oral RPV 25 mg once daily regimens demonstrated similar efficacy at the primary endpoint Week 48 (Maintenance Phase Week 24) (Table 87). These data supported selection of CAB LA regimens for the Phase IIb Study 200056; the selected CAB LA Q8W IM regimen was predicted to maintain plasma CAB Ctau consistent with oral CAB 10 mg once daily and the selected CAB LA Q4W IM regimen was predicted to maintain

plasma CAB Ctau between that observed with oral CAB 10 mg and 30 mg once daily regimens.

In addition, these data supported selection of oral CAB 30 mg once daily + oral RPV 25 mg once daily as the OLI for Phase III studies. Dose selection for the middle dose (30 mg) was pre-specified if comparable efficacy and safety was observed. Oral CAB 30 mg is sufficiently high to assess safety and tolerability during a short OLI prior to IM administration.

Table 87 Maintenance of Virologic Suppression for Oral CAB + Oral RPV Once Daily Regimens

Virologic Response or PK Parameter	Study LAI116482			
	Oral CAB + Oral RPV 25 mg Once Daily [a]			Comparator [b]
	10 mg Once Daily (n=52)	30 mg Once Daily (n=53)	60 mg Once Daily (n=55)	EFV + 2 NRTIs (n=47)
Primary Endpoint Week 48 (Maintenance Week 24) Plasma HIV-1 RNA <50 c/mL n (%) [c]	48 (92)	48 (91)	53 (96)	44 (94)
Plasma CAB Ctau (μg/mL) geometric mean (min-max) [d]	1.34 (0.2-5.2) [n=50]	3.93 (1.3-9.6) [n=51]	8.22 (3.5-21.7) [n=49]	-
Plasma CAB Ctau/PA-IC90 geometric mean (min-max) [d,e]	8.07 (1.20-31.3)	23.7 (7.83-57.8)	49.5 (21.1-131)	-

Data Source: GSK Doc. # 2014N216014_00 Week 96 Table 7.5, Table 9.4

a. The combinations of oral CAB (10 mg, 30 mg, and 60 mg once daily) + oral RPV 25 mg once daily were evaluated as maintenance regimens in HIV-1-infected subjects with virologic suppression following 24 weeks induction with oral CAB + 2 NRTIs.
b. Subjects in the comparator arm received EFV 600 mg once daily + 2 NRTIs for induction therapy; subjects with virologic suppression continued this regimen for the maintenance phase of the study.
c. The proportion of subjects achieving plasma HIV-1 RNA <50 c/mL is per the Snapshot (MSDF) Analysis (ITT-ME Population).
d. Plasma CAB Ctau = individual average of Week 26 and Week 36 values
e. CAB PA-IC90 = 0.166 μg/mL

CAB LA + RPV LA: Maintenance Phase Exposure-Response

In the Phase IIb Study 200056, the efficacy of dual ARV CAB + RPV Q4W and Q8W regimens were similar to triple ARV oral CAB 30 mg + 2 NRTIs once daily regimen at the primary endpoint Maintenance Week 48 (Table 88). These efficacy data supported progression of the CAB + RPV Q4W and CAB + RPV Q8W regimens into Phase III studies.

Table 88 Maintenance of Virologic Suppression for CAB + RPV Q4W and Q8W Regimens in Phase IIb Study 200056

Virologic Response or PK Parameter (Maintenance Phase Week 48)	Study 200056		
	CAB + RPV Regimen [a]		Oral Comparator Regimen [a]
	Q8W [b] (n=115)	Q4W [c] (n=115)	CAB 30 mg Once Daily + ABC/3TC (n=56)
Primary Endpoint Maintenance Phase Week 48 Plasma HIV-1 RNA <50 c/mL n (%) [d]	106 (92)	105 (91)	50 (89)
Plasma CAB Ctau (μg/mL) geometric mean (min-max) [e]	1.49 (0.0-4.3) [n=112]	2.56 (1.5-6.7) [n=98]	4.54 (1.6-8.7) [n=51]
Plasma CAB Ctau/PA-IC90 geometric mean (min-max) [e,f]	8.98 (0-25.9)	15.4 (9.04-40.4)	27.3 (9.64-52.4)
Plasma RPV Ctau (ng/mL) geometric mean (min-max) [e]	63.2 (24.2-196) [n=100]	92.1 (43.0-219) [n=102]	-
Plasma RPV Ctau/PA-IC90 geometric mean (min-max) [e,f]	5.27 (2.02-16.3)	7.68 (3.58-18.3)	-

Data Source: GSK Doc. # 2016N273084_00 Table 7.1001, Table 10.1003, Table 10.1004

a. ART-naïve subjects received oral CAB 30 mg once daily + ABC/3TC for 20 weeks (+ oral RPV 25 mg once daily added for the last 4 weeks) as induction therapy and then were randomized to remain on this regimen or switch to the CAB LA + RPV LA Q4W or Q8W regimen.
b. CAB LA + RPV LA Q8W Regimen: Initial dose of CAB LA 800 mg IM + RPV 900 mg IM, then CAB LA 600 mg IM at Week 4 (no RPV), then CAB LA 600 mg IM + RPV 900 mg IM at Week 8 and Q8W
c. CAB LA + RPV LA Q4W Regimen: Initial dose of CAB LA 800 mg IM + RPV 600 mg IM, then CAB LA 400 mg IM + RPV 600 mg IM Q4W
d. The proportion of subjects achieving plasma HIV-1 RNA <50 c/mL is per the Snapshot Analysis (ITT-ME Population).
e. Ctau = the individual average of Weeks 40, 44, and 48 for Q4W and Weeks 16, 24, 32, 40, and 48 for Q8W
f. CAB PA-IC90 = 0.166 μg/mL; RPV PA-IC90 = 12 ng/mL

For the Phase III studies, the CAB LA and RPV LA initial injection doses were modified to align number of injections and dose volumes for both products, and these modified initial injection doses were also implemented in the extension period of the Phase IIb Study 200056 (referred to in that study as 'optimized'). The modifications included:

- Selection of CAB LA initial injection of 600 mg (3 mL) (from 800 mg [two 2 mL injections]) for both Q4W and Q8W regimens
- Selection of RPV LA initial injection of 900 mg (3 mL) for the Q4W regimen, similar to the initial injection for the Q8W regimen
- Administration of an additional RPV LA 900 mg dose as a second injection 4 weeks after the initial injection for the Q8W regimen to align with the CAB LA 600 mg dose administered at that time point.

These dose modifications were supported by modeling and simulation using PopPK models based on data available at that time from the maintenance period of Phase IIb Study 200056. Safe and efficacious plasma CAB and RPV concentrations were predicted to be achieved and RPV concentrations were predicted to approach steady state more rapidly.

The efficacy data from the 2 Phase III Studies 201584 and 201585 in HIV-1-infected subjects with virologic suppression support the proposed dual ARV combination of CAB + RPV monthly. In both studies, monthly CAB + RPV Q4W was non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects, with few cases of plasma HIV-1 RNA ≥50 c/mL per the Snapshot Algorithm in either arm (Table 87).

Based on the efficacy results from Phase III Studies 201584 and 201585, CAB + RPV Q4W was an appropriate active control (reference) against which CAB + RPV Q8W was tested in the Phase IIIb Study 207966. The efficacy data from the Phase IIIb Study 207966 support the proposed dual ARV combination of CAB + RPV every 2 months because CAB + RPV Q8W was non-inferior to CAB + RPV Q4W in maintaining virologic suppression in HIV-1 infected subjects, with few cases of plasma HIV-1 RNA ≥50 c/mL per the Snapshot Algorithm in either arm (Table 89).

Table 89 Week 48 Virologic Outcomes and Observed Drug Concentrations for CAB + RPV Q4W & Q8W Regimens in Phase III Studies (Data for Subjects with No Prior Exposure to CAB LA + RPV LA)

Virologic Response or PK Parameter (Maintenance Phase Week 48)	CAB + RPV Q8W [a]	CAB + RPV Q4W [a]			Oral Comparator Regimens	
	207966 [b,c] (n=327)	207966 [b,c] (n=327)	201584 [b] (n=283)	201585 [b] (n=308)	201584 [b] CAR (n=283)	201585 [b] CAR (n=308)
Primary Endpoint Plasma HIV-1 RNA >50 c/mL[d]; n (%)	5 (1.5)	5 (1.5)	6 (2.1)	5 (1.6)	7 (2.5)	3 (1.0)
Secondary Endpoint Plasma HIV-1 RNA <50 c/mL[d]; n (%)	306 (94)	300 (92)	265 (94)	285 (93)	264 (93)	294 (95)
PK Parameter Following Initial Injection [e] geometric mean (min-max)						
Plasma CAB Ctau (μg/mL)	1.57 (0.235-8.22) [n=273]	1.52 (0.292-5.94) [n=267]	1.56 (0.296-4.71) [n=250]	1.23 (0.156-5.88) [n=252]	-	-
Plasma CAB Ctau/PA-IC90	9.46 (1.42-49.5)	9.16 (1.76-35.8)	9.40 (1.78-28.4)	7.41 (0.940-35.4)	-	-
Plasma RPV Ctau (ng/mL)	47.6 (11-168) [n=272]	45.0 (9.8-248) [n=267]	41.2 (8.2-237) [n=251]	38.6 (1.9-180) [n=251]	-	-
Plasma RPV Ctau/PA-IC90	3.97 (0.917-14.0)	3.75 (0.817-20.7)	3.43 (0.683-19.8)	3.22 (0.158-15.0)	-	-
PK Parameter Week 48 geometric mean (min-max)						
Plasma CAB Ctau (μg/mL)	1.58 (0.260-5.49) [n=217]	2.71 (0.874-8.90) [n=236]	3.13 (0.910-74.2) [n=197]	2.84 (0.406-8.53) [n=217]	-	-
Plasma CAB Ctau/PA-IC90 [f]	9.52 (1.57-33.1)	16.3 (5.27-53.6)	18.9 (5.48-447)	17.1 (2.45-51.4)	-	-
Plasma RPV Ctau (ng/mL)	65.4 (11.5-204) [n=217]	89.3 (22.3-417) [n=235]	82.4 (22.3-214) [n=197]	90.3 (8.1-256) [n=216]	-	-
Plasma RPV Ctau/PA-IC90 [f]	5.45 (0.958-17.0)	7.44 (1.86-34.8)	6.87 (1.86-17.8)	7.53 (0.675-21.3)	-	-

Data Source:

- 207966: GSK Doc. # 2019N406358_01 Table 2.4, Table 2.10, Table 4.5, Table 4.6
- 201584: GSK Doc. # 2017N345267_00 Table 2.1, Table 2.7, Table 4.3, Table 4.4
- 201585: GSK Doc. # 2018N370336_00 Table 2.1, Table 2.8, Table 4.3, Table 4.4

a. CAB + RPV Regimens consist of OLI + Initiation IM Injection + Continuation IM Injections

- OLI: CAB 30 mg once daily + RPV 25 mg once daily for 4 weeks
- Initiation IM Injection: CAB LA 600 mg + RPV LA 900 mg started on the same day as the last OLI dose
- Continuation IM Injections:
    - CAB LA + RPV LA Q4W: CAB LA 400 mg + RPV LA 600 mg 4 weeks after initial IM injection and Q4W thereafter
    - CAB LA + RPV LA Q8W: CAB LA 600 mg + RPV LA 900 mg 4 weeks after initial IM injection then Q8W thereafter

b. Study Designs

- 207966: ART-experienced subjects who were virologically suppressed on their current ART switched to CAB + RPV Q8W (test regimen) or Q4W (active control [demonstrated safety and efficacy in Studies 201584 and 201585])
- 201584: ART-naïve subjects received ABC/DTG/3TC FDC (or DTG + 2 other NRTIs) for 20 weeks as induction therapy and then were randomized to switch to the CAB + RPV Q4W (test) or remain on the oral regimen (CAR, active control).
- 201585: ART-experienced subjects who were virologically suppressed on their current ART were randomized to switch to the CAB + RPV Q4W (test) or to continue this regimen (CAR, active control).

c. Subjects with no prior exposure to CAB + RPV in Study 207966 are included in this summary.

d. The proportion of subjects achieving plasma HIV-1 RNA >50 c/mL and <50 c/mL is per the Snapshot Analysis (ITT-E Population).

e. Ctau was collected 4 weeks after the initial IM injection; for 207966, this was Study Week 8 (because the initial injection was administered on Study Week 4b).

f. CAB PA-IC90 = 0.166 μg/mL; RPV PA-IC90 = 12 ng/mL.

3.1.1.3. Multivariable analyses evaluating the relationship of viral factors and subject characteristics, dosage regimen, and plasma drug concentrations with virologic outcome across Phase III/IIIb Studies 201584, 201585, and 207966

The majority of subjects (94%; n=1531) across 3 Phase III/IIIb studies (201584, 201585, and 207966, irrespective of prior exposure to CAB+RPV) maintained virologic suppression through Week 48 [GSK Doc. # 2019N406358_01, GSK Doc. # 2017N345267_00, GSK Doc. # 2018N370336_00].

A MVA was performed using data from 1039 HIV-infected adults with no prior exposure to CAB + RPV pooled from Phase III/IIIb studies (201584, 201585, and 207966) to explore potential predictors of virologic outcomes through Week 48 in the pooled CAB + RPV LA treatment group [GSK Doc. # 2020N452718_01]. A logistic regression model was used to examine the influence of 10 covariates (Table 90) known or suspected to contribute to virologic outcome, including drug PK and factors impacting drug exposure, key virus characteristics, and dosing interval (Q8W vs. Q4W), on the occurrence of CVF [GSK Doc. # 2020N452718_01 Table 2].

Through Week 48 in these Phase III/IIIb studies, 13/1039 (1.25%) subjects included in the MVA population met CVF criteria while receiving CAB + RPV (for details see GSK Doc. # 2020N452718_01 Section 4.2 and Table 2).

Four covariates were significantly associated ($p<0.05$ for each adjusted OR) with increased risk of CVF (Table 90):

- RPV RAMs at Baseline (determined through PBMC-based HIV-1 DNA sequencing in Study 201585 and Study 207966)
- HIV-1 Subtype A6/A1 (associated with integrase L74I polymorphism)
- RPV Ctrough 4 weeks following initial injection dose (per halving concentration)
- BMI (per unit increase in kg/m^2) (associated with CAB PK)

A significant association with CVF was not observed for the other 6 variables (Table 90).

Table 90 Multivariable Logistic Regression Analysis of CVF through Week 48 (CAB + RPV Naïve Pooled ITT-E-LA)

Parameter	Full Model OR (95% CI), p-value[a]	Backwards Elimination Model OR (95% CI), p-value[a]
RPV RAM(s) at Baseline	30.23 (6.25–>99), <0.001	40.36 (8.81–>99), <0.001
Log_2 of post hoc Week 8 RPV trough concentration	3.85 (1.15–14.29)[b], 0.029	5.00 (1.79–16.67)[b], 0.002
Baseline ViiV HIV-1 Subtype A6/A1	2.37 (0.34–22.14), 0.394	5.92 (1.62–22.89), 0.008
BMI (kg/m^2) at Baseline	1.08 (0.96–1.22), 0.192	1.13 (1.02–1.24), 0.020
Pre-specified INSTI mutation (excluding L74I non-M mixture) at Baseline	0.16 (0.01–1.05), 0.057	0.14 (0.01–0.91), 0.038
NNRTI RAM(s) (excluding RPV RAMs) at Baseline	2.64 (0.72–9.21), 0.137	2.78 (0.78–9.63), 0.111
Q8W regimen	2.76 (0.65–11.68), 0.164	2.77 (0.67-11.38), 0.156
Log_2 of post hoc Week 8 CAB trough concentration	0.66 (0.25–1.74), 0.395	Eliminated from model
L74I (non-M mixture) INSTI mutation at Baseline	2.51 (0.33–13.85), 0.347	Eliminated from model
Female at birth	1.09 (0.26–4.36), 0.899	Eliminated from model

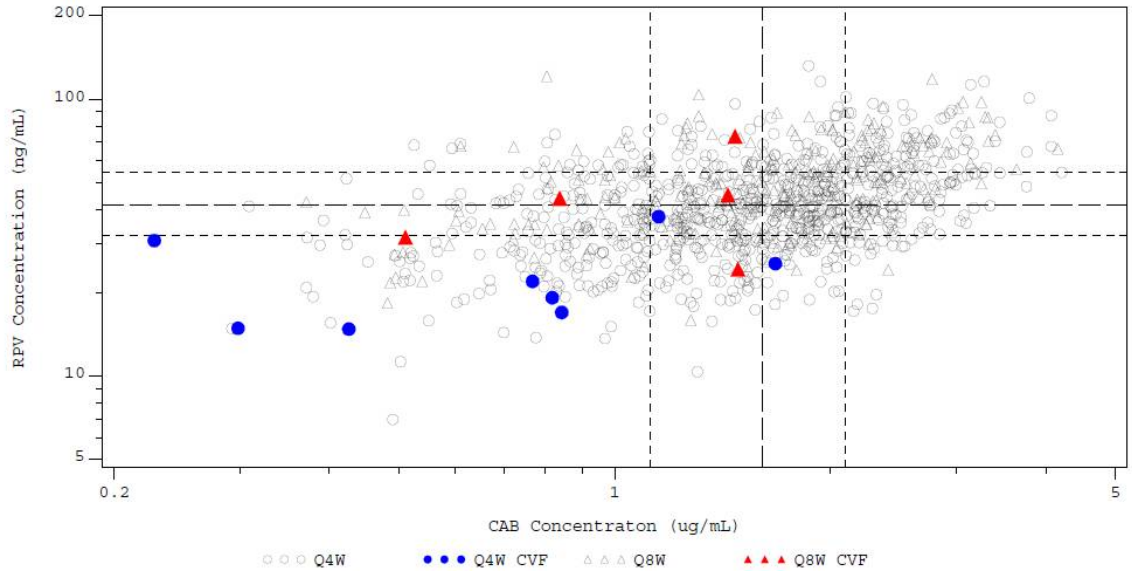
Data Source: GSK Doc. # 2020N452718_01 Table 4.

a. OR, 95% penalized profile CI, and penalized likelihood ratio p-values are provided. Backwards elimination used a significance threshold of alpha=0.2.

b. CAB and RPV PK parameters were log2-transformed; therefore, the corresponding ORs are per halving of each variable. Full Model OR: 0.26 (95% CI: 0.07, 0.87) and Final Model OR: 0.20 (95% CI: 0.06, 0.56); results in table are reciprocal of these so that all ORs are in same direction.

Although the factor for dosing regimen was retained in the final model (the model-building algorithm for iterative backward elimination is largest p>0.20), the OR and corresponding p-value are not statistically significant at the alpha threshold of 0.05 (OR [95% CI] = 2.77 [0.67, 11.38]; p=0.156; Table 90). Initiation injections are the same for both the Q4W and Q8W regimens; therefore, an association of low Week 8 concentrations with efficacy is not regimen dependent. Seven of the 8 subjects on Q4W dosing who met CVF criteria had Week 8 trough concentrations of CAB and/or RPV in the first quartile, while 3 of the 5 subjects with Q8W dosing and CVF also had first quartile CAB and/or RPV concentrations (Figure 23).

Figure 23 Relationship between CVF and CAB + RPV Dose Regimen by Week 8 CAB/RPV Trough Concentration (CAB + RPV Naïve Pooled ITT-E-LA)

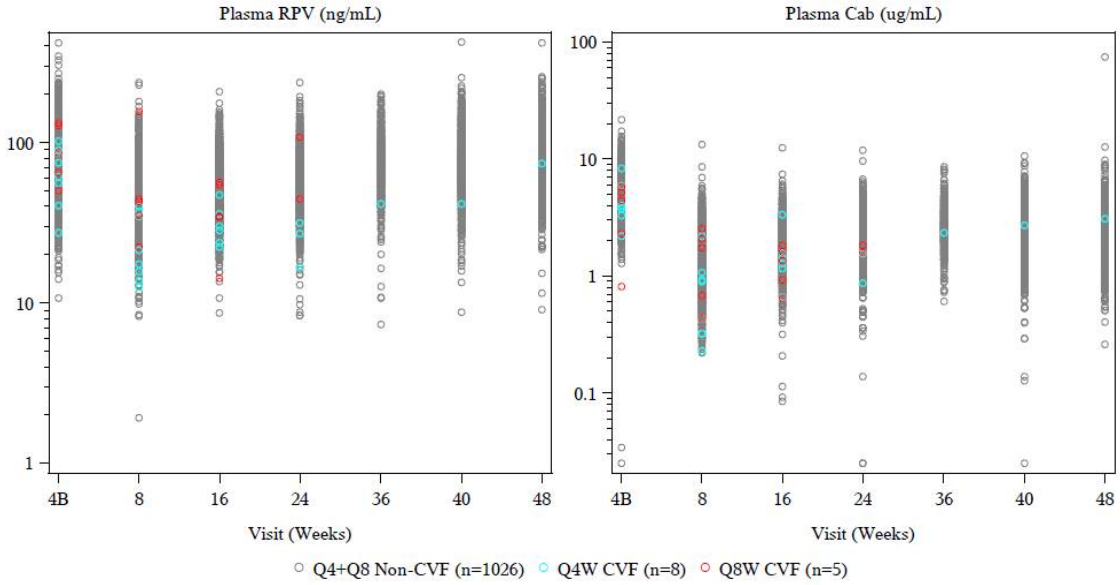


Data Source: GSK Doc. # 2020N452718_01 Figure 3.
Note: Clarification for legend: Q4W non-CVF are unfilled circles and Q8W non-CVF are unfilled triangles.
Note: The population is based on MVA population (n=1039).
Note: The Y reference lines are Q1=32.10, median=41.50, and Q3=54.30.
Note: The X reference lines are Q1=1.12, median=1.61, and Q3=2.10.

Initiation injections are the same for both regimens, and second injections are administered 4 weeks after the first injections for both regimens, with a higher dose for Q8W (3 mL of each product) compared with Q4W (2 mL of each product). Therefore, concentrations are similar through Week 12 and begin to diverge between regimens, thereafter, becoming most apparent after Week 24. While accumulation of both CAB and RPV levels to steady state on the Q4W dose regimen is observed, Q8W demonstrates modest accumulation of RPV and limited, to no accumulation of CAB over time. In Study 207966, differential accumulation resulted in 51%, 67%, and 71% higher geometric mean CAB trough concentrations for the Q4W regimen compared with the Q8W regimen at Week 16, Week 24, and Week 48, respectively, and 25%, 28%, and 37% higher geometric mean RPV concentrations for the Q4W regimen compared with the Q8W regimen at Week 16, Week 24, and Week 48, respectively [GSK Doc. # 2019N406358_01].

If the relatively lower trough values observed with Q8W on repeat dosing were a causal driver of the differential response, a higher CVF rate beyond Week 24 would be expected. Most CVFs, however, occurred by Week 24 across Studies 201584, 201585, and 207966 for subjects on either the Q4W or Q8W dosage regimen (Figure 24).

Figure 24 CVF by RPV and CAB Trough Concentration by Visit through Week 48 (CAB + RPV Naïve Pooled ITT-E-LA)



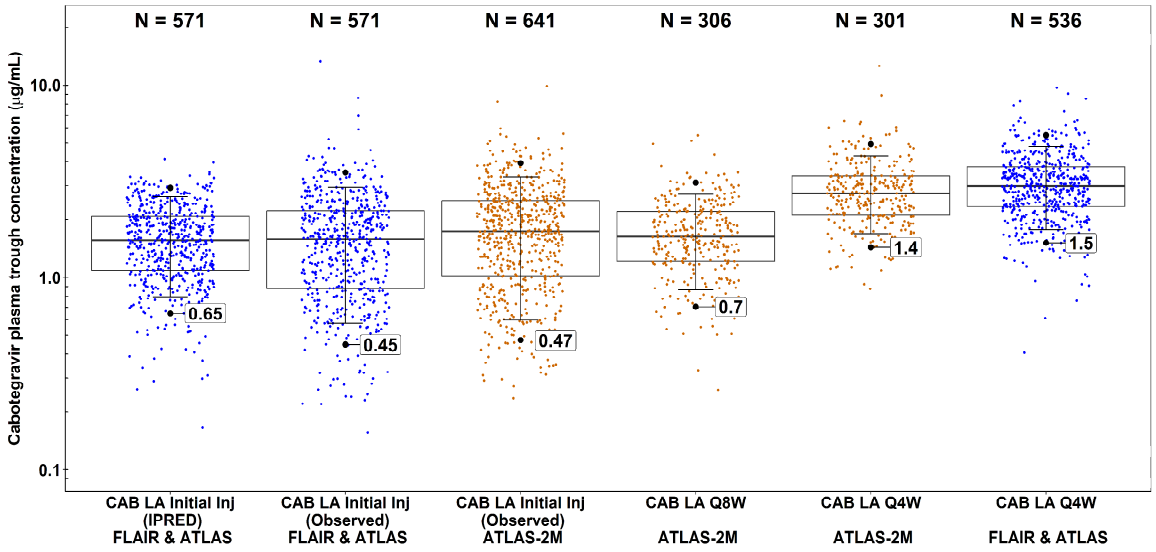
Data Source: GSK Doc. # 2020N452718_01 Figure 4.

The MVA performed on pooled Phase III/IIIb studies (201584, 201585, and 207966) using data from HIV-infected adults with no prior exposure to CAB + RPV, CVF occurred infrequently (1.25%). RPV Ctrough, RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and high BMI had a statistically significant association with virologic failure. However, regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%)—no Baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following Baseline factors was associated with an increased risk of CVF: RPV resistance mutations, HIV-1 Subtype A6/A1, or BMI ≥30 kg/m^2 [GSK Doc. # 2020N452718_01].

3.1.1.4. Plasma CAB Ctau Used to Guide Dose Recommendations

The time to achieve steady state is prolonged with an LA regimen, as observed for CAB LA, but efficacious concentrations are achieved following the initial IM injection. A plasma CAB Ctau of 0.65 µg/mL is the model-predicted (IPRED) 5th percentile of Ctau after the initial injection in the Phase III studies (201584 and 201585) that demonstrated that CAB + RPV Q4W is noninferior to CAR (Section 2.2). The model-predicted value of 0.65 µg/mL is higher than the observed 5th percentile of CAB Ctau (0.45 µg/mL) after the initial injection and is used for conservative interpretation of simulated data. The observed 5th percentile plasma CAB Ctau was similar in Phase IIIb Study 207966 (0.47 µg/mL) and the efficacy of the CAB + RPV Q8W regimen in Study 207966 provides further support for use of the CAB Ctau value of 0.65 µg/mL (Figure 25, Table 89). Recommendations for re-initiation of CAB LA after missed doses or oral therapy were based on simulations where ≥95% of patients achieve a plasma CAB Ctau ≥0.65 µg/mL.

Figure 25 Comparison of CAB Ctau Concentrations Following Initial Injection and at Week 48 Across Studies and Regimens in HIV-1-infected Patients



Data Source: GSK Doc. # 2019N421460_00 Figure 2

For each boxplot, the middle of the box is the median, the outside of the box is the IQR, the whiskers are the 10th and 90th percentiles, black dots are the 5th and 95th percentiles, colored dots are individual subject concentrations.

CAB LA Initial Inj: plasma CAB Ctau 4 weeks following the initial IM injection of CAB 600 mg (+ RPV 900 mg).

CAB LA Q4W: plasma CAB Ctau at Week 48 for IM CAB 400 mg Q4W (+ RPV 600 mg Q4W).
CAB LA Q8W: plasma CAB Ctau at Week 48 for IM CAB 600 mg Q8W (+ RPV 900 mg Q8W).
Note: CAB LA Q8W and Q4W ATLAS-2M (Week 48) is for the stratum with no prior CAB LA + RPV LA exposure.

FLAIR = Study 201584, ATLAS = Study 201585, ATLAS-2M = Study 207966.

3.1.2. CAB Exposure-Response Relationships for Safety Endpoints

A plasma CAB Cmax of 13.1 µg/mL represents the geometric mean Cmax value observed with chronic dosing of the highest oral CAB regimen of 60 mg once daily for up to 96 weeks. No safety concerns were associated with these concentrations.

In the TQT study, a supratherapeutic dose of oral CAB 150 mg Q12h x 3 doses had no effect on cardiac repolarization, there was no relationship between plasma CAB concentrations and ddQTcF, and there were no other safety findings with this regimen [Data Source: GSK Doc. # 2014N208600_00 Section 5]. The geometric mean CAB Cmax of 22.5 µg/mL observed with the supratherapeutic dose is approximately 2.8-fold, 5.4-fold, and 5.6-fold above the 30 mg oral once-daily dose, the CAB LA 400 mg monthly dose, and the CAB LA 600 mg every 2 months dose, respectively (Table 91).

No relationships between plasma CAB concentrations and safety parameters of interest, including QTc, ALT, and total bilirubin, were identified in the CAB + RPV Phase III Studies 201584, 201585, and 207966 [Data Source: GSK Doc. # 2017N345267_00

Section 8.5; GSK Doc. # 2018N370336_00 Section 8.5; GSK Doc. # 2019N406358_01 Section 8.5].

Table 91 Summary of Plasma CAB Cmax for Highest Doses Tested vs. Proposed Doses

Cmax (μg/mL) [a] Geometric mean				Cmax Ratio		
Oral CAB 150 mg Q12h x 3 doses	Oral CAB 30 mg QD	CAB LA 400 mg IM monthly	CAB LA 600 mg IM every 2 months	Oral CAB 150 mg Q12h x 3 dose vs. Oral CAB 30 mg QD	Oral CAB 150 mg Q12h x 3 dose vs. CAB LA 400 mg IM monthly	Oral CAB 150 mg Q12h x 3 dose vs. CAB LA 600 mg IM every 2 months
22.5	8.0	4.2	4.02	2.8	5.4	5.6
Oral CAB 60 mg QD x 96 weeks	Oral CAB 30 mg QD	CAB LA 400 mg IM monthly	CAB LA 600 mg IM every 2 months	Oral CAB 60 mg QD vs. Oral CAB 30 mg QD	Oral CAB 60 mg QD vs. CAB LA 400 mg IM monthly	Oral CAB 60 mg QD vs. CAB LA 600 mg IM every 2 months
13.1	8.0	4.2	4.02	1.6	3.1	3.3

Data Source:
Oral CAB 150 mg Q12h x 3 doses: GSK Doc. # 2014N208600_00 Table 12
Oral CAB 60 mg once daily: GSK Doc. # 2014N216014_00, Table 9.4
Oral CAB 30 mg once daily: GSK Doc. # 2018N384611_01 Table 17
CAB LA 400 mg IM monthly: GSK Doc. # 2018N384611_01 Table 17
CAB LA 600 mg IM every 2 months: GSK Doc. # 2019N421460_00, Table 14
a. Cmax is at steady-state for oral CAB once daily doses and at Week 48 for CAB LA

3.1.3. Summary of CAB Pharmacokinetics for Proposed CAB + RPV Dosage Regimens

CAB LA + RPV LA is a complete ARV regimen; the safety and efficacy of the proposed CAB + RPV monthly and CAB + RPV every 2 months regimens were established in Studies 201584, 201585, and 207966 (Section 2.1.1.1, m2.7.3, m2.7.4).

CAB + RPV Regimens consist of OLI + Initiation IM Injection + Continuation IM Injections.

- OLI: CAB 30 mg once daily + RPV 25 mg once daily for 1 month (at least 28 days)
- Initiation IM Injection: CAB LA 600 mg + RPV LA 900 mg administered on the same day as the last OLI dose
- Continuation IM Injections:
  - CAB LA + RPV LA monthly: CAB LA 400 mg + RPV LA 600 mg 1 month after initiation IM injection and monthly thereafter
  - CAB LA + RPV LA 2-monthly: CAB LA 600 mg + RPV LA 900 mg 1 month after initiation IM injection then every 2 months thereafter

Plasma CAB PK parameters for the proposed regimens are summarized in Table 92.

Table 92 Summary (Geometric Mean [5th, 95th Percentile]) of CAB PK Parameters following Administration of Proposed CAB + RPV Regimens in HIV-infected Subjects

Drug	Dosing Phase	Dosage Regimen	Plasma CAB PK Parameter		
			AUC(0-tau) (μg•h/mL)	Cmax (μg/mL)	Ctau (μg/mL)
CAB	Oral Lead-In [a]	30 mg PO once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
	Initial Injection [b]	600 mg IM Initial Dose	1,591 (714, 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
	Monthly Injection [c]	400 mg IM monthly	2,415 (1494, 3645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
	Every 2 months Injection [c]	600 mg IM Every 2 months	3764 (2431, 5857)	4.02 (2.26, 6.83)	1.61 (0.80, 2.99)

Data Source: GSK Doc. # 2018N384611_01 Table 17; GSK Doc. # 2019N421460_00, Table 14

- OLI, initial injection, and monthly injection: GSK Doc. # 2018N384611_01 Table 17
- Every two months injection: GSK Doc. # 2019N421460_00 Table 14

a. OLI PK parameter values represent steady-state.
b. Initial Injection Cmax values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose.
c. Monthly and every 2 months injection PK parameter values represent Week 48 (11th injection for monthly and 6th injection for every 2 months).

PK parameter values were based on individual post-hoc estimates from the final PopPK model and are presented as geometric mean (5^{th}, 95^{th} percentile).

3.1.4. Missed Injections and Use of Oral Therapy for Management of Planned Missed Injections

3.1.4.1. Impact of Delayed Doses on CAB PK

Across Phase III studies, most (98 to 99%) of the injection visits were within the allowable ±7-day window. One to 3% of subjects received oral therapy to cover delays in LA dosing during maintenance treatment, and the majority resumed LA dosing thereafter. No cases of CVF or virologic blips were observed during the period of oral therapy or following resumption of CAB LA + RPV LA dosing. See module 2.7.4 Section 3.6.2 for details on oral therapy experience across clinical studies.

CAB LA and RPV LA doses should be administered within ± 7 days of the scheduled day and adherence to the injection dosing schedule is recommended. Doses administered beyond the 7-day window are considered missed doses and may result in <95% of patients achieving plasma CAB Ctau >0.65 μg/mL (Section 3.1.1.4, Table 93, Table 94).

Table 93 Impact of Missed CAB LA Injection for Monthly Regimen

	Time Since Last Injection (Dose Delay) Proportion (%) of Subjects with Plasma CAB Ctau >0.65 μg/mL (at time of delay)							
Delayed Injection	**4W (No delay)**	**5W (1W delay)**	**6W (2W delay)**	**7W (3W delay)**	**8W (4W delay)**	**10W (6W delay)**	**12W (8W delay)**	**16W (12W delay)**
2nd IM injection	93.3[a]	92.3	90.1	87.6	81.2	61.2	37.9	10.2
3rd IM injection	98.1	97.8	97.2	94.0	91.3	79.4	64.9	35.3
4th IM injection	99.2	99.0	98.2	96.1	92.9	85.3	72.5	48.4

Data Source: GSK Doc. # 2018N384611_01 Table 22

a. Less than 95% of subjects were predicted to achieve a plasma CAB Ctau >0.65 μg/mL following the first injection, which may be a result of a difference in sampling times between the simulation (exactly 4 weeks) and IPRED (mean 3.9 weeks; range 2.1 to 5.1 weeks).

Table 94 Impact of Missed CAB LA Injection for Every 2 Months Regimen

	Time Since Last Injection (Dose Delay) Proportion (%) of Subjects with Plasma CAB Ctau >0.65 μg/mL (at time of delay)							
Delayed Injection	**4W (No delay)**	**5W (1W delay)**	**6W (2W delay)**	**7W (3W delay)**	**8W (4W delay)**	**10W (6W delay)**	**12W (8W delay)**	**16W (12W delay)**
2nd IM injection	94.3 [a]	92.8	90.7	87.5	80.8	60.8	38.8	10.2
Delayed Injection	**8W (No delay)**	**9W (1W delay)**	**10W (2W delay)**	**11W (3W delay)**	**12W (4W delay)**	**14W (6W delay)**	**16W (8W delay)**	**20W (12W delay)**
3rd IM injection	95.7	92.5	88.3	83.6	77.8	65.2	51.9	28.1
4th IM injection	95.2 [b]	91.3 [c]	87.2	82	77.1	65.9	55.1	36

Data Source: GSK Doc. # 2019N421460_00 Table 19.

a. Less than 95% of subjects were predicted to achieve a plasma CAB Ctau >0.65 μg/mL following the first injection, which may be a result of a difference in sampling times between the simulation (exactly 4 weeks) and IPRED (mean 3.9 weeks; range 2.1 to 5.1 weeks).
b. 95.24% for the 5th or subsequent injections.
c. 91.1% for the 5th or subsequent injections.

3.1.4.2. Recommendations for Resuming Injection Dosing After Missed Injections, with or without Oral Therapy

If a patient misses a scheduled dose, the next dose should be given as soon as possible, and the time since the last dose will determine how LA dosing should be resumed. Recommendations for resuming injection dosing after missed injections (Table 95, Table 96) are based on simulations aimed at keeping plasma CAB Ctau >0.65 μg/mL in >95% of patients (Table 97, Table 98). A conservative approach was taken regarding the time-frame in which re-initiation with the loading dose is recommended. The

recommendations are irrespective of whether oral CAB + RPV dosing was used during the interruption in the IM dosing regimen.

If a patient plans to miss a scheduled injection by more than 7 days, oral therapy (oral CAB 30 mg + oral RPV 25 mg once daily) should be used. Oral therapy is recommended for a duration of up to 2 months, consistent with Phase III study conduct. Daily oral therapy should start at the time of the planned missed injections and end on the day injection dosing was restarted. The impact of oral therapy on the CAB plasma concentration-time profile is presented in population PK reports [Data Source: GSK Doc. # 2018N384611_01 Section 5.3.4; GSK Doc. # 2019N421460_00 Section 4.3.4].

Table 95 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy (Monthly Regimen)

Time Since Last Injection	Recommendation
≤2 months	Continue with the monthly 2 mL (400 mg) injections dosing schedule as soon as possible.
>2 months	Re-initiate the patient with the 3-mL (600 mg) injections, and then continue to follow the monthly 2 mL (400 mg) injection dosing schedule.

Table 96 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy (Every Two Months Regimen)

Missed Injection Visit	Time Since Last Injection	Recommendation (all injections are 3 mL)
Injection 2	≤2 months	Resume with 3 mL (600 mg) injections as soon as possible and continue with the every 2 month injection dosing schedule.
	>2 months	Re-initiate the patient with the 3 mL (600 mg) injections, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every 2 month injection dosing schedule.
Injection 3 or later	≤3 months	Resume with 3 mL (600 mg) injections as soon as possible and continue with the every 2 month injection dosing schedule.
	>3 months	Re-initiate the patient on the 3 mL (600 mg) injections, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every 2 month injection dosing schedule.

Table 97 Impact of Resuming CAB LA 400 mg (2 mL) or 600 mg (3 mL) IM Following Missed Injection (Monthly Regimen)

	Time Since Last Injection (Dose Delay) (Resume Dosing [R] or Reinitiate Dosing [RI]) Proportion (%) of Subjects with Plasma CAB Ctau >0.65 μg/mL **(1 month after resuming dosing)**						
Delayed Injection	**6W (2W delay) [R, 2mL]**	**7W (3W delay) [R, 2mL]**	**8W (4W delay) [R, 2mL]**	**12W (8W delay) [R, 2mL]**	**12W (8W delay) [RI, 3mL]**	**16W (12W delay) [R, 2mL]**	**16W (12W delay) [RI, 3mL]**
2nd IM injection	98.0	98.6	98.3	97.1	99.1	96.2	99.0
3rd IM injection	99.7	99.1	99.4	99.1	99.7	98.2	99.6
4th IM injection	99.7	99.8	99.6	99.4	99.9	99.4	99.8

Data Source: GSK Doc. # 2018N384611_01 Table 23

R: Resume with 2 mL injections as soon as possible and continue with the monthly injection dosing schedule.

RI: Re-initiate the patient with the 3-mL injections, then follow the monthly 2 mL injection dosing schedule.

Table 98 Impact of Resuming [R] or Reinitiating [RI] CAB LA 600 mg IM Every 2 Months Regimen Following Missed Injection (Every Two Months Regimen)

	Time Since Last Injection (Dose Delay) (Resume Dosing [R] or Reinitiate Dosing [RI]) Proportion (%) of Subjects with Plasma CAB Ctau >0.65 μg/mL **(8 weeks after resuming dosing)**									
Delayed Injection	**6W (2W delay) [R]**	**7W (3W delay) [R]**	**8W (4W delay) [R]**	**8W (4W delay) [RI]**	**10W (6W delay) [R]**	**10W (6W delay) [RI]**	**12W (8W delay) [R]**	**12W (8W delay) [RI]**	**16W (12W delay) [R]**	**16W (12W delay) [RI]**
2nd IM injection	94.7	94.2	93.7	95	92.8	94.8	92.2	94.7	90.9	94.7
Delayed Injection	**10W (2W delay) [R]**	**11W (3W delay) [R]**	**12W (4W delay) [R]**	**12W (4W delay) [RI]**	**14W (6W delay) [R]**	**14W (6W delay) [RI]**	**16W (8W delay) [R]**	**16W (8W delay) [RI]**	**20W (12W delay) [R]**	**20W (12W delay) [RI]**
3rd IM injection	94.4	94.1	93.8	95	93.3	95	92.8	94.9	92.1	94.8
4th IM injection	94.4	94.2	93.9	95	93.4	95	93	95	92.4	94.9

Data Source: GSK Doc. # 2019N421460_00 Table 20.

R: Resume with 3 mL injections as soon as possible and continue with the every 2 months injection dosing schedule.

RI: Re-initiate the patient with the 3 mL injections, followed by a second 3 mL initiation injection one month later. Then follow the every 2 months injection dosing schedule.

3.1.5. Management of CAB + RPV Discontinuation

Alternative HAART should be initiated as soon as feasible, no later than 1 month following discontinuation of the CAB + RPV monthly regimen and no later than 2 months following discontinuation of the CAB + RPV every 2 months regimen, to maintain suppression of viral load and to reduce the chance of CAB or RPV resistance emerging while concentrations of CAB and RPV are waning. Based on the in vitro and clinical drug interaction profile, CAB and RPV are not expected to alter concentrations of other ARV medications including protease inhibitors, NNRTIs, NRTIs, INIs, entry inhibitors, and ibalizumab (Section 3.2.9.2).

3.1.6. Clinically Relevant Drug Interactions

Drug interactions resulting in contraindication or precaution with CAB are described in Table 99 and in the text following the table. Further discussion of CAB drug interaction data is presented in Section 3.2.9.

Table 99 Established and Other Potentially Significant Drug Interactions for CAB + RPV

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
Anticonvulsants: Carbamazepine Oxcarbazepine Phenobarbital Phenytoin	↓Cabotegravir	Co-administration is **contraindicated** with CAB due to potential for loss of therapeutic effect and development of resistance.
Antimycobacterials: Rifampin Rifapentine Rifabutin [a]	↓Cabotegravir	

↑ = Increase, ↓ = Decrease, ↔ = No change.

a. Clinically relevant decrease in RPV with rifabutin co-administration; plasma CAB concentrations are not significantly decreased.

Co-administration of oral CAB with antacids containing polyvalent cations may result in decreased plasma concentrations.

- Antacids containing polyvalent cations must be administered at least 2 hours before or 4 hours after oral CAB + oral RPV.

3.1.7. Unexpectedly high Post Injection Concentrations

Occasional 2h post-injection sampling was performed at specified visits in Phase IIb/III studies to evaluate injection performance. For the Phase IIIb Study 207966 (ATLAS-2M), 2h post-injection sampling was no longer performed per protocol. Approximately 2500 2h post-injection samples were analyzed for each CAB and RPV (Table 102). CAB 2h plasma concentrations above 22.5 μg/mL, the geometric mean Cmax following oral CAB 150 mg q12h in the TQT study, were considered high at 8- to 14-fold above

expected pre-dose concentrations for monthly and every 2 month regimens (as minimal absorption from IM injections would be expected) and 5.6-fold above Cmax for oral CAB 30 mg once daily. RPV 2h concentrations above 800 ng/mL were considered high as these were 9.7- to 12-fold above expected pre-dose concentrations (and minimal absorption from IM injections would be expected). These criteria were met for 17 CAB samples and 21 RPV samples (Table 100, Table 101, Table 102), likely due to inadvertent partial injection into a vein (maladministration), with an overall rate of occurrence across the program of 0.68% for CAB and 0.84% for RPV (Table 102). For either drug, unexpectedly high 2h concentrations were not observed on more than one occasion in any subject, consistent with random occurrence. Maladministration of an IM injection, with partial intravenous administration, could also result in lower than expected CAB or RPV plasma concentrations at the next injection visit. This is more likely to result in a low pre-dose concentration when it occurs following an initiation injection compared to it occurring later on in-treatment when absorption from prior injections is ongoing.

Table 100 Cross Study Listing of Subjects with Unexpectedly High CAB 2h Post Injection Concentrations

Study	Subject	Visit	CAB (μg/mL)	CAB Next Available Ctau (μg/mL)
201585/ 207966 (CAR switch subjects)	[redacted]	Week 4b	39.3	2.02 (Week 8)
		Week 48	23.0	2.29 (Week 52)
		Week 48	28.3	2.38 (Week 52)
		Week 56b	67.8	0.108 (Week 60) [a]
		Week 56b	47.8	1.41 (Week 60)
201584		Week 48	23.7	1.95 (Week 52)
		Week 48	30.9	3.37 (Week +52)
		Week 48	104	3.89 (Week 52)
		Week 48	70.9	1.46 (Week 52)
		Week 96	26.3	1.52 (Week 100)
		Week 96	56.8	2.9 (Week 100)
		Week 96	28.2	3.31 (Week 100)
200056		Day 1	29.4	1.85 (Week 4)
		Day 1	24.6	8.66 (Week 4)
		Week 48	47.1	0.996 (Week 56)
		Week 32	53.6	2.36 (Week 36)
		Week 48	23.7	1.33 (Week 56)

Data Source: GSK Doc. # 2019N399072_00 Week 96 Listing 121; GSK Doc. # 2019N421511_00 Week 96 Listing 32; GSK Doc. # 2018N380094_00 Week 160 Listing 10.1002; GSK Doc. # 2018N360914_00 Week 128 Listing 4.1001

a. <PA-IC90 (0.166 μg/mL)

Table 101 Cross Study Listing of Subjects with Unexpectedly High RPV 2h Post Injection Concentrations

Study	Subject	Visit	RPV (ng/mL)	RPV Next Available Ctau (ng/mL)
201585/ 207966 (CAR switch subjects)	[redacted]	Week 4b	1830	1.92 (Week 8) [a]
		Week 48	1850	62.3 (Week 52)
		Week 56b	960	Not available
201584		Week 48	1210	93.7 (Week 52)
		Week 48	2200	101 (Week 52)
		Week 48	1090	88.9 (Week 52)
		Week 96	858	119 (Week 100)
		Week 96	811	72.1 (Week 100)
		Week 96	1140	71 (Week 100)
		Week 100	2190	11.3 (Week 104a)
		Week 104b	1430	Not available
200056		Week 32	1020	65.9 (Week 36)
		Day 1	2390	NQ (Week 8) [b]
		Week 48	4170	69.4 (Week 56)
		Day 1	830	39.4 (Week 8)
		Week 32	1720	58.4 (Week 36)
		Week 48	1260	68 (Week 56)
		Week 48	887	76.3 (Week 56)
		Day 1	2170	NQ (Week 8) [c]
207966	[redacted] [d]	Unscheduled	1400	Withdrawn
	[redacted] [e]	Unscheduled	1450	Withdrawn

Data Source: GSK Doc. # 2019N399072_00 Week 96 Listing 122; GSK Doc. # 2019N421511_00 Week 96 Listing 33; GSK Doc. # 2018N380094_00 Week 160 Listing 10.1004; GSK Doc. # 2018N360914_00 Week 128 Listing 4.1002; GSK Doc. # 2019N406358_01 Week 48 Listing 30

a. Week 8 HIV RNA 61 c/mL (RPV < PA-IC90 (12 ng/mL), CAB pre-dose 2.52 μg/mL), HIV RNA <50 c/mL at Week 12 (pre-dose RPV 17.8 ng/mL; CAB 2.63 μg/mL) and at all other.
b. W8 concentration nonquantifiable (NQ), PDVF confirmed at Week 8
c. W8 concentration nonquantifiable (NQ), RPV 1.71 ng/mL at Week 4
d. Post-injection reaction (see Section 2.1.7, m2.7.4)
e. Post-injection reaction (see Section 2.1.7, m 2.7.4)

Table 102 Summary of Incidence of Unexpectedly High 2h Post Injection Concentrations

Study	CAB			RPV		
	Concentrations >22.5μg/mL [a]	Total 2h conc values [b]	Rate (%)	Concentrations >800ng/mL [c]	Total 2h conc values [d]	Rate (%)
200056	5	716	-	8	707	-
201585	5	788	-	3	786	-
201584	7	995	-	8	1000	-
207966	0	2	-	2	2	-
Overall	**17**	**2501**	**0.68**	**21**	**2495**	**0.84**

Data Source:

a. GSK Doc. # 2018N380094_00 Week 160 Listing 10.1002; GSK Doc. # 2018N360914_00 Week 128 Listing 4.1001; GSK Doc. # 2019N399072_00 Week 96 Listing 121; GSK Doc. # 2019N421511_00 Week 96 Listing 32; GSK Doc. # 2019N406358_01 Week 48 Listing 29

b. GSK Doc. # 2018N380094_00 Week 160 Listing 10.1001; GSK Doc. # 2018N360914_00 Week 128 Listing 4.1001; GSK Doc. # 2019N399072_00 Table 14.1 (Q4W) and Table 14.2 (CAR switch); GSK Doc. # 2019N421511_00 Week 96 Table 4.1; GSK Doc. # 2019N406358_01 Week 48 Listing 29.

c. GSK Doc. # 2018N380094_00 Week 160 Listing 10.1004; GSK Doc. # 2018N360914_00 Week 128 Listing 4.1002; GSK Doc. # 2019N399072_00 Listing 122; GSK Doc. # 2019N421511_00 Week 96 Listing 33; GSK Doc. # 2019N406358_01 Week 48 Listing 30.

d. GSK Doc. # 2018N380094_00 Week 160 Table 10.1002; GSK Doc. # 2018N360914_00 Week 128 Table 4.1002; GSK Doc. # 2019N399072_00 Table 14.3 (Q4W) and Table 14.4 (CAR switch); GSK Doc. # 2019N421511_00 Week 96 Table 4.2; GSK Doc. # 2019N406358_01 Week 48 Listing 30.

3.2. Cabotegravir

3.2.1. Comparison of Pharmacokinetics between Healthy and HIV-1-infected Subjects

Similar plasma CAB exposure between healthy and HIV-1-infected subjects supports extrapolation of data generated in healthy subjects, such as drug and food interactions and the TQT study, to the HIV-1-infected population. Plasma CAB PK parameter values following administration of CAB LA and oral CAB are similar between healthy and HIV-1-infected subjects based on results of cross-study comparisons (Table 103, Table 104). Consistent with this, population (healthy vs. HIV-infected) was not a significant covariate in the PopPK analysis [Data Source: GSK Doc. # 2018N384611_01 Table 15]

Table 103 Comparison of Plasma CAB PK between Healthy and HIV-infected Subjects Receiving CAB LA

CAB LA Regimen	Study (Population) [n]	PK Sampling (time relative to dose)	Dosing Interval (Dose, Injection No.)	Plasma CAB PK Parameter Geometric Mean (CVb%)					
				AUC(0-tau) (μg.h/mL)	Cmax (μg/mL)	C144 (μg/mL)	Ctau/C648 (μg/mL)	tmax [a] (day)	t1/2 (days)
800 mg IM Single Dose	LAI114433 (Healthy) [n=6]	Dose 1: 0, 4, 8, 12, 24, 48, 72, 96, 120, 144 (D7), 216, 312, 480, 648h (D28), then Week 5, 6, 8, 10, 12, then Q4wk [b]	D1 (800 mg, Injection 1)	1497 (79.2)	3.3 (75.1)	3.48 [a] (0.80-8.27)	2.0 (76.9)	7.58 (5.0-147)	25.4 (51.7) [c]
800 mg IM Q12W	201120 (Healthy) [n=93]	Dose 1: 0, 144, 648h, then Week 8, 12		3415 (42.5)	4.26 (88.6)	4.96 [a] (0.373-13.7) [n=70]	2.46 [a] (0.426-6.12) [n=73]	7.76 (4.95-57.0)	18.4 (48.4) [n=61]
800 mg IM D1 + 400 mg IM Q4W	LAI115428 Cohort 3 (Healthy) [n=10]	Dose 1: 0, 4, 48, 144 (D7), 312, 480, 648h (D28)		1252 (61)	2.74 (72)	2.27 [a] (0.66-7.24)	1.78 (41)	6 (6–28)	-
	200056 (HIV) [n=115]	Dose 1: 0 [d], 2 [d], 144 (D7), 648h (D28)		-	-	3.72 [a] (0.506-17.4)	1.84 [a] (0.47-5.49) [n=114]	-	-
800 mg IM D1 + 400 mg IM Q4W	LAI115428 Cohort 3 (Healthy) [n=10]	Dose 4: 0, 4, 48, 144, 312, 480, 648h	W12-W16 (400 mg Injection 4)	2473 (26)	4.41 (31)	4.28 [a] (2.36-6.78)	3.27 (27)	6 (2–13)	30.5 (37) [n=6]
	200056 (HIV) [n=115]	Dose 4: 0, 144, 648h	W12-W16 (400 mg Injection 4)	-	-	-	2.13 [a] (0.815-6.55) [n=112]	-	-
		Dose 6: 0, 144, 648h	W24-W28 (400 mg Injection 6)	1858 (37) [n=84]	3.50 (39) [n=97]	-	2.35 [e] (32) [n=108]	6.9 (0–29)	-
		Dose 10: 0, 144, 648h	W40-W44 (400 mg Injection 10)	2017 (41) [n=80]	3.50 (37) [n=95]	-	2.56 [e] (32) [n=98]	6.9 (0–28)	-

Data Source: GSK Doc. # 2013N159605_00 Table 11.2, Table 11.4; GSK Doc. # 2013N159813_01 Table 3.1, Table 14; GSK Doc. # 2016N273084_00 Week 48 Table 10.1001, Table 10.1010; Table 58; GSK Doc. # 2016N269422_00 Week 81 Table 9.1, Table 9.2

a. Data presented as median (minimum-maximum)
b. Study LAI114433: After Week 12, subjects continued plasma PK sampling Q4W until plasma CAB concentration was <0.10 μg/mL or the subject reached Week 24 and any AEs were resolved/stabilized.
c. Study LAI1114433 t1/2 presented as range of geometric means across the CAB LA IM treatments of 100, 200, 400, and 800 mg IM.
d. Study 200056: The last dose of oral CAB (induction phase) was administered on same day as CAB LA Injection 1; therefore, 0 h and 2 h concentrations reflect oral dosing and are not reported in this table.
e. Study 200056 W24-W28 Ctau was the individual average of Weeks 20, 24, 28, 32 and W40-44 Ctau was the individual average of Weeks 40, 44, and 48.

Table 104 Comparison of Plasma CAB PK between Healthy and HIV-infected Subjects Receiving Oral CAB 30 mg Tablet Once Daily

Population	Study (n)	Study Part	Plasma CAB PK Parameter			
			Geometric mean (CVb%)			Median (min-max)
			AUC(0-tau) (μg.h/mL)	Cmax (μg/mL)	Ctau (μg/mL)	tmax (h)
Healthy Subjects	LAI115428 (n=43)	Oral alone	147 (27)	8.30 (26)	4.87 (30)	2.0 (1.0-8.0)
	LAI116815 (n=12)	MDZ DDI	120 (25)	7.01 (23)	4.09[a] (2.38-5.88)	2.00 (1.00-4.0)
	205712 (n=12)	Oral alone	104 (28.3)	6.36 (24.7)	3.36 (34.3)	3.00 (1.00-4.00)
HIV-infected Subjects	LAI116482 (n=12)	Induction Phase +2 NRTIs	134 (32)	7.49 (28)	4.20 (40)	2.0 (1.0–8.0)
	200056 (n=246)	Induction Phase +2 NRTIs	-	-	4.22 (43)	-
	201585 W4b	OLI +RPV	-	7.78 (33) [n=283]	4.69 (41) [n=259]	-
	201584 W4b	OLI +RPV	-	8.33 (42) [n=267]	5.22 (56) [n=243]	-
	207966 W4b (Q8W group)	OLI +RPV	-	-	5.18 (45) [n=282]	-
	207966 W4b (Q4W group)	OLI +RPV	-	-	5.29 (43) [n=292]	-

Data Source: GSK Doc. # 2013N159813_01 Table 14; GSK Doc. # 2014N208332_00 Table 14, Table 3.2; GSK Doc. # 2017N334381_00 Table 11; GSK Doc. # 2014N216014_00 Week 96, Table 52; GSK Doc. # 2015N246053_00 Week 32 Table 57; GSK Doc. # 2017N345267_00 Week 48 Table 4.3; GSK Doc. # 2018N370336_00 Week 48 Table 4.3; GSK Doc. # 2019N406358_01 Table 4.5
W4b = Week 4b visit. This visit represents the day the final OLI doses and initial LA doses were administered. Plasma concentrations at the Week 4b visit reflect steady-state conditions following oral administration with negligible contribution from initial IM injections.

3.2.2. Dose Proportionality

Overall, plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat dose administration of CAB LA 100 to 800 mg IM and oral CAB 5 to 60 mg (Table 105). Following single-dose administration of a higher dose of oral CAB 150 mg, geometric mean plasma CAB Cmax (10.4 μg/mL) and AUC(0-inf) (418 μg.h/mL, Table 58) were markedly lower than expected compared with oral CAB 30 mg (geometric mean Cmax of 3.61 μg/mL and AUC(0-inf) of 146 μg.h/mL, Table 76).

Table 105 Summary of Dose Proportionality in Plasma CAB PK Parameters by Route of Administration, Dosage Form, Dosage Regimen, and Population (Power Model)

CAB Dosage Regimen	Plasma CAB PK Parameter	Slope (90% CI)
CAB LA Single Dose Healthy Subjects (Study LAI114433)		
100, 200, and 400 mg IM Single Dose	AUC(0-inf)	0.814 (0.601, 1.03)
	Cmax	0.722 (0.437, 1.01)
400 mg (2 x 200 mg) and 800 mg (2 x 400 mg) IM Single Dose	AUC(0-inf)	1.13 (0.588, 1.67)
	Cmax	1.26 (0.456, 2.06)
CAB Oral Suspension Single Dose & Once Daily Healthy Subjects (Study ITZ111451)		
5, 10, 25, and 50 mg Single Dose	AUC(0-t)	0.926 (0.885, 0.968)
	Cmax	0.847 (0.801, 0.894)
5, 10, 25 mg Once Daily	AUC(0-tau)	0.986 (0.892, 1.080)
	Cmax	0.938 (0.847, 1.030)
	Ctau	1.006 (0.892, 1.120)
CAB Oral Tablet Once Daily HIV-1-infected Subjects (Study LAI116482, Intensive PK Subgroup)		
10, 30, and 60 mg Once Daily	AUC(0-tau)	0.907 (0.763, 1.051)
	Cmax	0.873 (0.747, 1.000)
	Ctau	0.817 (0.649, 0.986)

Data Source: GSK Doc. # 2013N159605_00 Table 11.5; GSK Doc. # RM2008/00633/00 Table 23, Table 24; GSK Doc. # 2014N216014_00 Week 96 Table 9.6

3.2.3. Accumulation and Time to Steady-State

For CAB LA, time to steady-state is driven by administration of a higher initial dose and the absorption rate following IM injection. The time to steady state was approximately

44 weeks following administration CAB LA as an initial dose (800 mg or 600 mg IM) on Day 1 followed by 400 mg IM Q4W in Phase III Studies 201585 and 201584 [Data Source: GSK Doc. # 2017N345267_00 Section 8.1; GSK Doc. # 2018N370336_00 Section 8.1]. Steady state was achieved by 48 weeks following administration of CAB LA as an initial dose of 600 mg IM on Day 1 and at Week 4, followed by 600 mg IM Q8W in Phase IIIb Study 207966 [Data Source: GSK Doc. # 2019N406358_01 Section 8.3]. The time to achieve steady state is prolonged with CAB LA with efficacious concentrations achieved following the initial dose (Section 3.1.1.4).

Steady-state plasma CAB concentrations are achieved by Day 7 following once daily administration of oral CAB in HIV-1-infected subjects (Section 2.6.3.2, Section 2.6.3.3), consistent with the approximate 2.5-fold accumulation (Table 106) and a t1/2 of approximately 41 hours (Table 109).

Table 106 Summary of Accumulation in Plasma CAB PK Parameters Following Administration of Oral CAB in HIV-1-infected Subjects

CAB Dosage Regimen (Study)	N	Day 10 vs. Day 1 Geometric Mean Ratio (90% CI)		
		AUC(0-tau)	Cmax	Ctau
CAB Oral Tablet 5 mg Once Daily (ITZ112929)	7	2.36 (2.09, 2.66)	1.96 (1.68, 2.28)	2.48 (2.14, 2.88)
CAB Oral Tablet 30 mg Once Daily (ITZ111451)	8	2.51 (2.27, 2.78)	2.24 (1.99, 2.53)	2.62 (2.35, 2.93)

Data Source: GSK Doc. # RM2009/00485/00 Table 12; GSK Doc. # RM2008/00633/00 Table 25

3.2.4. Time Invariance

Based on cross-study comparison, plasma CAB PK is time-invariant because plasma CAB AUC(0-tau) following repeat dosing was similar to AUC(0-inf) following single dose administration of oral CAB (Table 107).

Table 107 Cross-Study Assessment of Time Invariance Following Oral CAB Administration in Healthy Subjects

CAB 30 mg PO Tablet Once Daily		CAB 30 mg PO Tablet Single Dose	
Study (n)	AUC(0-tau) [a] (μg.h/mL)	Study (n)	AUC(0-inf) [a] (μg.h/mL)
LAI115428 (n=43)	147 (27)	LAI117020 Treatment A (n=22)	141 (20)
LAI116815 (n=12)	120 (25)	201741 Treatment B (n=18)	135 (26)
205712 (n=12)	104 (28.3)	205696 Treatment A (n=21)	143 (28)
-	-	LAI117010 (n=15)	146 (23.9)

Data Source: GSK Doc. # 2013N159813_01 Table 14; GSK Doc. # 2014N208332_00 Table 14; GSK Doc. # 2017N334381_00 Table 11; GSK Doc. # 2015N248022_00 Table 10; GSK Doc. # 2014N206383_00 Table 10; GSK Doc. # 2016N298724_00 Table 3.3; GSK Doc. # 2015N263476_00 Table 9.

a. Data presented as geometric mean (CVb%)

3.2.5. Pharmacokinetic Variability

3.2.5.1. Between-Subject Variability

Moderate %CVb in plasma CAB PK was observed following repeat-dose administration of CAB. Following administration of CAB LA 400 mg Q4W in healthy or HIV-1 infected subjects, %CVb in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 26 to 39% across studies (Table 103). Following administration of oral CAB 30 mg once daily, %CVb in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 26 to 34% across healthy subject studies and 28 to 56% across HIV-1 infected subject studies (Table 104). Higher between-subject variability (41 to 89%) in plasma CAB PK was observed with single-dose administration of CAB LA (Table 103). In Phase III studies, %CVb in plasma CAB Ctau at Week 48 ranged from 39 to 47%, [Data Source: GSK Doc. # 2017N345267_00 Table 4.3; GSK Doc. # 2018N370336_00 Table 4.3; GSK Doc. # 2019N406358_01 Table 4.5 (subjects with no prior CAB + RPV exposure)].

3.2.5.2. Within-Subject Variability

Within-subject variability in plasma CAB PK was low following administration of oral CAB. Within-subject variability in plasma CAB AUC(0-tau), Cmax, and Ctau ranged from 7 to 11% following repeat dose administration of oral CAB 30 mg once daily (Table 108). Plasma CAB AUC(0-inf), Cmax, and C24 ranged from 13 to 32% following single-dose administration of oral CAB 30 mg (Table 108). Within-subject variability data are not available for CAB LA because CAB LA studies were parallel design.

Table 108 Summary of Within-Subject Variability in Plasma CAB PK in Healthy Subjects Receiving Oral CAB 30 mg Tablet

Oral CAB Dosage Regimen	Study [N]	%CVw		
		Cmax	AUC [a]	Ctau [b]
30 mg Once Daily	205712 [N=12]	11.2	7.6	6.9
30 mg Single Dose	LAI116585 [N=18]	20.7	21.6	21.0
30 mg Single Dose	LAI117020 Part A [N=22]	25.6	23.3	24.0
30 mg Single Dose	LAI117020 Part B [N=15]	19.0	15.7	17.4
30 mg Single Dose	201741 Cohort 1 [N=18]	19.9	18.5	19.3
30 mg Single Dose	201741 Cohort 2 [N=18]	26.6	24.2	31.7
30 mg Single Dose	205696 [N=21]	20.0	20.5	20.5
30 mg Single Dose	LAI117010 [N=15]	12.6	19.3	21.0

Data Source: GSK Doc. # 2017N334381_00 Table 3.5; GSK Doc. # 2012N152984_00 Table 3.6; GSK Doc. # 2014N206383_00, Table 3.9, Table 3.10; GSK Doc. # 2015N248022_00 Table 3.6; GSK Doc. # 2016N298724_00 Table 3.5; GSK Doc. # 2015N263476_00 Table 3.5.

a. AUC = AUC(0-inf) for single dose and AUC(0-tau) for once daily.

b. Ctau = C24 for single dose.

3.2.6. Absorption, Distribution, Metabolism, Excretion

Table 109 Summary of CAB ADME Properties

	Cabotegravir	
	Oral	**LA**
Absorption		
Relative bioavailability of oral to LA [a]	0.756	
tmax [b]	3 hours	7 days
Effect of moderate-fat meal (relative to fasting): AUC(0-inf) ratio [c]	1.08 (0.978, 1.20)	NA
Effect of high-fat meal (relative to fasting): AUC(0-inf) ratio [c]	1.14 (1.02, 1.28) Administer oral CAB with or without food	NA
Polyvalent cations [d]	Chelation effect in vitro ↓plasma CAB exposure; dose separation with antacids	NA
Distribution		
% bound to human plasma proteins [e]	>99.8	
Blood-to-plasma ratio [f]	0.52	
Cervical tissue-to-plasma ratio [g]	0.16 - 0.20	
Vaginal tissue-to-plasma ratio [g]	0.19 - 0.28	
Rectal tissue-to-plasma ratio [g]	0.00 - 0.08	
CSF-to-plasma ratio [h]	0.003 (CSF-to-plasma unbound >1.0)	
Metabolism		
Metabolism [i]	UGT1A1 UGT1A9 (minor)	
Elimination		
Major route of elimination	Metabolism	
CL/F [j]	0.21 L/h	0.151 L/h
t1/2 [k, l]	41 hours	5.6 to 11.5 weeks
% of dose excreted as total radioactivity (unchanged drug) in feces [m, n]	58.5 (46.8)	ND
% of dose excreted as total radioactivity (unchanged drug) in urine [n]	26.8 (0.0)	ND

a. Relative bioavailability of oral CAB vs. CAB LA is based on PopPK estimate (F1); Data Source: GSK Doc. # 2018N384611_01, Table 15
b. tmax presented as median; Data Source: GSK Doc. # 2015N246053_00 Week 32 Table 10.1003; GSK Doc. # 2016N273084_00 Week 48 Table 10.1003, Table 11.
c. Food effect results presented as geometric mean ratio (90% CI) of fed vs. fasted; CAB Data Source: GSK Doc. # 2014N206383_00 Table 11; GSK Doc. # 2016N298724_00 Table 9. The moderate-fat meal was comprised of approximately 670 kcal and 30% fat, and the high-fat meal was comprised of approximately 870 kcal and 53% fat.
d. Polyvalent cation interaction. Data Source: GSK Doc. # 2019N401615_00. In Phase III studies, polyvalent cation antacids were administered at least 2 hours before or 4 hours after oral CAB for consistency with the recommendation for oral RPV. Dose separation is not relevant for CAB LA administered IM because the interaction with oral CAB occurs in the GI tract.

e. Plasma protein binding based on average values for oral CAB 30 mg (Data Source: GSK Doc. # 2016N274024_00 Table 10; GSK Doc. # 2016N273991_00) and CAB LA Q4W IM and Q8W IM (Table 20; GSK Doc. # 2018N367168_00 Table 6).
f. Blood-to-plasma ratio represents ratio of geometric mean total radioactivity AUC(0-inf) for blood vs. plasma for oral [^{14}C]-CAB. CAB Data Source: GSK Doc. # 2013N167401_01 Table 11.
g. Tissue-to-plasma ratios presented as range of overall median values for single doses of CAB LA 400 mg (1 x 400 mg) IM (samples collected at 2 and 8 weeks) and CAB LA 400 mg (2 x 200 mg) IM (samples collected at 4 and 12 weeks); Data Source: GSK Doc. # 2013N159605_00 Table 11.10.
h. CSF-to-plasma ratio presented as median for CAB LA Q4W and Q8W IM. Data Source: GSK Doc. # 2018N367168_00 Table 3.1 and Table 3.5. CSF-to-unbound plasma ratio based on overall median concentration in CSF vs. overall median unbound concentration in plasma at corresponding time point. Data Source: GSK Doc. # 2018N367168_00 Table 3.1 and Table 3.5.
i. Metabolism; Data Source: Section 2.6.1.2; m2.6.4, Section 5.1.1, Section 5.1.2.
j. CL/F presented as geometric mean for oral CAB [Data Source: GSK Doc. # 2016N298724_00 Table 3.3] and as estimate from the CAB PopPK analysis for CAB LA; Data Source GSK Doc. # 2018N384611_01 Table 15.
k. t1/2 presented as geometric mean for oral CAB [Data Source: GSK Doc. # 2016N298724_00 Table 3.3] and as PopPK estimates for males and females for CAB LA [Data Source: GSK Doc. # 2018N384611_01 Section 5.2.3.1].
l. CAB LA exhibits absorption-rate limited PK, which is reflected in a long apparent t1/2 following IM administration compared with oral CAB administration.
m. Data obtained following oral CAB human radiolabeled studies. Data Source: GSK Doc. # 2013N167401_01 Table 8.
n. The mean total recovery of radioactivity in urine and feces was 85.3% of the administered dose; Data Source: GSK Doc. # 2013N167401_01 Table 8.

3.2.6.1. Absorption

Following single dose administration of CAB LA 800 mg IM, plasma CAB concentrations were quantifiable by the first PK sampling time point (4 hours post injection) and gradually rose to reach Cmax at approximately 7 days (Table 103). High variability in plasma CAB tmax (range of 2 to 213 days across all dose levels) was evident in Study LAI114433, a study that incorporated long-term PK sampling following administration of single doses of CAB LA [Data Source: GSK Doc. # 2013N159605_00 Table 9].

CAB LA exhibits absorption rate-limited (flip-flop) PK because CAB is slowly absorbed into the systemic circulation following IM injection into the gluteus medius muscle and the rate of absorption following IM administration of CAB LA (0.000733 h^{-1}) is much slower than the rate of CAB elimination from plasma [Data Source: GSK Doc. # 2018N384611_01 Table 15]. CAB LA absorption rate-limited PK is reflected in a long apparent t1/2. The PopPK estimate of plasma CAB half-life after IM dosing was 5.6 weeks for males and 11.5 weeks for females [GSK Doc. # 2018N384611_01 Section 5.2.3.1], compared with a t1/2 of 41 hours, representing systemic elimination, following oral CAB [Data Source: GSK Doc. # 2016N298724_00 Table 3.3].

CAB is rapidly absorbed following oral administration, with an absorption rate of 1.41 h^{-1} [Data Source: GSK Doc. # 2018N384611_01 Table 15] and a median tmax of 3 hours (Table 109). The absolute bioavailability of oral CAB is predicted to be high based on low CL/F (Section 3.2.6.4), oral relative bioavailability of 76% compared with CAB LA, and minimal impact of food on plasma CAB absorption (exposure) and absorption rate [Data Source: GSK Doc. # 2018N384611_01 Table 15; m2.7.1 Section 3.2]. Because

food had minimal impact on plasma CAB exposure following oral dosing, CAB may be taken with or without food.

HIV INIs are known to chelate with polyvalent cations, resulting in decreased absorption; chelation was demonstrated for CAB in vitro (Section 3.2.9.1). In CAB Phase III studies, antacids containing polyvalent cations were to be administered at least 2 hours before or 4 hours after oral CAB doses if needed. Dose separation is not relevant for CAB LA, which is administered IM, because the interaction with oral CAB occurs in the GI tract.

3.2.6.2. Distribution

QWBA studies of [^{14}C]-CAB administered orally in rats demonstrated that radioactivity was widely distributed and slowly absorbed with most tissues exhibiting their highest concentrations at 1-day post-dose (m2.6.4 Section 4.2.2.1). Excluding the GI tract, tissues with high concentrations of radioactivity at this time point included blood, lung, bulbourethral gland, renal medulla, adrenal medulla and pigmented skin. Except for the GI tract, concentrations of radioactivity in blood were higher relative to other tissues at all sampling times after dosing. Concentrations of radioactivity measured in the brain were low but quantifiable up to and including 7 days. In a pre- and postnatal development study CAB was detected in the first-generation pups suggesting the presence of CAB in maternal milk (m2.6.4 Section 4.2.2.1).

In humans, the estimate of plasma CAB Vc/F was 5.27 L and Vp/F was 2.43 L [Data Source: GSK Doc. # 2018N384611_01 Table 15]. These volume estimates, along with the assumption of high F, suggest some distribution of CAB to the extracellular space.

Following single dose administration of CAB LA 400 mg IM, the median cervical tissue:plasma ratio was 0.16 to 0.20 and the vaginal tissue:plasma ratio 0.19 to 0.28 (Table 45). Median CAB concentrations in cervical and vaginal tissues were approximately equivalent to the in vitro PA-IC90 (0.166 μg/mL) at 4, 8, and 12 weeks after dosing, assuming a density of 1 g of tissue/mL of homogenate (Table 44). CAB concentrations in rectal tissue were lower than in cervical and vaginal tissues.

One week following a steady-state CAB LA (Q4W or Q8W) injection, median concentrations of CAB in the CSF were higher than corresponding median unbound CAB concentrations in plasma, suggesting that therapeutic CAB concentrations are achieved in the CSF (Section 2.1.2.5). Consistent with therapeutic CAB concentrations in CSF, HIV-1 RNA in the CSF (n=16) were <50 c/mL in 100% and <2 c/mL in 15/16 (94%) of sub-study subjects. At the same time point, HIV-1 RNA in plasma (n=18) were <50 c/mL in 100% and <2 c/mL in 12/18 (66.7%) of subjects (Section 2.1.2.5).

CAB is highly bound to human plasma proteins based on ex vivo and in vitro data. In healthy subjects with normal organ function, the median CAB unbound fraction was 0.11 to 0.166% (99.8 to 99.9% bound) (Section 2.6.5.1, Section 2.6.5.2). In HIV-1-infected subjects, the median CAB unbound fraction was 0.075 to 0.103% (99.9% bound) (Section 2.1.2.5). The ex vivo unbound fraction estimate is lower than the in vitro estimate of 0.62% (99.4% bound). In vitro protein binding was independent of CAB concentrations over the range of 1 to 20 μg/mL, but a lower unbound fraction of 0.47% (99.5% bound) was observed at 0.50 μg/mL (m2.6.4 Section 4.1.1). Ex vivo plasma

unbound fraction was higher in subjects with HI (Section 2.6.5.1) and RI (Section 2.6.5.2).

Although CAB is highly bound to plasma proteins, the risk of clinically relevant interactions via displacement from plasma protein binding sites is expected to be low. EMA guidance [EMA, 2012] suggests that possible displacement interactions be evaluated for highly bound drugs that have narrow therapeutic windows, high hepatic extraction ratios, high renal extraction ratios, and are administered intravenously. CAB does not meet any of these criteria. Therefore, the potential for drug interactions at the level of distribution is considered low, and thus, studies to evaluate this were not performed.

CAB is bound to albumin and is not saturating the binding sites, therefore, the risk of clinically relevant interactions via displacement from plasma protein binding sites by CAB is expected to be low. EMA guidance [EMA, 2012] for DDIs as perpetrators suggests that if a drug is extensively protein bound to a specific binding site and present at concentrations saturating the binding sites, the risk of displacement of other drugs known to be subject to clinically relevant displacement interactions could be evaluated. Therefore, the potential for drug interactions at the level of distribution is considered low, and thus, studies to evaluate this were not performed.

Blood total radiocarbon was approximately 52% of plasma radiocarbon AUC(0-inf) (Section 2.6.1.2). The low radiocarbon concentrations in blood suggest minimal association of CAB with red blood cells.

CAB is a substrate of Pgp and BCRP, but because of its high permeability no alteration in oral absorption would be expected by co-administration of either Pgp or BCRP inhibitors (m2.6.4 Section 9).

3.2.6.3. Metabolism

The metabolism of CAB was characterized by in vitro, ex vivo, and in vivo studies with oral formulations. The pathway(s) and extent of CAB metabolism are independent of formulation and route of administration (Section 3.2.7).

In Vitro and Ex Vivo Metabolism

The route of metabolism for [^{14}C]-CAB in rat, monkey and human hepatocytes was by glucuronidation of CAB (m2.6.4 Section 5.1.1.3). In human liver, kidney and intestinal microsomal incubations, [^{14}C]-CAB was metabolized to a single UDPGA-dependent metabolite, M1 (CAB glucuronide, GSK3388352) (m2.6.4 Section 5.1.1.5). Data from human liver microsomes and recombinant UGT enzymes suggest that UGT1A1 is the primary enzyme involved in the glucuronidation of CAB in vitro with contribution from UGT1A9 (m2.6.4 Section 5.1.1.5).

The formation and hepatic disposition of GSK3388352 was investigated following perfusion of CAB through isolated perfused rat livers; GSK3388352 was formed in the liver and excreted in the bile as well as in perfusion media (m2.6.4 Section 5.1.2.1).

A glutathione adduct of CAB was detected in rat, monkey and human liver microsomes, but not dog liver microsomes (m2.6.4 Section 5.1.1.6). Covalent binding of CAB-associated radioactivity to liver microsomes was moderate in human (180 pmol-eq/mg of protein/h) and high in rat and monkey (984 and 794 pmol-eq/mg of protein/h) m2.6.4 Section 5.1.1.1). In addition, no microscopic liver findings were observed in mice, rats, or monkeys after repeat administration of doses at or below the NOAEL. In vitro levels of binding to human liver microsomes ≥200 pmol-eq/mg of protein/h are considered an indicator of the potential for hepatotoxicity when compounds are dosed at ≥100 mg/day [Sakatis, 2012]. The hepatic safety of CAB in HIV-1 infected subjects is discussed in the ISS (ISS Section 2.1.6.2).

In Vivo Metabolism

In the human mass balance study, CAB was the predominant circulating metabolite in plasma, representing 80.5 to 100% of plasma total radiocarbon in pooled plasma samples collected 2 to 24 hours post-dose and the majority of the plasma radiocarbon AUC(0-inf); no metabolites were quantified in pooled plasma samples (Table 53). Based on metabolic profiling in urine, feces, and bile, glucuronidation leading to formation of GSK3388352 (M1) is the primary metabolic pathway, accounting for 20% of the administered dose (Table 56). Glucose conjugation leading to formation of M2 is a minor pathway for CAB metabolism; M2 was detected, but not quantified, in urine. Unchanged CAB and GSK3388352 (M1) were detected in duodenal bile samples.

CAB is the major component in plasma and the glucuronic acid metabolite is the predominant component in urine, regardless of route of administration (Table 110).

Table 110 Percent of Drug-Related Material Represented by CAB and its Major Metabolite in Pooled Plasma and Urine Following IM, SC and Oral Administration in Humans

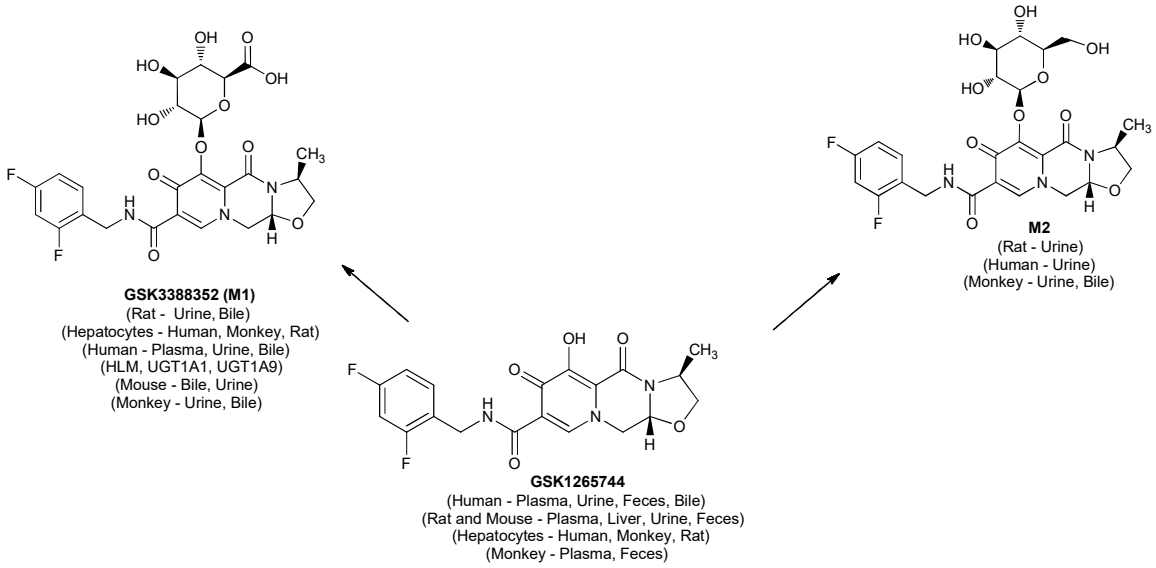
Matrix	Route of Administration (Frequency)	Dose (mg)	Sample pooling period	Proportion (%) of Drug-Related Material		
				CAB	Glucuronic Acid Metabolite (GSK3388352, M1)	Glucose Conjugation (M2)
Plasma	IM single dose	200	Day 1-Week 4	>99%	<1%	ND
		400				
		800				
	SC single dose	200	Day 1-Week 4	>99%	200 mg: ND 400 mg: <1%	ND
		400				
	Oral once daily x 14 days	30	0-8 h, 24 h	>95%	<5%	ND
	Oral single dose	30	2 h, 6 h, 12 h, 24 h	Mean 92.6% Range 80.5-100%	ND	ND
Urine	IM single dose	200	Day 3-Week 4	<5%	>90%	<5%
		400				
		800				
	SC single dose	200	Day 3-Week 4	<5%	>90%	<5%
		400				
	Oral once daily x 14 days	30	0-8 h, 8-24 h	<10%	>85%	<5%
	Oral single dose	30	0-144 h	ND	75%	<LLQ

Data Source: GSK Doc. # 2011N115920_00, GSK Doc. # 2012N143472_00, GSK Doc. # 2013N167401_01
ND = Not detected
IM and SC samples from Study LAI114433
Oral samples from Study LAI115428 (once daily x 14 days) and Study LAI117008 (single dose mass balance study)

Oxidation of CAB accounts for <1% dose in humans. In human studies LAI115428 and LAI114433, mass spectrometric analyses determined that M3 (a metabolite formed by oxidation, fluorine loss and cysteine conjugation) represented <1% of the drug-related material present in the urine following oral, IM, and SC administration [Data Source: GSK Doc. # 2011N115920_00, GSK Doc. #2012N143472_00].

In nonclinical species, CAB was also excreted unchanged in feces and absorbed drug was primarily metabolized by glucuronidation to GSK3388352 (M1). No unique metabolites were identified in humans compared with toxicological species. The proposed metabolic pathways for CAB in humans as well as in various animal species are provided in Figure 26. Toxicological species achieved higher plasma CAB Cmax and AUC values compared to humans (m2.4 Section 4).

Figure 26 Metabolic Profile of CAB



M2 is the preferred structure based on metabolic precedence and comparison with M1.
M3 (+cysteine, +O, -F) and M4 (+pentose) were also detected in human urine (<1% dose)
Two other minor metabolites were observed that were specific to the nonclinical species.
HLM = Human liver microsomes.

Data Source: m2.4 Section 3.1.4.2

CAB has two chiral centers. There was no evidence for the in vivo epimerization of CAB to any of its stereoisomers, gsk001*, gsk003* or GSK2044154, in human plasma samples following repeat oral administration of CAB for 14 days (m2.6.4 Section 5.2.4.1), nor in rat, dog, monkey or human hepatocytes (m2.6.4 Section 5.1.1.4).

3.2.6.4. Excretion

Following single dose administration of [^{14}C]-CAB 30 mg oral solution in humans, 85.3% of the administered dose was recovered in the excreta; 58.5% of the dose was recovered in feces and 26.8% was recovered in urine (Table 55). CAB accounted for 46.8% of the administered dose in feces and was not detected in urine. The glucuronide metabolite GSK3388352 (M1) represented the majority of the radioactivity recovered in urine. Both CAB and GSK3388352 were detected in bile.

CAB is a low clearance drug; from the PopPK analysis, the estimate of plasma CAB CL/F was 0.151 L/h [Data Source: GSK Doc. # 2018N384611_01 Table 15]. Following administration of oral CAB in healthy subjects, the terminal half-life is approximately 41 hours and CL/F is 0.21 L/h [Data Source: GSK Doc. # 2016N298724_00 Table 3.3]. CAB LA has a longer apparent t1/2 due to absorption rate-limited PK (Section 3.2.6.1).

From the PopPK analysis, following discontinuation of the CAB LA (administered to steady state), 47% (Q4W) and 45% (Q8W) of patients overall were predicted to have quantifiable plasma CAB concentrations (>LLQ [0.025 µg/mL]) 1 year after the last IM injection and 17% (Q4W) and 12% (Q8W) of patients overall were predicted to have

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quantifiable plasma CAB concentrations 96 weeks after the last IM injection [Data Source: GSK Doc. # 2018N384611_01 Section 5.3.7; GSK Doc. # 2019N421460_00 Section 4.3.7]. In the Phase IIb Study 200056, 4 of 12 subjects presenting for the 12-month follow-up visit had quantifiable CAB concentrations ranging from 0.045 to 0.083 μg/mL (all below the in vitro PA-IC90 of 0.166 μg/mL), and CAB was below the LLQ of 0.025 μg/mL for the remaining 8 subjects (Section 2.1.2.4).

3.2.7. Rationale for Extrapolation of Oral CAB PK data to CAB LA

Results from oral CAB RI, HI, TQT, and drug interaction studies can be extrapolated to CAB LA because:

1. Pathways of CAB metabolism and elimination and the extent of CAB metabolism are independent of formulation and route of administration, as evidenced by:
    - Absorption rate was the only PK parameter in the model that differed between oral CAB and CAB LA [Data Source: GSK Doc. # 2018N384611_01 Table 15].
    - The absolute bioavailability of oral CAB is predicted to be high, suggesting that CAB is metabolized in the liver, not in the GI tract (Section 3.2.6.1).
    - Oral CAB was excreted unchanged in feces and as the glucuronide metabolite in urine, supporting that glucuronidation is the primary metabolic pathway (Section 2.6.1.2).
    - CAB is the major component in plasma and the glucuronide metabolite is the predominant component in urine, regardless of route of administration (Section 3.2.6.3).
    - The rate of glucuronide metabolite formation from CAB was lower in human intestinal microsomes (3.3 pmol/min/mg) than in human liver microsomes (14 pmol/min/mg) (m2.6.4 Section 5.1.1.5), supporting that the CAB is predominantly metabolized in the liver, not in the GI tract.
    - Plasma CAB PK was associated with UGT1A1 polymorphisms for both CAB LA and oral CAB (Section 3.2.8.4), supporting that glucuronidation in the liver is an important metabolic pathway for both CAB LA and oral CAB.
2. Plasma CAB concentrations achieved with the CAB LA monthly and every 2 months regimens are within the range of concentrations achieved with oral CAB 10 mg to 30 mg once daily (Table 92, Figure 25).

3.2.8. Dose Recommendations Based on Intrinsic Factors

3.2.8.1. Hepatic Impairment

No dosage adjustment of CAB is required for patients with mild or moderate HI. Moderate HI had minimal impact on plasma CAB Cmax and AUC(0-inf) and geometric mean (90% CI) plasma CAB C2h_unb in subjects with moderate HI was 1.40-fold (0.798, 2.46-fold) the value in healthy subjects. This increase in plasma CAB C2h_unb (approximate Cmax_unb) is not considered clinically relevant based on safety observed with higher doses (Section 3.1.2). Given that plasma CAB Cmax is lower following LA

administration, subjects with mild or moderate HI would be expected to have lower unbound Cmax than observed following oral dosing. CAB has not been studied in patients with severe HI.

3.2.8.2. Renal Impairment

CAB may be administered without dose adjustment in patients with mild, moderate, or severe RI. Severe RI had minimal impact on plasma CAB Cmax and AUC(0-inf) and geometric mean (90% CI) plasma CAB C2h_unb in subjects with severe RI was 1.32-fold (0.807, 2.15-fold) the value in healthy subjects. This increase in plasma CAB C2h_unb (approximate Cmax_unb) is not considered clinically relevant based on safety observed with higher doses (Section 3.1.2).

CAB has not been studied in subjects with ESRD on renal replacement therapy. CAB is not expected to be cleared by renal replacement therapies, such as hemodialysis or peritoneal dialysis, due to CAB's high protein binding and because absorption is slow from the CAB LA IM depot site, such that minimal drug would be available to dialysis.

3.2.8.3. Covariates Evaluated in PopPK Analysis

Of the 1647 subjects included in the CAB PopPK analysis, 424 (25.7%) were female, the median (min-max) age was 36 years (18-74 years), 20 subjects (1.2%) were ≥65 years of age, 1102 (66.9%) were White, 394 (23.9%) were Black/African American, 56 (3.4%) were Asian, and 5.7% were of other (or unknown) races (Table 34). A total of 11,443 (94%) of 12,169 CAB injections were administered unsplit. Needle length ranged from 1 to 2.5 inches, but the 1.5-inch needle length was predominantly used (representing 88.5% of all available needle length data), regardless of BMI.

CAB PK variability was explained by gender, BMI, needle length, and split injection, which were statistically significant covariates of CAB LA absorption rate (KA2), and current smoker status, which was a statistically significant covariate of CAB CL/F (weight scaling on CL/F, V2/F, Q/F, and V3/F was also implemented) in the final CAB PopPK model; however, the effects of these covariates are not considered clinically relevant (Section 2.2).

From the PopPK model, age had no effect on CAB PK and no dose adjustment is needed; CAB PK data in subjects of >65 years old are limited.

Based on individual post-hoc PK parameter estimates from the final PopPK model, there was a trend to slightly higher CAB exposure in subjects from North East Asia (n=20) compared with other races (n=720), reflecting population difference in significant covariates including lower body weight and BMI in the subjects from North East Asia. A separate evaluation of CAB PK parameters estimated in Study 201584 showed that Japanese patients (n=8) had approximately 20% higher CAB steady-state trough concentrations following IM dosing compared with the overall study population (Section 2.2).

The CAB LA dose volume (2 mL or 3 mL) can be accommodated by a single (unsplit) injection. Split (initial) injections examined in Phase IIb were safe and effective.

Phase IIb and Phase III protocols recommended a 1.5-inch needle length for most subjects and stated that longer needle lengths may be required for participants with higher BMIs (example >30 kg/m^2) to ensure that injections were administered IM as opposed to subcutaneously. Use of a longer needle in high BMI subjects had minimal impact on plasma CAB exposure parameters based on PopPK analysis (Figure 12), but these results may not be robust given the limited number of subjects with high BMI using needles longer than 1.5 inches in Phase III studies.

3.2.8.4. Pharmacogenetics

Genetically predicted UGT1A1 activity was associated with plasma CAB PK parameters following CAB LA and oral CAB, supporting that glucuronidation in the liver is an important metabolic pathway for both CAB LA and oral CAB (Table 111). The magnitude of difference among the UGT1A1 activity categories was not clinically relevant. The UGT1A9 genetic variant (*1B) was not associated with plasma CAB PK [Data Source: GSK Doc. # 2016N297524_00 Section 4.2.2].

Table 111 Summary of Steady-State Plasma CAB PK by Genetically Predicted UGT1A1 Activity

CAB Regimen (Study)	Plasma CAB PK Parameter	Plasma CAB PK Summary Mean (min-max) [n]			Fold-Change Low vs. Normal UGT1A1 Activity
		Normal	Reduced	Low	
CAB LA Q4W (200056, Week 48)	Cmax	3.70 (1.93-7.26) [n=39]	3.56 (1.53-6.66) [n=49]	4.52 (1.91-11.5) [n=15]	1.22
	AUCtau	2189 (1210-6501) [n=39]	2001 (277-3466) [n=49]	2589 (1230-6256) [n=15]	1.18
	Ctau	2.51 (0-5.12) [n=25]	2.67 (1.01-5.49) [n=37]	3.56 (1.68-6.11) [n=8]	1.41
CAB LA Q8W (200056, Week 48)	Cmax	3.36 (1.56-8.08) [n=42]	4.01 (1.03-10.5) [n=50]	3.84 (1.66-6.28) [n=17]	1.14
	AUCtau	3167 (323-9755) [n=42]	3507 (583-9288) [n=50]	3614 (2008-4773) [n=17]	1.14
	Ctau	1.44 (0.55-3.8) [n=36]	1.71 (0.191-2.99) [n=38]	1.66 (0.-3.13) [n=15]	1.16
Oral CAB 30 mg once daily (200056)	Ctau	4.07 (1.02-8.51) [n=71]	4.72 (1.06-19.3) [n=85]	5.61 (1.49-12.6) [n=28]	1.38
Oral CAB 30 mg once daily (meta-analysis of six	Cmax	7.64 (4.21-11.3) [n=24]	8.62 (4.73-11.4) [n=26]	9.75 (5.40-13.0) [n=9]	1.3

Phase I and Phase II studies)	AUCtau	131 (81.9-193) [n=24]	156 (89.3-217) [n=26]	185 (84.1-233) [n=9]	1.4
	Ctau	4.03 (1.02-8.51) [n=128]	4.72 (1.06-19.3) [n=162]	6.06 (1.49-12.6) [n=56]	1.5

Data Source: GSK Doc. # 2016N297524_00 Table 1, Table 3, Figure 18.11, Figure 18.12, Figure 18.13; GSK Doc. # 2018N380094_00 Week 160 Table 59, Table 60
UGT1A1 activity:
Low: 2 copies of *28 (TA7), *37 (TA8) and/or *6 alleles
Reduced: 1 copy of *28 (TA7), *37 (TA8) and/or *6 alleles
Normal: Wild-type (do not carry *28, *37, or *6)
Note: UGT1A1*36 (TA5) slightly increases UGT1A1 activity; due to the small number of subjects (n=2 for CAB LA and n=13 for oral CAB) who carried this allele, the *36 allele was categorized as "*1 allele" (wildtype) for the analysis. No subject carried *36/*36 in this dataset.
Estimates of fold-change in plasma CAB PK parameters between genetically predicted low and normal UGT1A1 activity groups were based on comparison of mean data for each group; no formal statistical test/model was applied.

3.2.8.5. Hepatitis C

There was no apparent impact of HCV infection on plasma CAB PK. CAB PK concentrations observed in 18 subjects with HCV reactive at Baseline were within the range observed for all subjects [Data Source: GSK Doc. # 2019N421511_00 Table 47]. None of these subjects met CVF criteria at Week 48 or Week 96.

3.2.9. Drug Interactions

Results from oral CAB drug interaction studies can be extrapolated to CAB LA because pathways of CAB metabolism and elimination and the extent of CAB metabolism are independent of formulation and route of administration and because plasma CAB concentrations achieved with the CAB LA Q4W regimen are within the range of concentrations achieved with oral CAB 10 mg to 30 mg once daily (Section 3.2.7).

3.2.9.1. Impact of Co-administered Drug on CAB PK (CAB as Victim)

Except for strong inducers of UGT1A1, such as RIF, and chelation with antacids containing polyvalent cations (applicable to oral CAB only), CAB is not expected to be a victim of clinically meaningful drug interactions (Table 112; Table 113).

Table 112 Effects of Concomitant Medications on CAB PK

Concomitant Drug Regimen	N	Oral CAB Regimen	Geometric Mean Ratio (90% CI) of CAB PK parameters with/without co-administered drugs No Effect = 1.00			Study	Clinical Recommendation
			Ctau	AUC	Cmax		
RIF 600 mg Once Daily	15	30 mg Single Dose	ND	0.41 (0.36, 0.46)	0.94 (0.87, 1.02)	LAI117010 (Section 2.6.6.3)	Contraindicated Co-administration results in significant decreases in plasma CAB concentrations, which may result in loss of virologic response and possible resistance.
RBT 300 mg Once Daily	12	30 mg Once Daily	0.738 (0.702, 0.776)	0.786 (0.743, 0.831)	0.825 (0.761, 0.895)	205712 (Section 2.6.6.2)	No dose adjustment[a]
ETV 200 mg BID	12	30 mg Once Daily	1.00 (0.94, 1.06)	1.01 (0.96, 1.06)	1.04 (0.99, 1.09)	ITZ111839 (Section 2.6.6.6)	No dose adjustment[b]
RPV 25 mg Once Daily	11	30 mg Once Daily	1.14 (1.04, 1.24)	1.12 (1.05, 1.19)	1.05 (0.96, 1.15)	LAI116181 (Section 2.6.6.1)	No dose adjustment

Data Source: GSK Doc. # 2015N263476_00 Table 3.5; GSK Doc. # 2017N334381_00 Table 3.5; GSK Doc. # RM2009/00483/00 Table 11.6; GSK Doc. # 2011N130484_00 Table 11.10
AUC=AUC(0-inf) for single dose CAB and AUC(0-tau) for repeat dose CAB
a. CAB + RPV is proposed as a complete regimen; co-administration of rifabutin is contraindicated with RPV.
b. CAB + RPV is proposed as a complete regimen; co-administration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended. There are no DDI limitations to the ARV regimens that can be given after discontinuation of CAB + RPV.

CAB Dose Recommendations with UGT Inducers

In vitro and in vivo data indicate that CAB is primarily metabolized by UGT1A1 with some involvement from UGT1A9 (Section 3.2.6.3). Oxidation of CAB accounts for <1% dose and therefore CAB is not subject to CYP-mediated interactions (Section 3.2.6.3).

At the proposed doses, CAB must not be co-administered with strong inducers, such as rifampin, because plasma CAB concentrations are reduced to a clinically significant extent, which may result in loss of virologic response and possible resistance (Table 112). Based on results of the rifampin drug interaction study and the proposed CAB doses, CAB should not be co-administered with other strong inducers such as rifapentine, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin.

Co-administration of CAB with weak and moderate inducers, such as rifabutin and etravirine, do not reduce plasma CAB concentrations to a clinically relevant extent (Table 112). However, concomitant use of CAB LA + RPV LA with rifabutin is contraindicated

because clinically relevant decreases in RPV are observed with rifabutin co-administration.

CAB Dose Recommendations with UGT Inhibitors

Results from the PGx analysis estimated a 40% higher plasma CAB AUC(0-tau) (~30% lower CL/F) in subjects with genetically predicted low UGT1A1 activity (Section 3.2.8.4). PopPK simulations that implemented a 30% reduced plasma CAB CL/F inform the impact of reduced UGT activity on plasma CAB PK [Data Source: GSK Doc. # 2018N384611_01 Figure 24]. Based on these data, plasma CAB Cmax is not predicted to exceed the Cmax observed with oral CAB 60 mg once daily. The impact of a UGT1A1 or UGT1A9 inhibitor has not been studied clinically, but no significant impact is expected based on the PGx and PopPK results as well as PBPK modeling of the impact of UGT inhibitors, where predicted increases in geometric mean plasma CAB AUC(0-tau) and Cmax were ≤11% when oral CAB 30 mg once daily was co-administered with ATV (UGT1A1 inhibitor) or mefenamic acid (UGT1A9 inhibitor) [Data Source: GSK Doc. # 2018N389974_00, Table 14].

CAB Dose Recommendations with Antacids Containing Polyvalent Cations

HIV INIs are known to chelate with polyvalent cations, resulting in decreased absorption. Chelation was demonstrated for CAB in vitro with results similar to DTG [Data Source: GSK Doc. # 2019N401615_00].

In Phase III studies, antacids containing polyvalent cations were to be administered at least 2 hours before or 4 hours after oral CAB doses (for consistency with the recommendation for oral RPV). Dose separation is not relevant for CAB LA, which is administered IM, because the interaction with oral CAB occurs in the GI tract. The impact of the Phase III dose separation strategy was not evaluated in a separate PK study. Based on data with other INIs, administration of antacids containing divalent cations 4 hours after oral CAB is not expected to impact plasma CAB exposure; however, reduced plasma CAB exposure is expected when antacids containing polyvalent cations are administered 2 hours before oral CAB (Table 113). Oral CAB 30 mg once daily is the recommended dose for the OLI. Because oral CAB 10 mg once daily (67% of 30 mg dose) demonstrated efficacy in both induction and maintenance of virologic suppression (Section 3.1.1.1, Section 3.1.1.2), a reduction in plasma CAB exposure when antacids containing polyvalent cations are administered 2 hours before oral CAB 30 mg is not expected to be clinically relevant during the 1-month OLI or during oral therapy (up to 2 months). No dose separation is required with mineral supplements, such as calcium and iron, because the reduction in plasma CAB exposure is not expected to be clinically relevant based on magnitude of reduction observed for other INIs (Table 113).

Table 113 Summary of Impact of Polyvalent Cation-containing Products on Plasma INI PK

Co-administered Drug	INI Dose	Geometric Mean Ratio (90% CI) of INI PK parameters with/without co-administered drug No Effect = 1.00		
		Cmax	AUC	Cmin
Simultaneous Administration				
Maximum strength antacid 20 mL	Bictegravir 50 mg single dose, fasted	0.20 (0.16, 0.24)	0.21 (0.18, 0.26)	-
Maximum strength antacid 20 mL	Dolutegravir 50 mg single dose, fasted	0.28 (0.23, 0.33)	0.26 (0.22, 0.32)	0.26 (0.21, 0.31)
Calcium carbonate 1200 mg	Bictegravir 50 mg single dose, fasted	0.58 (0.51, 0.67)	0.67 (0.57, 0.78)	-
Calcium carbonate 1200 mg	Dolutegravir 50 mg single dose, fasted	0.63 (0.50, 0.81)	0.61 (0.47, 0.80)	0.61 (0.47, 0.80)
Ferrous fumarate 324 mg	Bictegravir 50 mg single dose, fasted	0.29 (0.26, 0.33)	0.37 (0.33, 0.42)	-
Ferrous fumarate 324 mg	Dolutegravir 50 mg single dose, fasted	0.43 (0.35, 0.52)	0.46 (0.38, 0.56)	0.44 (0.36, 0.54)
Administration 2 hours After INI				
Maximum strength antacid 20 mL	Bictegravir 50 mg single dose, fasted	0.93 (0.88, 1.00)	0.87 (0.81, 0.93)	-
Maximum strength antacid 20 mL	Dolutegravir 50 mg single dose, fasted	0.82 (0.69, 0.98)	0.74 (0.62, 0.90)	0.70 (0.58, 0.85)
Calcium carbonate 1200 mg	Dolutegravir 50 mg single dose, fasted	1.00 (0.78, 1.29)	0.94 (0.72, 1.23)	0.90 (0.68, 1.19)
Ferrous fumarate 324 mg	Dolutegravir 50 mg single dose, fasted	0.99 (0.81, 1.21)	0.95 (0.77, 1.15)	0.92 (0.74, 1.13)
Administration 2 hours Before INI				
Maximum strength antacid 20 mL (2 h before BIKTARVY, fasted)	Bictegravir 50 mg single dose, fasted	0.42 (0.33, 0.52)	0.48 (0.38, 0.59)	-

Data Source: per BIKTARVY labeling; per TIVICAY labeling.
Maximum strength antacid contained 80 mg aluminum hydroxide, 80 mg magnesium hydroxide, and 8 mg simethicone, per mL

CAB Dose Recommendations with Transporter Inhibitors

In vitro, CAB is a Pgp and BCRP substrate, but because of its high permeability, no alteration in absorption is expected when co-administered with either Pgp or BCRP inhibitors (m2.6.4 Section 9).

3.2.9.2. Impact of CAB on PK of Co-administered Drugs (CAB as Perpetrator)

Based on clinical drug interaction, PBPK modelling, mechanistic static modelling, and in vitro data, no clinical drug interaction risk was identified for co-administrated substrates of drug metabolizing enzymes CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17 and substrates of drug transporters Pgp,

BCRP, BSEP, MRP2, OCT1, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2K, MRP4, and OCT2 (Table 114, Table 115, m2.6.5 Section 12, m2.6.5 Section 8.1).

Table 114 Effect of CAB on the PK of Concomitant Medications

Concomitant Drug Regimen		N	Oral CAB Regimen	Geometric Mean Ratio (90% CI) of Co-administered drug PK parameters with/without CAB No Effect = 1.00			Study	Clinical Recommendation
				Ctau	AUC(0-tau)	Cmax		
MDZ 3 mg Single Dose		12	30 mg Once daily	ND	1.10 (0.95, 1.26)	1.09 (0.94, 1.26)	LAI116815 (Section 2.6.6.5)	No dose adjustment
RPV 25 mg Once Daily		11	30 mg Once daily	0.92 (0.79, 1.07)	0.99 (0.89, 1.09)	0.96 (0.85, 1.09)	LAI116181 (Section 2.6.6.1)	No dose adjustment
LNG/ EE Once Daily	LNG 0.15 mg	19	30 mg Once daily	1.07 (1.01, 1.15)	1.12 (1.07, 1.18)	1.05 (0.959, 1.15)	LAI117011 (Section 2.6.6.4)	No dose adjustment
	EE 0.03 mg			1.00 (0.919, 1.10)	1.02 (0.968, 1.08)	0.922 (0.827, 1.03)		

Data Source: GSK Doc. # 2014N208332_00 Table 3.11; GSK Doc. # 2011N130484_00 Table 11.15; GSK Doc. # 2015N227688_00 Table 3.6, Table 3.10

Table 115 Mechanistic Static PK and PBPK Modeling-Predicted Lack of Clinically Relevant Drug Interactions for CAB as Perpetrator: Predictions Based on CAB Concentrations for Oral CAB 30 mg Once Daily

Metabolizing Enzyme or Transporter	CAB Inhibitor Potency In Vitro (μM)	Substrate(s)	Predicted Geometric Mean Ratio of Co-administered drug PK parameters with/without CAB No Effect = 1.00	
PBPK Model			**AUC**	**Cmax**
OAT1 / OAT3	IC50: 0.81 / 0.41 (Ki: 0.405 / 0.205)	Adefovir, tenofovir, oseltamavir, cidofovir, ciprofloxacin, cefuroxime, methotrexate, baricitinib, S44121	≤1.18	≤1.12
OAT3	**Sensitivity Analyses:** a. 4-fold increase in potency (Ki=0.05 μM) b. 3-fold increase plasma CAB dose (90 mg) c. 10-fold increase in CAB Fu	Methotrexate	≤1.25	-
Static Model			**AUC**	**AUC Sensitivity Analyses (5x Cmax or 10x Fu)**
OAT1	IC50: 0.812	Worst case (fe=1)	1.20	2.0
OAT3	IC50: 0.411	Furosemide (fe=0.721)	1.26	1.92
MATE1	IC50: 18.2	Worst case (fe=1)	1.01	≤1.09
MATE2K	IC50: 14.2	Worst case (fe=1)	1.01	≤1.12
UGT1A3	IC50: 12	Worst case (fm=1)	1.0	≤1.2
UGT1A9	IC50:46	Worst case (fm=1)	1.0	1.0

OAT1/3 interaction predictions based on PBPK model; Data Source: GSK Doc. # 2018N389974_00 Table 12, Figure 8, Figure 9, Figure 10
OAT1/3, UGT1A3/9, and MATE1/2K interaction predictions based on Static PK model; Data Source: GSK Doc. # 2015N258625_00 Table 2, Table 4, Table 5, Table 6

Dose Recommendations for OAT1 and OAT3 Substrates When Co-administered with CAB

No dose adjustment is required when CAB is co-administered with OAT1/3 substrates, including sensitive substrates with narrow therapeutic indices, such as methotrexate. CAB is not a clinically relevant inhibitor of OAT1/3 based on mechanistic static and PBPK modeling (Table 115) and the renal safety data for oral CAB in combination with the sensitive OAT1/3 substrate TDF.

In the oral CAB Phase II Study LAI116482, 149/243 (61%) of subjects received TDF/FTC as background NRTIs at the start of the study and 94/243 (39%) received

ABC/3TC [Data Source: GSK Doc. # 2013N168724_00 Week 24 Table 11]. Overall rates of graded renal safety lab abnormalities were similar between oral CAB and EFV regimens and there were no graded creatinine clearance abnormalities in any treatment arm [Data Source: GSK Doc. # 2013N168724_00 Week 24 Table 11, Table 34, Table 8.135, Table 8.136, Table 8.152].

Dose Recommendations for CYP3A Substrates When Co-administered with CAB

No dose adjustment is required when CAB is co-administered with CYP3A substrates. A clinical drug interaction study demonstrated that CAB is not a CYP3A inhibitor or inducer because co-administration of oral CAB 30 mg once daily did not impact plasma MDZ (sensitive CYP3A substrate) exposure (Table 114).

Dose Recommendation for Hormonal Contraceptives

No dose adjustment is required when CAB is co-administered with progestin- and estrogen-containing contraceptives because oral CAB did not impact plasma LNG or EE exposures (Table 114).

Dose Recommendations for ARV Medications

In a clinical drug interaction study, CAB had no impact on plasma RPV exposure and RPV had no impact on plasma CAB exposure (Table 112, Table 114); these data supported co-administration of CAB + RPV in clinical safety and efficacy studies.

See Section 3.1.5 for recommendations regarding initiation of alternative HAART regimens following discontinuation of CAB LA + RPV LA.

3.2.9.3. Summary of Predicted Drug Interaction

The following recommendations for important co-medications are proposed based on extrapolating observed clinical drug interaction results, mechanistic static PK and PBPK modeling, and in vitro data (Table 116).

Table 116 Recommendations Based on Predicted Drug Interactions with CAB

Concomitant Drug Class: Drug Name	Anticipated Effect on Concentration of CAB or Concomitant Drug	Clinical Comment
Strong UGT1A1 inducers (rifampin[a], rifapentine, carbamazepine, oxcarbazepine, phenobarbital, and phenytoin)	Decreased CAB concentrations	Co-administration is contraindicated due to potential for loss of therapeutic effect and development of resistance
Moderate and weak UGT1A1 inducers (e.g. rifabutin [a], etravirine [a])	No drug interaction expected	No dose adjustment necessary
UGT1A1 inhibitors (e.g. atazanavir)	No clinically relevant drug interaction expected	No dose adjustment necessary
Antacids containing polyvalent cations (e.g., Mg, Al or Ca)	Decreased CAB concentrations (for oral CAB only)	Administer antacid at least 2 hours before or 4 hours after oral CAB dosing.

Concomitant Drug Class: Drug Name	Anticipated Effect on Concentration of CAB or Concomitant Drug	Clinical Comment
Proton Pump Inhibitors (e.g. lansoprazole, esomeprazole, omeprazole, pantoprazole)	No drug interaction expected	No dose adjustment necessary
Histamine-2 receptor antagonists (e.g. cimetidine, ranitidine, famotidine, nizatidine)	No drug interaction expected	No dose adjustment necessary
Statins (e.g. atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin)	Statins are mostly substrates of CYP3A4, BCRP, and OATP No drug interaction expected	No dose adjustment necessary
HBV medications (e.g. adefovir, entecavir, lamivudine, telbivudine, tenofovir disoproxil fumarate, tenofovir alafenamide)	HBV medications are primarily excreted in urine and are substrates of BCRP, Pgp, and OCT No drug interaction expected	No dose adjustment necessary
HCV medications (e.g. ledipasvir, sofosbuvir, velpatasvir, voxilaprevir, ombitasvir, paritaprevir, dasabuvir, glecaprevir, pibrentasvir, elbasvir, grazoprevir)	HCV medications are mostly substrates of CYP3A4, BCRP, OATP, and Pgp No drug interaction expected	No dose adjustment necessary
Opioid Dependence Treatments (e.g. methadone, buprenorphine)	Methadone and buprenorphine are metabolized by CYP3A4. No drug interaction expected	No dose adjustment necessary

a. Interaction studied

4. SPECIAL STUDIES

Please note that m2.7.2.4, Special Studies (Summary of Microbiology/Virology) is provided as a standalone module.

5. CONCLUSIONS

5.1. Overall Conclusions

- CAB LA + RPV LA is a complete ARV regimen; the safety and efficacy of the proposed monthly regimen was established in 2 Phase III studies (201584 and 201585) and the safety and efficacy of the proposed every 2 months regimen was established in the Phase IIIb Study 207966.
    - The proposed CAB monthly regimen for HIV-1-infected subjects is oral CAB 30 mg once daily for 1 month followed by an initial dose of CAB LA 600 mg IM and subsequent monthly doses of CAB LA 400 mg IM, administered with the proposed RPV monthly regimen.
    - The proposed CAB every 2 months regimen is oral CAB 30 mg once daily for 1 month followed by 2 initial doses of CAB LA 600 mg IM 1 month apart and

subsequent doses every 2 months of CAB LA 600 mg IM when administered with the proposed every 2 months RPV regimen in HIV-infected individuals.

- The rate of CVF in subjects in individual studies 201584, 201585, and 207966 receiving the Q4W or Q8W regimen was low, and overlapping plasma CAB and RPV concentrations in subjects with CVF vs. subjects with HIV-RNA <50 c/mL made it difficult to establish a relationship between plasma concentration and the occurrence of virologic failure. Multiple factors, including plasma concentrations and viral phenotype, may be associated with the occurrence of virologic failure.
- CVF is an infrequent multifactorial event, with a rate of ~1% in the LA arms across 3 Phase III studies (201584, 201585, and 207966) through Week 48.
- In an MVA using data pooled from Phase III/IIIb studies (201584, 201585, 207966), RPV Ctrough, archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and high BMI (≥30 kg/m^2) had a statistically significant association with virologic failure. However, regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%), and no Baseline factor when present in isolation was predictive of virologic failure.
- No relationships between plasma CAB concentrations and safety parameters of interest were identified in the CAB + RPV Phase III studies.
- CAB may be administered without dose adjustment in patients with mild and moderate HI (Child-Pugh A and B), mild to severe renal impairment who did not require renal replacement therapy, and regardless of age (≥18 years of age), gender, race, body size (weight, BMI), smoker status, or UGT1A1 polymorphism.
- Drug Interactions Requiring Contraindication with CAB:
  - Metabolism: UGT1A1 and/or CYP3A inducers RIF, RBT (CAB LA in combination with RPV LA), rifapentine, CBZ, oxcarbazepine, phenobarbital, and phenytoin.
- Because absorption is prolonged following IM administration of CAB LA, CAB can be detected in plasma for more than a year in some individuals. Alternative HAART should be initiated as soon as feasible, no later than 1 month following discontinuation of the monthly CAB LA regimen or no later than 2 months following discontinuation of the every 2 months CAB LA regimen, to maintain suppression of viral load and so reduce the chance of any CAB resistance emerging while concentrations are waning.

5.2. Detailed Conclusions for CAB + RPV Regimen

5.2.1. Summary of CAB PK for Proposed CAB + RPV Dosage Regimens

The proposed monthly and every 2 months CAB regimens achieve plasma concentrations similar to those from efficacious oral CAB 10 mg (Table 86) and 30 mg once daily doses (Table 117).

Table 117 Summary (Geometric Mean [5th, 95th Percentile]) of CAB PK Parameters following Administration of Proposed CAB + RPV Regimens in HIV-infected Subjects

Drug	Dosing Phase	Dosage Regimen	Plasma CAB PK Parameter		
			AUC(0-tau) (μg•h/mL)	Cmax (μg/mL)	Ctau (μg/mL)
CAB	Oral Lead-In [a]	30 mg PO once daily	145 (93.5, 224)	8.0 (5.3, 11.9)	4.6 (2.8, 7.5)
	Initial Injection [b]	600 mg IM Initial Dose	1,591 (714, 3,245)	8.0 (5.3, 11.9)	1.5 (0.65, 2.9)
	Monthly Injection [c]	400 mg IM monthly	2,415 (1,494, 3,645)	4.2 (2.5, 6.5)	2.8 (1.7, 4.6)
	Every 2 months Injection[c]	600 mg IM Every 2 months	3764 (2431, 5857)	4.02 (2.26, 6.83)	1.61 (0.80, 2.99)

Data Source: GSK Doc. # 2018N384611_01 Table 17; GSK Doc. # 2019N421460_00, Table 14

- OLI, initial injection, and monthly injection: GSK Doc. # 2018N384611_01 Table 17
- Every two months injection: GSK Doc. # 2019N421460_00 Table 14

a. OLI PK parameter values represent steady state.
b. Initial Injection Cmax values primarily reflect values following oral dosing because the initial injection was administered on the same day as the last oral dose.
c. Monthly and every 2 months injection PK parameter values represent Week 48 (11th injection for monthly and 6th injection for every 2 months).

PK parameter values were based on individual post-hoc estimates from the final PopPK model and are presented as geometric mean (5^{th}, 95^{th} percentile).

5.2.2. Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy (Monthly Regimen)

Table 118 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy (Monthly Regimen)

Time Since Last Injection	Recommendation
≤2 months	Continue with the monthly 2 mL (400 mg) injections dosing schedule as soon as possible.
>2 months	Re-initiate the patient with the 3-mL (600 mg) injections, and then continue to follow the monthly 2 mL (400 mg) injection dosing schedule.

Table 119 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy (Every Two Months Regimen)

Missed Injection Visit	Time Since Last Injection	Recommendation (all injections are 3 mL)
Injection 2	≤2 months	Resume with 3 mL (600 mg) injections as soon as possible and continue with the every 2 month injection dosing schedule.
	>2 months	Re-initiate the patient with the 3 mL (600 mg) injections, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every 2 month injection dosing schedule.
Injection 3 or later	≤3 months	Resume with 3 mL (600 mg) injections as soon as possible and continue with the every 2 month injection dosing schedule.
	>3 months	Re-initiate the patient on the 3 mL (600 mg) injections, followed by a second 3 mL (600 mg) initiation injection one month later. Then follow the every 2 month injection dosing schedule.

5.2.3. Exposure-Response

- The rate of CVF in subjects in individual studies 201584, 201585, and 207966 receiving the Q4W or Q8W regimen was low. Plasma CAB and RPV concentrations at the SVF visit for subjects with CVF overlapped with plasma concentrations of subjects with HIV-RNA <50 c/mL at the corresponding visit, making it difficult to establish a relationship between plasma concentrations and the occurrence of virologic failure. Multiple factors, including PK and viral phenotype, may be associated with the occurrence of virologic failure.
- In a MVA using data from HIV-infected adults with no prior exposure to CAB + RPV pooled from Phase III/IIIb studies (201585, 201584, and 207966), the rate of CVF was low, 1.25%, through Week 48. RPV Ctrough, archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and high BMI had a statistically significant association with virologic failure. However, regardless of these factors, a high proportion of subjects continued to maintain viral suppression (94%). No Baseline factor, when present in isolation, was predictive of virologic failure. However, a combination of at least 2 of the following Baseline factors was associated with an increased risk of CVF: RPV resistance mutations, HIV-1 Subtype A6/A1, or BMI ≥30 kg/m^2.
- No relationships between plasma CAB concentrations and safety parameters of interest, including QTc, ALT, and total bilirubin, were identified in the CAB + RPV Phase III Studies 201584, 201585, and 207966.

5.2.4. Special Populations

The recommendations for use in subjects with hepatic or renal impairment are independent of dosing regimen and are the same for the monthly regimen and every 2 months regimen.

- CAB may be administered without dose adjustment in patients with mild and moderate HI (Child-Pugh A and B). The effect of severe HI (Child-Pugh C) on CAB has not been studied.
- CAB may be administered without dose adjustment in patients with mild to severe renal impairment who did not require renal replacement therapy.

There were no covariates with a clinically relevant impact on the plasma CAB PK following Q4W or Q8W dosing, including gender, race, age (≥18 years of age), UGT1A1 polymorphisms, smoker status, and body size (weight, BMI).

CAB concentrations in subjects who were hepatitis C antibody positive at Baseline were similar to the overall population.

5.2.5. Drug Interactions

CAB plasma concentrations achieved with the Q4W and Q8W regimen are within the range of plasma concentrations observed with oral CAB 10 to 30 mg once daily. Recommendations for drug interactions are the same for the monthly regimen and every 2 months regimen.

CAB (LA and Oral):

- CAB is contraindicated with the UGT1A1 inducers RIF, rifapentine, CBZ, oxcarbazepine, phenobarbital, and phenytoin due to potential for loss of therapeutic effect and development of resistance. The use of RBT with CAB LA +RPV LA is also contraindicated.
- There is no significant drug interaction between CAB and RPV, the 2 components of the regimen.
- Because of the low DDI liability for CAB as perpetrators, there are no co-medications that require dose adjustment when given together with CAB and there are no DDI limitations to the ARV regimens that can be given after discontinuation of CAB.
- No dose adjustments are needed for CAB when co-administered with UGT or CYP inhibitors.

CAB (Oral Only):

- Antacids containing polyvalent cations must be administered at least 2 hours before or 4 hours after oral CAB.

5.3. Cabotegravir

5.3.1. CAB LA and Oral CAB

- Similar plasma CAB exposure between healthy and HIV-1-infected subjects supports extrapolation of data generated in healthy subjects, such as drug and food interactions and the TQT study, to the HIV-1-infected population.
- Because plasma CAB concentrations achieved with the CAB LA monthly and every 2 months regimens are within the range of concentrations achieved with oral CAB 10 mg to 30 mg once daily and because pathways of CAB metabolism and elimination and the extent of CAB metabolism are independent of formulation and route of administration, results from oral CAB renal impairment, HI, TQT, and drug interaction studies can be extrapolated to CAB LA.
- Overall, plasma CAB exposure increases in proportion or slightly less than in proportion to dose following single and repeat dose administration of CAB LA 100 to 800 mg IM and oral CAB 5 to 60 mg, but markedly less than dose proportional at a higher dose of oral CAB 150 mg.
- Plasma CAB PK is time-invariant.
- From the PopPK analysis, the estimate of plasma CAB Vc/F was 5.27 L and Vp/F was 2.43 L.
- CAB is highly (>99.8%) bound to human plasma proteins.
- Blood total radiocarbon was approximately 52% of plasma total radiocarbon AUC(0-inf). The low radiocarbon concentrations in blood suggest minimal association of CAB with red blood cells.
- Following single dose administration of [^{14}C]-CAB 30 mg oral solution, 85.3% of the administered dose was recovered in the excreta; 58.5% of the dose was recovered in feces (as unchanged CAB) and 26.8% of the dose was recovered in urine (predominantly as the glucuronide metabolite).
- Based on metabolic profiling of human urine, feces, and bile, glucuronidation leading to formation of GSK3388352 (M1) is the primary metabolic pathway, accounting for 20% of the administered dose. Unchanged CAB and the glucuronide metabolite GSK3388352 were detected in duodenal bile samples.
- UGT1A1 is the primary enzyme involved in the glucuronidation of CAB, with minor contribution from UGT1A9.
- Weak and moderate inducers, such as RBT and ETV, do not reduce plasma CAB concentrations to a clinically relevant extent. No adjustment is required when oral CAB is co-administered with RBT.
- Oxidation of CAB accounts for <1% dose and therefore CAB is not subject to CYP-mediated interactions.
- No unique metabolites were identified in humans compared with toxicological species.

- CAB is a low clearance drug; the estimate of plasma CAB CL/F was 0.151 L/h.
- In the TQT study, a supratherapeutic dose of oral CAB 150 mg Q12h x 3 doses had no effect on cardiac repolarization and there was no relationship between plasma CAB concentrations and ddQTcF.

5.3.2. CAB LA

- Following single dose administration of CAB LA 800 mg IM, plasma CAB concentrations were quantifiable by the first PK sampling time point (4 hours post injection) and gradually rose to reach Cmax at approximately 7 days.
- CAB LA exhibits absorption rate-limited (flip-flop) PK, which is reflected in a long apparent t1/2, with an estimate of 5.6 weeks for males and 11.5 weeks for females following IM administration.
- The time to achieve steady-state is prolonged with CAB LA with efficacious concentrations achieved following the initial IM injection. The time to steady-state was approximately 44 weeks following administration of the monthly and every 2 months regimen, consistent with the slow absorption rate following IM injection.
- Following single dose administration of CAB LA 400 mg IM, the median cervical tissue:plasma ratio was 0.16 to 0.20 and the vaginal tissue:plasma ratio was 0.19 to 0.28. Median CAB concentrations in cervical and vaginal tissues were approximately equivalent to the in vitro PA-IC90 (0.166 μg/mL) at 4, 8, and 12 weeks after dosing, assuming a density of 1 g of tissue/mL of homogenate. CAB concentrations in rectal tissue were lower than in cervical and vaginal tissues.
- One week following a steady-state CAB LA (Q4W or Q8W) injection, median concentrations of CAB in the CSF were higher than corresponding median unbound CAB concentrations in plasma.
- Consistent with therapeutic CAB concentrations in the CSF, mean plasma HIV-1 RNA levels were <50 c/mL in 18/18 (100%) of subjects across Q8W and Q4W arms using the Abbott RT assay and <2 c/mL in 9/15 (60%) of subjects in the Q8W arm and 3/3 (100%) in the Q4W arm using the SuperLow Assay.
- CAB LA is contraindicated with RBT because RBT may decrease CAB plasma concentrations.

5.3.3. Oral CAB

- CAB is rapidly absorbed following oral administration, with a median tmax of 3 hours.
- Oral CAB can be taken with or without food. When dosed with oral RPV, oral CAB should be taken with a meal (m2.7.1).
- Steady-state is achieved by Day 7 following once daily administration of oral CAB, consistent with the approximate 2.5-fold accumulation and a t1/2 of approximately 41 hours.

- Antacids containing polyvalent cations must be administered at least 2 hours before or 4 hours after oral CAB.
- Oral CAB can be administered with RBT without dose adjustment.
- CAB is a substrate of Pgp and BCRP, but because of its high permeability no alteration in oral absorption would be expected by co-administration of either Pgp or BCRP inhibitors.

6. APPENDIX

Appendix Table 1 Tabular Listing of all Cabotegravir Clinical Pharmacology Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
ITZ111451	First in human; single and repeat dose escalation; safety and tolerability; PK	Part A: To assess safety, tolerability and PK of oral single doses Part B: To assess safety, tolerability and PK of oral repeat doses Part C: To evaluate safety, tolerability, and antiviral activity of oral CAB in HIV-infected subjects	Part A: Single dose escalation Part B: Repeat dose escalation for 10 days Part C: Placebo-controlled, monotherapy for 10 days followed by 3-drug ARV therapy	Part A: Healthy subjects Part B: Healthy subjects Part C: HIV-infected subjects	Part A: 18 enrolled 17 completed; 16/2; 31.3 (18-54) Part B: 30 enrolled 30 completed; 29/1; 28.8 (19-48) Part C: 11 enrolled 10 completed; 11/0; 39.6 (27-51)	Part A: CAB 5, 10, 25, 50 mg, placebo, oral suspension; single dose, fasted Part B: CAB 5, 10, 25 mg, placebo, oral suspension; once daily x 14 days, fasted Part C: CAB 30 mg, placebo, oral tablet, once daily x 10 days, fasted	Complete
ITZ111682	Relative Bioavailability	Evaluate relative bioavailability of oral tablet	Open-label, single dose, randomized, parallel study	Healthy subjects	45 enrolled 45 completed; 36/9; 33.2 (19-55)	CAB 10 mg oral solution, single dose, fasted CAB 10 mg (2x5 mg) tablet, single dose, fasted CAB 10 mg (2x5 mg) tablet, single dose, fed	Complete
ITZ111839	Drug interaction	To assess the potential for a drug interaction between CAB and etravirine (ETV)	Open-label, repeat dose, two-period, single-sequence study	Healthy subjects	12 enrolled 12 completed; 12/0; 30.7 (23-48)	CAB 30 mg once daily for 10 days; oral tablet CAB 30 mg once daily + ETV 200 mg q12h for 14 days; oral tablet	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
LAI116181	Drug interaction	To assess the potential for a drug interaction between CAB and rilpivirine (RPV)	Open-label, repeat-dose, single sequence, three-period study	Healthy subjects	12 enrolled 11 completed; 24/4; 31.4 (18-50)	CAB 30 mg once daily for 12 days; oral tablet RPV 25 mg once daily for 12 days; oral tablet CAB 30 mg once daily + RPV 25 mg once daily for 12 days	Complete
ITZ112929	Safety and tolerability	To evaluate safety, tolerability, and antiviral activity of oral CAB in HIV-infected subjects	Placebo-controlled, monotherapy for 10 days followed by 3-drug ARV therapy	HIV-infected subjects	9 enrolled 9 completed; 7/2; 39.2 (31-48)	CAB 5 mg or placebo once daily x 10 days	Complete
LAI114433	Safety and tolerability; single dose escalation	Assess safety, tolerability, and PK of single dose of injectable CAB	Placebo-controlled, single dose escalation	Healthy subjects	72 enrolled 58 completed; 39/33; 35.1 (18-55)	CAB 100 mg IM CAB 100 mg SC CAB 200 mg IM CAB 200 mg SC CAB 400 mg IM CAB 400 mg SC CAB 800 mg IM	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
LAI115428	Safety and tolerability; repeat dose	To investigate the safety, tolerability, and PK of CAB LA following each IM or SQ dose and to investigate the safety, tolerability, and PK of RPV LA IM doses when given in combination with CAB LA IM doses	Open-label, repeat-dose, parallel study	Healthy subjects	47 enrolled 40 received LA 37 completed injections 31 enrolled in long term follow-up 30 completed long term follow-up; 30/17; 39.5 (18-64)	Lead-in (all cohorts): CAB 30 mg; oral tablet for 21 days Cohort 1: CAB 800 mg IM, then 200 mg SC q month x 3 doses Cohort 2: CAB 800 mg IM, then 200 mg IM q month x 3 doses; RPV 1200 mg IM (month 3) and 900 mg IM (month 4) Cohort 3: CAB 800 mg IM, then 400 mg IM q month x 3 doses; RPV 1200 mg IM (month 3) and 600 mg IM (month 4) Cohort 4: CAB 800 IM q 3 months x 2 doses	Complete
LAI116585	Relative Bioavailability	To evaluate the relative bioavailability of two new CAB 30 mg free acid capsule formulations compared to a tablet of the current sodium salt formulation in the fasted state	Randomized, open-label, balanced, 3-way crossover study	Healthy subjects	18 enrolled 18 completed; 10/8; 36.7 (21-60)	CAB 30mg tablet sodium salt formulation, single dose, fasted; CAB 30mg capsule free acid [redacted] formulation, single dose, fasted; CAB 30mg capsule free acid [redacted] formulation, single dose, fasted	Complete
LAI116815	Relative Bioavailability and drug interaction	To evaluate the relative bioavailability of two new formulations of different particle size of CAB	Open label, single-dose, parallel study	Healthy subjects	43 enrolled 33 completed; 35/8; 34.8 (20-64)	Lead in (all treatments) CAB 30mg tablet for 14 days Midazolam 3 mg probe x 2 doses (n=12) Treatment A: 400 mg IM ([redacted] nm) Treatment B: 400 mg IM ([redacted] μm)	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
		400mg LA given IM compared to the current formulation ([redacted]nM [redacted])				Treatment C: 400 mg IM ([redacted] µm)	
LAI117008	Mass balance and supratherapeutic PK	To determine the total recovery and relative excretion of total radioactivity in urine and feces after a single, oral solution dose of [^{14}C]-CAB. and to describe the PK of plasma following a supratherapeutic dose	Two-part study: Open-label, single-dose, mass balance study Open-label, placebo-controlled, randomized single-dose study	Healthy subjects	Part A: 6 enrolled 6 completed; 6/0; 41.2 (32-53) Part B: 10 enrolled 9 completed; 3/7; 31.7 (20-49)	Part A: Treatment A: 14C-CAB 30 mg, oral solution, single dose Part B: Treatment B: CAB 150 mg (30mg x 5 tablets), single dose Placebo, single dose	Complete
LAI117010	Drug interaction	To evaluate the effect of rifampin (RIF) on the PK of oral CAB	Single-center, open-label, fixed-sequence crossover study	Healthy subjects	15 enrolled 15 completed; 10/5; 48.5 (21-65)	CAB 30 mg, single-dose, oral tablet, RIF 600 mg (2 x 300mg) once daily for 13 days, oral tablet CAB 30 mg single dose + RIF 600mg once daily for 8 days	Complete
LAI117011	Drug interaction	To demonstrate the lack of an effect of CAB 30mg on the exposure of levonorgestrel (LNG) and ethinyl estradiol (EE) in	Open-label, fixed-sequence crossover study	Healthy subjects (females)	20 enrolled 19 completed; 0/20; 26.5 (18-39)	EE 0.03mg/LNG 0.15mg for 10 days; oral tablet EE/LNG + CAB 30 mg once daily for 11 days; oral tablet	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
		healthy female subjects					
205712	Drug interaction	To compare steady state CAB exposure following 30 mg oral dose once daily with and without rifabutin (RBT) 300 mg once daily	Single-center, open-label, fixed-sequence, 2-period crossover study	Healthy subjects	15 enrolled 12 completed; 15/0; 43.7 (27-59)	CAB 30 mg once daily; oral tablet for 14 days RBT 300 mg (150mg x 2) once daily + CAB 30 mg once daily for 14 days; oral tablet	Complete
LAI117020	Relative bioavailability	To evaluate the relative bioavailability of two new CAB 30mg sodium salt tablet formulations compared to a tablet of the current sodium salt formulation in the fasted state and to evaluate the effect of a moderate-fat meal on the bioavailability of the selected tablet formulation	Randomized, two-part, open-label, crossover study	Healthy subjects	Part A: 24 enrolled 22 completed; 14/10; 41.8 (20-60) Part B: 15 enrolled 15 completed; 10/5; 40 (20-59)	Treatment A: 30 mg current formulation, sodium salt, [redacted], [redacted]mg [redacted], single-dose, fasted Treatment B: 30 mg formulation [redacted], [redacted]mg [redacted], single-dose, fasted Treatment C: 30 mg formulation [redacted], [redacted]mg [redacted], single-dose, fasted	Complete
201741	Relative bioavailability	To assess the oral bioavailability of four new CAB sodium salt tablet formulations relative to the current CAB	Single-center, randomized, open-label, two cohort, 3-way crossover study	Healthy subjects	Cohort 1: 19 enrolled 18 completed; 11/8; 31.6 (19-57) Cohort 2:	Cohort 1: Treatment A = CAB 30 mg, [redacted] mg [redacted], [redacted], reference, fasted; Treatment B = CAB 30 mg, [redacted]mg [redacted], [redacted], fasted; Treatment C = CAB 30 mg, [redacted] mg [redacted]	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
		sodium salt formulation being used in Phase IIb studies			18 enrolled 18 completed; 16/2; 33.2 (21-48)	[redacted], [redacted], fasted Cohort 2: Treatment A = CAB 30 mg, [redacted] mg [redacted], [redacted], reference, fasted; Treatment D = CAB 30 mg, [redacted] mg [redacted], [redacted], fasted; Treatment E = CAB 30 mg, [redacted] mg [redacted] [redacted], fasted	
201479	Hepatic impaired	To compare plasma PK parameters of CAB in subjects with hepatic impairment to healthy controls matched in gender, age, and BMI	Open-label, parallel group, two-part, single-dose adaptive study Part 1: moderate HI Part 2: mild HI	Moderate and mild hepatically impaired subjects with matching, healthy control subjects with normal hepatic function	16 enrolled 16 completed 12/4; 58.6 (51-67)	Part 1: CAB 30 mg single-dose, oral tablet, fasted. Part 2 (not conducted): CAB 30 mg, single-dose, fasted.	Complete
201480	Renal impaired	To compare plasma PK parameters of CAB in subjects with severe renal impairment to healthy controls matched for gender, age, and BMI	Open-label, multiple center, single dose study	Subjects with severely impaired renal function and healthy, matching control subjects with normal renal function	16 enrolled 16 completed 12/4; 53.9 (35-69)	CAB 30 mg, single-dose, oral tablet, fasted	Complete
205696	Food effect	To evaluate the effect of a high-fat meal on the PK of CAB in healthy adult volunteers	Single-center, randomized, open-label crossover study	Healthy subjects	24 planned 24 enrolled; 16/8; 39.7 (23-66)	Treatment A: CAB 30 mg, single-dose, tablet, fasted Treatment B: CAB 30 mg, single-dose, tablet fed	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
LAI117009	QTc	To demonstrate a lack of effect of repeat oral doses of CAB (150 mg) (supratherapeutic dose) as determined by the Baseline-adjusted, maximum time-matched QTcF effect as compared to placebo	Randomized partial-blind, repeat dose, three-period, balanced crossover study	Healthy subjects	42 enrolled 36 completed; 33/9; 33.9 (19-54)	Treatment A: Three doses of CAB 150 mg (5 x 30mg tablets) q12 h Treatment B: Three doses of CAB placebo (5 tablets) q12 h Treatment C: A single dose of moxifloxacin 400mg (one 400mg tablet)	Complete
205162	PGx	Evaluate effects of UGT1A1 genotypes on oral CAB PK	Retrospective non-interven-tional PGx analysis	Healthy subjects (ITZ111839, LAI116181, LAI115428, LAI116815) HIV-1-infected, ARV naïve subjects (LAI116482, 200056)	Analyzed 1364	PK PGx analysis: Oral CAB 30mg once daily for at least 8 days Tolerability PGx analysis: Treatment received in LAI116482: Treatment A – CAB 10mg + NRTIs Treatment B – CAB 30mg + NRTIs Treatment C – CAB 60mg + NRTIs Treatment D – EFV + NRTIs	Complete
201120	HIV-1 PrEP Study	To evaluate the safety and tolerability of the injectable agent, CAB LA injectable (800 mg dose administered at 3 time points at 12 week intervals) through Week 41 in HIV-uninfected men	Randomized, double-blind, placebo controlled	Healthy subjects at low risk of acquiring HIV	Enrolled 127 CAB - 106 (105 exposed) Placebo - 21 IM injections -115 total CAB LA injections - 94 Placebo injections - 21 Completed - 104 CAB - 84 Placebo – 20	Arm 1: Daily oral CAB (30 mg tablets) for 4 weeks, followed by a 1-week washout period, to establish safety and tolerability, followed by IM injections of 800 mg of CAB LA at 3 time points at 12 week intervals: Week 5, Week 17, and Week 29. Arm 2: Daily oral matching placebo and IM 0.9% saline injections on the same schedule as Arm 1.	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
					127/0; 34.9 (20-61)		
LAI116585LAI117010LAI117011LAI1170202017 41, 201479, 201480, 205696, LAI116482 (LATTE), LAI115428LAI11681520 0056 (LATTE2), 201120 (ECLAIR), 201103 (HPTN077), 201584 (FLAIR), 201585 (ATLAS)	PopPK	To further characterize CAB PK based on data from healthy subjects and HIV-1 infected patients following administration as oral tablet and LA injection	PopPK analysis was performed in the following sequence of steps: (1) exploratory data analysis, (2) base model development, (3) covariate analysis, (4) model refinement, (5) model evaluation, and (6) evaluation of clinical relevance of covariates.	Healthy subjects and HIV-1 infected patients	1650 total subjects 458 Healthy subjects 1192 HIV-infected patients 1226/424 37.89 (18-74)	LAI116585, LAI117010, LAI117020, 201741, 201479, 201480, 205696: 30 mg (Na salt tablets) PO single dose LAI117011: 30 mg (Na salt tablets) PO QD × 11 days LAI116482: 10 mg tablet PO QD × 24 weeks; 30 mg tablet PO QD × 24 weeks; 60 mg (2 × 30mg) PO QD × 24 weeks LAI115428: 30 mg PO QD x 14 days LAI116815: Oral: 30mg PO QD, at SS LA: 400mg IM single dose ([redacted] nm [redacted]) 200056: Oral lead-in/induction 30 mg PO QD × 20 weeks, then switch to 1) 800mg IM × 1, then 400mg IM Q4W; or 2) 800mg IM × 1, then 600mg IM at Week 4, then 600mg IM Q8W starting at Week 8 201103: Oral lead-in 30 mg QD × 4 weeks, 1-week washout, then Arm 1: 800 mg IM Q12W × 3 Arm 2: 600 mg IM at Week 5, Week 9, and then Q8W × 3 201120: Oral lead-in 30mg QD × 4 weeks, 1-week washout, then 800 mg IM Q12W × 3 201584: Induction: ABC/DTG/3TC 1 tablet QD × 20 weeks followed by: Oral lead-in 30 mg PO QD × 4 weeks, switch to 600 mg IM × 1, then 400 mg IM	Complete

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age years (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
						Q4W 201585: Oral lead-in 30 mg PO QD × 4 weeks, switch to 600 mg IM × 1, then 400 mg IM Q4W	

201585 (ATLAS) (see Appendix Table 3 for details)
201584 (FLAIR) (see Appendix Table 3 for details)
200056 (LATTE-2) (see Appendix Table 3 for details)
LAI116482 (LATTE) (see Appendix Table 2 for details)
207966 (ATLAS-2M) (see Appendix Table 3 for details)

Degree of Blinding
O = Open
SB = Single Blind
DB = Double Blind

Degree of Control
UC = Uncontrolled
PLC = Placebo
AC = Active control

Treatment Assignment
R = Random
NR = Non-random

Treatment Sequence
PRL = Parallel
XO = Crossover
DR = Dose Rising

M = Male; F = Female;
DTG = Dolutegravir; RPV = Rilpivirine
PK = Pharmacokinetic
CAB = Cabotegravir
LA = Long-acting
IM = Intramuscular
PGx = Pharmacogenetics
BMI = Body mass index
NRTI = Nucleoside reverse transcriptase inhibitor

Appendix Table 2 Tabular Listing of all Oral CAB + Oral RPV Combination Clinical Pharmacology Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
LAI116482	HIV Treatment Study	A Phase IIb, dose ranging study of oral CAB in combination with nucleoside reverse transcriptase inhibitors for induction of HIV-1 virologic suppression followed by an evaluation of maintenance of virologic suppression when oral CAB is combined with oral rilpivirine in HIV-1-infected, antiretroviral therapy naive adult subjects	Randomized, Partially Blind, Dose Ranging with an Active Control	HIV positive, antiretroviral naive	Total – 244 Total Exposed - 243 Treatment A – 60 Treatment B – 60 Treatment C – 62 (61 Exposed) Treatment D – 62; 233/10; 35.1 (18-70)	Treatment A – CAB 10mg + NRTIs Treatment B – CAB 30mg + NRTIs Treatment C – CAB 60mg + NRTIs Treatment D – EFV + NRTIs Post Week 24, Treatments A, B and C discontinued NRTIs and initiate RPV Post Week 96, Treatment D completed the study and Treatments A, B and C continued on open-label 30 mg CAB+RPV	Complete

Appendix Table 3 Tabular Listing of all CAB LA + RPV LA Combination Clinical Pharmacology Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
201584	HIV Treatment Study	To demonstrate the non-inferior antiviral activity of switching to IM CAB LA + RPV LA every 4 weeks (monthly) compared to continuation of ABC/DTG/3TC over 48 weeks in HIV-1 ARV naïve participants	Randomized, open label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV positive, ARV naïve patients	566 Enrolled Maintenance Period CAB+RPV 244 Completed Week 96 220/63 35.9 (19-68)	**Induction Phase**: Oral ABC/DTG/3TC FDC once daily (or DTG + 2 NRTIs once daily for participants are HLA-B*5701 positive) **Maintenance Phase**: Oral CAB 30 mg + RPV 25 mg once daily for 4 weeks, then IM CAB LA 600 mg + RPV LA 900 mg at Week 4, followed by IM CAB LA 400 mg + RPV LA 600 mg at Week 8, Week 12, and then every 4 weeks thereafter; or to continue oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs) **Extension Phase**: Participants receiving CAB LA + RPV LA will continue to have access to the treatment until they no longer derive clinical benefit, commercially availability, or program termination; Subjects randomized to ABC/DTG/3TC FDC arm can complete a 4-week lead-in of oral CAB 30 mg + RPV 25 mg once daily at Week 100, then switch to IM CAB LA 600 mg + RPV LA 900 mg at Week 104, followed by IM CAB LA 400 mg + RPV LA 600 mg at Week 108, and continuing every 4 weeks thereafter.	Ongoing

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
201585	HIV Treatment Study	To demonstrate the non-inferior antiviral activity of switching to CAB LA 400 mg + RPV LA 600 mg every 4 weeks for 48 weeks (4 weeks oral CAB + RPV, 44 weeks LA therapy) compared to continuation of current antiretroviral therapy (current ART). This study will also provide important long-term antiviral activity, safety, tolerability and patient satisfaction data on CAB LA 400 mg + RPV LA 600 mg through at least Week 96.	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV positive, ARV experienced patients	310 Enrolled Maintenance Phase 281 Completed Extension Phase 23 Ongoing 209/99 41.6 (21-74)	**Maintenance Phase**: Arm 1: Switch to daily oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks followed by IM CAB LA + RPV LA every 4 weeks (Q4W) for 48 weeks; Arm 2: Continue current ART regimen for at least 52 weeks. **Extension Phase**: Arm 1: continue IM dosing regimen (Q4W) through at least Week 96; Arm 2: option to complete study or switch to oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks followed by CAB LA + RPV LA Q4W through at least Week 96. Participants can continue CAB LA + RPV LA Q4W until meeting protocol defined stopping criteria, products approved and commercially available or program termination.	Ongoing
207966	HIV Treatment Study	To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every 8 weeks (every 2 months) compared to CAB LA + RPV LA every 4 weeks (monthly) over 48 weeks in suppressed HIV-1-infected antiretroviral therapy (ART)-experienced participants	Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	Virologically suppressed HIV positive, ARV experienced patients	1049 Enrolled Randomized: Q8W: 524 Q4W: 525 Week 48 analysis Maintenance Phase Ongoing: Q8W: 486 Q4W: 481 Q8W: 385/137; 42.7 (20 – 83)	**Subjects transitioning from oral SOC Q4W** Oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks CAB LA: Week 4b: 600 mg (Initiation Dose) Week 8 and Q4W thereafter: 400 mg RPV LA: Week 4b: 900 mg (Initiation Dose) Week 8 and Q4W thereafter: 600 mg **Q8W** Oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks	Ongoing

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
					Q4W: 380/143; 42.3 (19 – 75)	CAB LA: Week 4b, Week 8, and Q8W thereafter: 600 mg RPV LA: Week 4b, Week 8, and Q8W thereafter: 900 mg **Subjects transitioning from 201585 Q4W** CAB LA: Day 1 and Q4W thereafter: 400 mg RPV LA: Day 1 and Q4W thereafter: 600 mg **Q8W** CAB LA: Day 1 and Q8W thereafter: 600 mg RPV LA: Day 1 and Q8W thereafter: 900 mg	
200056	HIV Treatment Study	To select an intramuscular dosing regimen of CAB LA plus RPV LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of two IM dosing regimens, relative to CAB 30 mg plus ABC/3TC orally once daily.	Randomized, multicenter, parallel group, open-label, three period study	HIV positive, ARV naïve patients	Planned 265 Induction Period: Enrolled 310 Exposed 309 Completed 288 Maintenance Period: Enrolled 286 262/24; 36.5 (19-64)	Induction Period (20 weeks): Oral CAB + abacavir/lamivudine (ABC/3TC) (or alternative NRTI backbone if HIS-B*5701 positive) Maintenance Period (2:2:1 randomization) (at least 96 weeks): IM CAB LA + RPV LA every 4 weeks, IM CAB LA + RPV LA every 8 weeks; Oral CAB + ABC/3TC (or alternative NRTI backbone if HIS-B*5701 positive) Extension Period: Both IM dosing regimens (every 4 or every 8 weeks until commercially available or program termination)	Ongoing

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects Gender M/F Mean Age (Range)	Treatment Details (Drug/Dose/Form/Route/Frequency/ Duration)	Study Status
200056	CSF sub-study	An assessment of the PK of CAB and rilpivirine (RPV) in plasma and cerebrospinal fluid (CSF) following LA intramuscular administration in subjects currently enrolled into the LATTE-2 Phase IIb study	Randomized, multicenter, parallel group, open-label, three period study CSF PK sub-study: open-label, multicenter, parallel study (Extension Phase)	HIV positive, ARV naïve patients	CSF PK sub-study 18 enrolled 18 completed; 15/3; 38.3 (23-58)	Subjects enrolled after Week 156 of LATTE 2 followed the same injection regimen as in LATTE 2 study design Extension Period: Both IM dosing regimens (every 4 or every 8 weeks until commercially available or program termination)	Complete

Appendix Table 4 Summary Results for Single Dose Oral Cabotegravir Clinical Pharmacology Pharmacokinetic Studies

Study	Population/No. Subjects Completed	Route of Administration Formulation/Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a]			
					Cmax (mg/L)	tmax (hr) Median (Range)	AUC (0-inf) (mg/L	t1/2 (hr)
ITZ111451	Part A: Healthy subjects/17	Oral Suspension	CAB 5 mg/7	Single dose (fasted)	1.15 (16)	0.5 (0.5-1.00)	26.6 (14) [b]	NR
			CAB 10 mg/7	Single dose (fasted)	2.15 (17)	1.00 (0.50 – 1.50)	51.7 (22) [b]	NR
			CAB 25 mg/7	Single dose (fasted)	4.38 (23)	1.50 (0.50 – 3.00)	117 (13) [b]	NR
			CAB 50 mg/7	Single dose (fasted)	8.57 (24)	1.50 (0.5 – 3.00)	231 (34) [b]	NR
ITZ111682	Healthy Subjects/45	Oral Suspension	CAB 10 mg/15	Single dose (fasted)	1.93 (16)	1.00 (0.50 – 2.00)	62.4 (21)	41.2 (14)
		Oral Tablet	CAB 10 mg/15	Single dose (fasted)	1.13 (23)	2.50 (1.50 – 3.50)	44.7 (37)	38.5 (15)
			CAB 10 mg/15	Single dose (fed)	1.18 (13)	4.00 (2.50 – 6.00)	51.6 (19)	42.2 (15)
LAI116585	Healthy Subjects/18	Oral Tablet (Na salt formulation)	CAB 30 mg/18	Single dose (fasted)	4.24 (19)	2.00 (1.0 – 4.0)	174 (25)	39.9 (21)
		Oral Capsule (free acid [redacted] formulation)	CAB 30 mg/18	Single dose (fasted)	3.43 (21)	3.00 (1.0 – 6.0)	152 (22)	41.4 (18)
		Oral Capsule (free acid [redacted] formulation)	CAB 30 mg/18	Single dose (fasted)	1.96 (28)	3.00 (2.0 – 4.0)	89.4 (29)	42.8 (23)
LAI117008	Part A: Healthy Subjects/6 Part B: Healthy Subjects/10	Oral Solution containing 14C-GSK1265744 of approximately 70 μCi (0.96 MBq) of radioactivity	CAB 30 mg/6	Single dose (fasted)	2.48 (21)	2.00 (0.98 – 3.00)	96.5 (25)	38.8 (10)
		Oral Tablet	CAB 150 mg/8	Single dose (fasted)	10.4 (26)	2.50 (1.00 – 4.03)	418 (32)	38.1 (16)
LAI117020	Part A: Healthy Subjects/22 Part B: Healthy Subjects/15	Oral Tablet (Na salt formulation – [redacted] mg)	CAB 30 mg/22	Single dose (fasted)	3.70 (23)	2.00 (1.0 – 6.0)	141 (20)	37.8 (18)
		Oral Tablet ([redacted] mg)	CAB 30 mg/22	Single dose (fasted)	2.38 (30)	3.00 (1.0 – 6.0)	72.0 (29)	38.4 (18)
			CAB 30 mg/15	Single dose (fed)	2.71 (16)	3.03 (2.0 – 8.0)	83.4 (20)	37.2 (16)
		Oral Tablet ([redacted] mg)	CAB 30 mg/22	Single dose (fasted)	1.98 (40)	3.00 (1.0 – 6.0)	82.0 (42)	36.3 (20)

Study	Population/No. Subjects Completed	Route of Administration Formulation/Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a]			
					Cmax (mg/L)	tmax (hr) Median (Range)	AUC (0-inf) (mg/L	t1/2 (hr)
201741	Cohort 1: Healthy Subjects/18 Cohort 2: Healthy Subjects/18	Oral Tablet (Na salt formulation – [redacted] mg)	CAB 30 mg/36	Single dose (fasted)	3.41 (26)	2.01 (0.5 – 6.0)	137 (29)	38.9 (18)
		Oral Tablet ([redacted] mg)	CAB 30 mg/18	Single dose (fasted)	3.43 (21)	3.00 (1.0 – 4.0)	135 (26)	38.4 (24)
		Oral Tablet ([redacted] mg)	CAB 30 mg/18	Single dose (fasted)	2.65 (29)	2.00 (1.0 – 4.0)	106 (27)	36.8 (12)
		Oral Tablet ([redacted] mg)	CAB 30 mg/18	Single dose (fasted)	3.15 (27)	2.01 (0.5 – 6.0)	129 (26)	37.4 (14)
		Oral Tablet ([redacted] mg)	CAB 30 mg/18	Single dose (fasted)	2.60 (36)	2.00 (0.5 – 4.0)	106 (33)	38.0 (14)
201479	Moderate and mild hepatically impaired subjects /8	Oral Tablet	CAB 30 mg/8	Single dose (fasted)	2.70 (41.1)	2.0 (1.0 – 4.0)	102 (37.3)	30.8 (32.2)
	Healthy control subjects with normal hepatic function/ 8		CAB 30 mg/8	Single dose (fasted)	3.55 (24.3)	2.0 (1.0 – 3.0)	127 (36.2)	37.2 (13.1)
201480	Subjects with severe renal impairment	Oral Tablet	CAB 30 mg/	Single dose (fasted)	3.34 (27)	2.00 (1.0 – 4.2)	143 (23)	39.2 (16)
	Healthy controls matched for gender, age, and BMI		CAB 30 mg/	Single dose (fasted)	3.37 (15)	2.00 (1.0 – 4.0)	140 (23)	40.5 (11)
205696	Healthy Subjects/22	Oral Tablet	CAB 30 mg/21	Single dose (fasted)	3.33 (27)	3.00 (1.0 – 4.0)	143 (28)	40.6 (15)
			CAB 30 mg/21	Single dose (fed)	3.85 (24)	3.00 (1.0 – 8.0)	163 (29)	40.6 (16)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) is presented.
b. AUC provided as 0-72hr for this part of the study

Appendix Table 5 Summary Results for Repeat Dose Oral Cabotegravir Clinical Pharmacology Pharmacokinetic Studies

Study	Population/No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a]				
					Cmax (mg/L)	tmax (hr) Median (Range)	AUC (0-tau) (mg/L)	t1/2 (hr)	Ctau (μg/mL)
ITZ111451	Part B: Healthy subjects/30 Part C: HIV-infected Individuals/10	Oral Suspension	CAB 5mg (Day 1)/8	once daily x 14 days (fasted)	1.17 (14)	0.75 (0.50 – 1.00)	13.7 (9) [b]	NR	NR
			CAB 5mg (Day 14)/8	once daily x 14 days (fasted)	2.08 (19)	0.63 (0.25 – 1.50)	32.5 (16) [b]	NR	1.06 (20)
			CAB 10mg (Day 1)/8	once daily x 14 days (fasted)	2.30 (13)	0.75 (0.50 – 1.50)	27.5 (13) [b]	NR	NR
			CAB 10mg (Day 14)/8	once daily x 14 days (fasted)	4.29 (15)	0.88 (0.50 – 1.50)	69.2 (18) [b]	NR	2.39 (23)
			CAB 25mg (Day 1)/8	once daily x 14 days (fasted)	4.73 (11)	1.00 (0.50 – 2.00)	63.6 (10) [b]	NR	NR
			CAB 25mg (Day 14)/8	once daily x 14 days (fasted)	9.47 (19)	1.25 (0.50 – 4.00)	160 (20) [b]	NR	5.40 (22)
			CAB 30 (Day 1)/8	once daily x 10 days (fasted)	2.84 (32)	1.50 (1.00 – 3.00)	41.5 (35) [b]	NR	NR
			CAB 30 (Day 10)/8	once daily x 10 days (fasted)	6.37 (23)	2.50 (1.00 – 4.00)	104 (28) [b]	31.5 (22)	NR
LAI115428	Healthy Subjects/40	Oral Tablet	CAB 30 mg/40	once daily x14 days	8.30 (26)	2.00 (1.0 – 8.0)	147 (27)	NR	4.87 (30)
LAI116815	Healthy Subjects/33	Oral Tablet	CAB 30 mg (Day 14)/12	once daily x 14 days	7.01 (23)	2.00 (1.0 – 4.0)	120 (25)	NR	NR
LAI116482	HIV-infected Subjects/41	Oral Tablet	CAB 10 mg/60	Week 36 once daily	-	-	-	-	1.34 [c] [1.1, 1.6] (58)
			CAB 30 mg/60	Week 36 once daily	-	-	-	-	3.93 [c] [3.5, 4.4] (44)
			CAB 60 mg/61	Week 36 once daily	-	-	-	-	8.22 [c] [7.4, 9.1] (37)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) is presented.
b. AUC provided as AUC(0-24h).
c. Geometric mean [95% CI] (CVb%)

Appendix Table 6 Summary Results for Single and Repeat Dose Injectable Suspension Cabotegravir Clinical Pharmacology Pharmacokinetic Studies

Study	Population/ No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a, u]				
					Cmax (mg/L)	tmax (days) Median (Range)	AUC (0-tau) (mg/L) [b, v]	t1/2 (days)	Ctau (μg/mL)
LAI114433	Healthy Subjects/58	Injectable Suspension for Intramuscular Injection	CAB 100 mg/6	Single dose (fasted)	0.2 (58.6)	9.00 (4.0 – 83.0)	920 (12.3) [c]	33.3 (66.8) [d]	NR
			CAB 200 mg/6	Single dose (fasted)	0.3 (28.9)	44.50 (27.0 – 170.1)	1234 (34.6) [c]	53.9 (32.2)	NR
			CAB 400 mg/14	Single dose (fasted)	0.7 (55.2)	69.00 (2.0 – 213.0)	2652 (29.8) [c]	38.3 (57.3) [e]	NR
			CAB 400 mg/8	Single dose (fasted)	1.4 (53.4)	13.00 (4.0 – 84.2)	2687 (53.0) [c]	31.7 (61.8) [f]	NR
			CAB two 400 mg/6	Single dose (fasted)	3.3 (75.1)	7.58 (5.0 – 148.0)	5872 (12.6) [c]	25.4 (51.7)	NR
		Injectable Suspension for Subcutaneous Injection	CAB 100 mg/6	Single dose (fasted)	0.2 (62.1)	16.50 (4.0 – 55.0)	689 (24.0) [c]	50.4 (76.9) [g]	NR
			CAB 200 mg/6	Single dose (fasted)	0.5 (48.6)	6.00 (3.0 – 27.0)	1706 (2.6) [c]	42.7 (53.1) [h]	NR
			CAB two 200 mg/6	Single dose (fasted)	0.9 (83.4)	27.00 (3.0 – 83.0)	2734 (22.3) [c]	42.8 (52.0)	NR
LAI115428	Healthy Subjects/37	Injectable Suspension for Intramuscular Injection	CAB two 400 mg/30	Single dose	2.50 (80)	13.00 (6.0 – 28.0)	1178 (63)	NR	1.76 (47)
			CAB two 400 mg /19	Quarterly x2 quarters	2.97 (79)	15.00 (2.0 – 83.0)	3570 (57)	24.9 (47)	0.89 (116)
		Injectable Suspension for Subcutaneous Injection	CAB 200 mg/10	Monthly x3 months	2.18 (23)	6.00 (0.0 – 28.0)	1287 (23)	46.6 (11)	1.77 (24)
LAI116815	Healthy Subjects/33	Injectable Suspension for Intramuscular Injection ([redacted]	CAB 400 mg/13	Single dose	0.91 (101)	28.00 (4.0 – 84.1)	2664 (20)	15.5 (40)	NR

Study	Population/ No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a, u]				
					Cmax (mg/L)	tmax (days) Median (Range)	AUC (0-tau) (mg/L) [b, v]	t1/2 (days)	Ctau (μg/mL)
		nm)							
		Injectable Suspension for Intramuscular Injection ([redacted] μm)	CAB 400 mg/12	Single dose	1.27 (131)	10.00 (2.0 – 56.9)	2717 (28)	17.5 (26)	NR
		Injectable Suspension for Intramuscular Injection ([redacted] μm)	CAB 400 mg/13	Single dose	0.70 (121)	21.00 (4.0 – 84.0)	2313 (18)	25.6 (29)	NR
201120	Healthy subjects at low risk of acquiring HIV/107	Injectable Suspension for Intramuscular Injection	CAB 800 mg	Dose administered at 3 time points at 12-week intervals					
			n=93	Injection 1	4.26 (89)	–	3415 (43)	18.4 [i] (48)	0.302 [j] (157)
			n=89	Injection 2	5.22 (78)	–	3873 (44)	NC [k]	0.331 [l] (165)
			n=85	Injection 3	4.91 (67)	–	4021 (36)	40.1 [m] (50)	0.387 [n] (150)
201584	HIV positive, ARV naïve patients/566	Injectable Suspension for Intramuscular Injection	CAB 400 mg/250	Week 8 (pre-dose) Single dose	–	–	–	–	1.56 (65)
			CAB 400 mg/227	Week 24 (pre-dose) Q4W	–	–	–	–	2.38 (37)
			CAB 400 mg/236	Week 41 (1-week post-dose) Q4W	–	–	–	–	4.03 (38)
			CAB 400 mg/197	Week 48 (pre-dose)	–	–	–	–	3.13

Study	Population/ No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a, u]				
					Cmax (mg/L)	tmax (days) Median (Range)	AUC (0-tau) (mg/L) [b, v]	t1/2 (days)	Ctau (µg/mL)
									(46)
			CAB 400 mg/194	Week 52 (pre-dose) Q4W	–	–	–	–	3.10 (37)
			CAB 400 mg/204	Week 56 (pre-dose) Q4W	–	–	–	–	3.05 (38)
			CAB 400 mg/206	Week 60 (pre-dose) Q4W	–	–	–	–	3.16 (39)
			CAB 400 mg/192	Week 80 (pre-dose) Q4W	–	–	–	–	2.64 (37)
			CAB 400 mg/195	Week 88 (pre-dose) Q4W	–	–	–	–	2.78 (36)
			CAB 400 mg/194	Week 96 (pre-dose) Q4W	–	–	–	–	2.80 (43)
			CAB 400 mg/239	Week 96 (2h post-dose) Q4W	–	–	–	–	3.16 (59)
201585	HIV positive, ARV experienced patients/618	Injectable Suspension for Intramuscular Injection	CAB 400 mg/252	Week 8 (pre-dose) Single dose	–	–	–	–	1.23 (76)
			CAB 400 mg/234	Week 24 (pre-dose) Q4W	–	–	–	–	2.25 (51)
			CAB 400 mg/251	Week 41 (1-week post-dose) Q4W	–	–	–	–	3.39 (54)
			CAB 400 mg/217	Week 48 (pre-dose) Q4W	–	–	–	–	2.84 (46)
			CAB + RPV (Initiation Dose at Week 4b)						
			CAB 400 mg/-	Week 56 (pre-dose) Q4W	–	–	–	–	NC[y]
			CAB 400 mg/-	Week 56 (2h post-dose) Q4W	–	–	–	–	NC[y]
			CAB 400 mg/-	Week 60 (pre-dose) Q4W	–	–	–	–	NC[y]

Study	Population/ No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a, u]				
					Cmax (mg/L)	tmax (days) Median (Range)	AUC (0-tau) (mg/L) [b, v]	t1/2 (days)	Ctau (μg/mL)
			CAB 400 mg/23	Week 96 (pre-dose) Q4W	–	–	–	–	2.99 (52)
			CAB 400 mg/22	Week 96 (2h post-dose) Q4W	–	–	–	–	3.13 (43)
			Extension Switch to CAB + RPV (Initiation Dose at Week 56b)						
			CAB 400 mg/167	Week 56 (pre-dose) Q4W	–	–	–	–	5.22 (45)
			CAB 400 mg/166	Week 56 (2h post-dose) Q4W	–	–	–	–	8.83 (46)
			CAB 400 mg/155	Week 60 (pre-dose) Q4W	–	–	–	–	1.44 (68)
			CAB 400 mg/28	Week 96 (pre-dose) Q4W	–	–	–	–	2.61 (39)
			CAB 400 mg/26	Week 96 (2h post-dose) Q4W	–	–	–	–	2.77 (34)
207966	Virologically suppressed HIV positive, ARV experienced patients/ Ongoing: Q8W: 486 Q4W: 481	Injectable Suspension for Intramuscular Injection	**Prior Exposure to CAB + RPV: 0 Weeks (n=326)**						
			Q8W/-	Day 1	-	-	-	-	ND
			Q8W/282	Week 4b[v]	-	-	-	-	5.18 (45)
			Q8W/273	Week 8[x]	-	-	-	-	1.57 (67)
			Q8W/262	Week 16	-	-	-	-	1.41 (58)
			Q8W/219	Week 24	-	-	-	-	1.44 (62)
			Q8W/268	Week 41	-	-	-	-	3.53 (53)
			Q8W/217	Week 48	-	-	-	-	1.58 (47)
			Prior Exposure to CAB + RPV: 1 to 24 Weeks (n=69)						
			Q8W/61	Day 1	-	-	-	-	1.79 (56)
			Q8W/1	Week 4b[v]	-	-	-	-	6.75[w]
			Q8W/62	Week 8[x]	-	-	-	-	1.65 (63)
			Q8W/54	Week 16	-	-	-	-	1.61 (69)
			Q8W/46	Week 24	-	-	-	-	1.62 (54)

Study	Population/ No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a, u]				
					Cmax (mg/L)	tmax (days) Median (Range)	AUC (0-tau) (mg/L) [b, v]	t1/2 (days)	Ctau (μg/mL)
			Q8W/61	Week 41	-	-	-	-	3.54 (51)
			Q8W/51	Week 48	-	-	-	-	1.77 (63)
			Prior Exposure to CAB + RPV: >24 Weeks (n=126)						
			Q8W/112	Day 1	-	-	-	-	3.17 (40)
			Q8W/-	Week 4b[v]	-	-	-	-	ND
			Q8W/105	Week 8[x]	-	-	-	-	2.52 (53)
			Q8W/92	Week 16	-	-	-	-	2.30 (41)
			Q8W/96	Week 24	-	-	-	-	2.10 (47)
			Q8W/109	Week 41	-	-	-	-	3.67 (46)
			Q8W/85	Week 48	-	-	-	-	1.83 (55)
			Prior Exposure to CAB + RPV: 0 Weeks (n=326)						
			Q4W/292	Week 4b	-	-	-	-	5.29 (43)[v]
			Q4W/267	Week 8[x]	-	-	-	-	1.52 (74)
			Q4W/253	Week 16	-	-	-	-	2.13 (46)
			Q4W/228	Week 24	-	-	-	-	2.41 (41)
			Q4W/236	Week 48	-	-	-	-	2.71 (39)
			Prior Exposure to CAB + RPV: 1 to 24 Weeks (n=67)						
			Q4W/54	Week 4b	-	-	-	-	1.8 (56)
			Q4W/57	Week 8[x]	-	-	-	-	2.06 (59)
			Q4W/59	Week 16	-	-	-	-	2.28 (41)
			Q4W/40	Week 24	-	-	-	-	2.68 (39)
			Q4W/53	Week 48	-	-	-	-	2.59 (38)
			Prior Exposure to CAB + RPV: >24 Weeks (n=128)						
			Q4W/109	Week 4b	-	-	-	-	2.98 (38)
			Q4W/102	Week 8[x]	-	-	-	-	3.01 (42)
			Q4W/104	Week 16	-	-	-	-	2.86 (46)
			Q4W/94	Week 24	-	-	-	-	3.08 (49)
			Q4W/97	Week 48	-	-	-	-	2.91 (45)

Study	Population/ No. Subjects Completed	Route of Administration Formulation/ Dosage Form	Dose/No. Subjects	Regimen	Geometric Mean Parameters (%CVb) [a, u]				
					Cmax (mg/L)	tmax (days) Median (Range)	AUC (0-tau) (mg/L) [b, v]	t1/2 (days)	Ctau (µg/mL)
200056	HIV positive, ARV naïve patients/286	Injectable Suspension for Intramuscular Injection	CAB 400 mg/115	Week 32 (Q4W)	3.50 [o] (39)	6.9 (0-29)	1858 [p] (37)	–	2.35 [q] (32)
			CAB 400 mg/115	Week 48 (Q4W)	3.50 [r] (37)	6.9 (0-28)	2017 [s] (41)	–	2.56 [t] (32)
			CAB 400 mg/69	Week 72 pre-dose (Q4W)	–	–	–	–	2.94 (35)
			CAB 400 mg/65	Week 96 pre-dose (Q4W)	–	–	–	–	2.95 (42)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) is presented.
b. Presented as AUC (0-tau)
c. AUC provided as AUC (0-inf) for this study
d. n = 3
e. n = 10
f. n = 7
g. n = 5
h. n = 4
i. n = 61
j. n = 84
k. n = 0
l. n = 71
m. n = 51
n. n = 66
o. n = 97
p. n = 84
q. n = 108
r. n = 95
s. n = 80
t. n = 98
u. For Study 207966, all concentrations are at pre-dose except for Week 41 which is 1-week post injection (~Cmax)
v. For Study 207966, Week 4b pre-dose concentrations were obtained following a 4-week OLI regimen of CAB 30 mg and RPV 25 mg once daily.
w. One subject with 1 to 24 weeks prior exposure received OLI in Study 201585 and restarted OLI in Study 207966. Week 4b pre-dose concentration for this subject was consistent with oral dosing.
x. Week 8 pre-dose concentrations were obtained following a CAB 600 mg IM dose administered either at Week 4b (0 prior exposure) or Day 1 (1 to 24 weeks prior exposure or >24 weeks prior exposure).
y. NC = not collected for the CAB + RPV arm at Week 56b or Week 60.

NR = Not Reported

Q4W = oral therapy with CAB 30 mg + RPV 25 mg once daily at Baseline (Day 1) for 28 days (±3 days) followed by IM CAB 600 mg + RPV 900 mg at Week 4b, IM CAB 400 mg + RPV 600 mg at Week 8 and Q4W thereafter.

Q8W = oral therapy with CAB 30 mg + RPV 25 mg once daily at Baseline (Day 1) for 28 days (±3 days) followed by IM CAB 600 mg + RPV 900 mg at Week 4b and Week 8 and Q8W thereafter.

Appendix Table 7 Summary Pharmacokinetic Parameters of Co-administered Drugs with Cabotegravir

Study	Population /Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/No. Subjects	CAB Regimen	Parameter of Co-administered Drug [a, b]		
					Cmax (ng/mL)	Ctau (ng/mL)	AUC (0-tau) (ng.h/mL)
ITZ111839	Healthy subjects	ETV/Oral Tablet	200 mg (+ 30 mg CAB)/12	Once daily (ETV q12h x 14 days) x 10 days	1.04 (0.99, 1.09)	1.00 (0.94, 1.06)	1.01 (0.96, 1.06)
LAI117010	Healthy subjects	RIF/Oral Tablet	600 mg (+30 mg CAB)/15	Once daily (RIF once daily x 13 days) x 8 days	0.94 (0.87, 1.02)	NR	0.41 (0.36, 0.46)
LAI116815	Healthy subjects	MDZ/Oral Tablet	3 mg (+30 mg CAB)/12	Once daily (MDZ single dose) x 1 day	1.09 (0.94, 1.26)	NR	1.10 (0.95, 1.26)
LAI116181	Healthy subjects	RPV/Oral Tablet	25 mg (+30 mg CAB)/11	Once daily (RPV once daily) x 12 days	0.96 (0.85, 1.09)	0.92 (0.79, 1.07)	0.99 (0.89, 1.09)
LAI117011	Healthy subjects (females)	LNG/EE/Oral Tablet	LNG = 0.15 mg/19	Once daily (LNG/EE once daily x 10 days) x 10 days	1.05 (0.959, 1.15)	1.07 (1.01, 1.15)	1.12 (1.07, 1.18)
			EE = 0.03 mg/19		0.922 (0.827, 1.03) [c]	1.00 (0.919, 1.10) [d]	1.02 (0.968, 1.08) [d]
205712	Healthy subjects	RBT/Oral Capsules	300 mg (+30 mg CAB)/12	Once daily (RBT once daily) x 14 days	0.825 (0.761, 0.895)	0.738 (0.702, 0.776)	0.786 (0.743, 0.831)

a. Geometric mean ratio (90% CI) of CAB PK parameters with/without co-administered drug
b. Drugs No Effect = 1.00
c. For EE, units are pg/mL
d. For EE AUC(0-tau), units are h•pg/mL

Module 2.7.2.4

Special Studies

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ABBREVIATIONS

AAG	α_1-acid glycoprotein
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
AZT	Azidothymidine
BCO	Biological cutoff
CAB	Cabotegravir
CAR	Current Antiretroviral Regimen
CCR5	Chemokine receptor 5
CDC	Centers for Disease and Prevention Control
CI	Confidence Interval
CIP4	Cell line derived from 293T cells
c/mL	Copies per milliliters
CSR	Clinical study report
CVF	Confirmed Virologic Failure
DNA	Deoxyribonucleic acid
DTG	Dolutegravir
EC50	Effective Dose 50
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FC	Fold Change
FTC	Emtricitabine
g	Gram
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
HBV	Hepatitis B Virus
HeLa CD4	Human cell line
HIV-1	Human Immunodeficiency Virus type 1
HSV	Herpes simplex virus
IC50	50% Inhibitory Concentration
ICH	International Conference on Harmonisation
IM	Intramuscular
IN	Integrase
INI	Integrase Inhibitor
INSTI	INtegrase Strand Transfer Inhibitor
IP	Investigational product
LA	Long acting
ITT-E	Intent to treat exposed
LPV	Lopinavir
MBI	Monogram Biosciences
mg	Milligrams
mL	Millilitre
Molt-4	Human T cell lymphocytic leukemia cell line

MT-2	Human T cell lymphocytic leukemia cell line
MT4	Human T cell lymphocytic leukemia cell line
M8166	Human T cell lymphocytic leukemia cell line
ND	Not done
NIH	National Institutes of Health
nM	Nano molar
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PBMC	Peripheral Blood Mononuclear Cells
PDVF	Protocol Defined Virologic Failure
PHA	Phytohemagglutinin
PHIV	Pseudotyped HIV
PI	Protease Inhibitor
PR	Proviral DNA Resistance Population
PRC	Proviral DNA Resistance Censored Population
PRO	Protease
RAL	Raltegravir
RAM	Resistance Associated Mutation
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse Transcriptase
SDM	Site Directed Mutant
[redacted]	[redacted]
SVF	Suspected Virologic Failure
TDF	Tenofovir disoproxil fumarate
vDNA	Viral DNA
VF	Virologic Failure
VL	Viral Load
WCENA	Canada, France, Germany, Italy, Spain, Sweden, United States; Latin America- Argentina, Mexico; East Asia- Republic of Korea; Oceania- Australia; Southern Africa- South Africa
VZV	Varicella Zoster Virus
µg	Microgram
3TC	Lamivudine

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1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not applicable.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

This section is not applicable.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

This section is not applicable.

4. SPECIAL STUDIES

A complete package of non-clinical and clinical virology data supporting the CAB + RPV development program is provided as part of this◦submission and is summarized in this document.◦The in vitro virology data for CAB (Section 4.1) were newly generated. The CAB + RPV in vivo clinical virology data were generated based on Phase 3 study 201585 (ATLAS,◦ (Section 4.2.1.1) and study 201585 (FLAIR, Section 4.2.1.2) and Phase 3B study 207966 (ATLAS-2M (Section 4.2.1.4) and Phase 2 study 200056 (LATTE-2 Section 4.2.2.1) and study LAI16482 (LATTE Section 4.2.2.2) studies. Note that the ongoing CAB studies for pre-exposure prophylaxis are not in scope of this document.

4.1. Nonclinical Virology - CAB

CAB inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.

CAB has low nM activity against wild type human immunodeficiency virus type 1 (HIV-1) and HIV-2 in a variety of cell lines, regardless of subtype. CAB has little or no activity against non-HIV viruses. Human serum increases the PA-EC_{50} >400-fold to 101 nM for PBMCs against HIV-1. CAB is additive or synergistic when assayed in combination with other antiretroviral agents.

When HIV-1 strain IIIB was passaged in the presence of CAB for 112 days, viruses having >10-fold reduction in susceptibility to CAB were not observed, but a 8.4-fold maximum fold change was observed for the passaged virus with IN substitutions T124A and S153Y.

- Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM CAB and increasing to 160 nM CAB selected for no substitutions in the IN region by Day 56 (FC=0.85-1.3).

- Passage of the Q148K mutant in the presence of 6.4 nM CAB selected for E138K, Q148K (FC=89-260) on Day 28 and was present throughout the remaining

passages up to 160 nM CAB with no additional substitutions selected up to Day 56.

- Passage of the Q148K mutant in the presence of 32 nM CAB selected for E138K, Q148K (FC=53-190) on Day 14. Virus with V72I, E138K, Q148K (FC=410) was also isolated at Day 56.

- Passage of the Q148R mutant selected E138K, Q148R and L74M, Q148R (FC=3-11) on Days 28 and 42, respectively, in the presence of 6.4 nM CAB, increasing to 160 nM CAB.

- Passage of Q148H in the presence of 6.4 nM CAB selected G140S, Q148H (FC=2) on Day 14 and a mixture of G140S, Q148H; E138K, G140S, Q148H (FC=17) and L74M, V75A, G140S,Q148H (FC=21-160) by Day 42.

- Passage of the Q148H mutant in the presence of 32 nM CAB selected for G140S, Q148H by Day 28 and T122N, G140S, Q148H (FC=16), G140S, Q148H, M154I (FC=2.2) and G56S, G140S, Q148H, G149A (FC=55-130) by Day 56.

HIV-1 viruses (25 with single mutations, Table 16, and Table 17 with two or more mutations, Table 17) were produced from wildtype virus NL-432 using site directed mutagenesis. CAB showed anti-HIV activity with FC <5 in viral susceptibility for 22 of 25 INI-resistant mutant viruses with single mutations; for DTG 24/25 mutant viruses had FC <5. While both CAB and DTG had >5-FC with G118R, only CAB had >5 FC with Q148K and Q148R. F121Y and T124A caused no increase in FC for either CAB or DTG. N155H resulted in 1.7 FC to CAB and 0.99 FC to DTG.

Among the multiple site directed mutants, the highest FC was observed with mutants containing Q148K or Q148R. E138K, Q148H each gave just 0.92 FC to CAB while E138K, Q148K gave 81 FC to CAB. G140C, Q148R and G140S, Q148R gave 22 and 12 FC to CAB, respectively. While N155H alone did not alter susceptibility to CAB, the combination of N155H and Q148R gave 61 FC to CAB.

A series of in vitro studies have been conducted to investigate the virology of CAB. A listing of these studies is provided in Table 1.

Table 1 List of Virology (Primary Pharmacodynamic) Non-Clinical Studies Performed with CAB

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	GLP	Testing Facility
In vitro antiviral activity of the HIV integrase inhibitor, GSK1265744 GSK Document Number RH2007/00068/00	Human MT-4 cells and Human PBMCs	In vitro	No	GSK
Antiviral and biochemical activity of HIV integrase inhibitor ERC-265744 GSK Document Number RH2007/00218/00 (CJ-2007-ERC-265744-001)	Human MT-4 cells and Human PBMCs	In vitro	No	GSK and [redacted]
Analysis of Antiviral Mechanism of S-265744 sodium on HIV Replication by Quantitative PCR GSK Document Number RH2010/00019/00	Human MT-4 cells	In vitro	No	[redacted]
Cytotoxicity evaluation of the HIV-1 integrase inhibitor GSK1265744A in human B and T cell lines and peripheral blood lymphocytes GSK Document Number RH2007/00034/00	Human B and T Cells and Human PBMCs	In vitro	No	GSK
Testing of GSKD against a panel of HIV-1 and HIV-2 virus isolates in fresh human PBMCs and macrophage cells. GSK Document Number RH2008/00133/00	Human PBMCs and Human Monocyte / Macrophages	In vitro	No	[redacted]
Testing of GSK1247744 against multiple clinical isolates of HIV-1 GSK Document Number RH2007/00092/01	Human PBMCs	In vitro	No	GSK

Module 2.7.2.4 Special Studies

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	GLP	Testing Facility
Anti-HIV activity of ERC-265744 against INI-resistant HIV-1 strains GSK Document Number RH2007/00213/00 (E-265744-EB-001-R)	Human HeLa-CDr	In vitro	No	GSK and [redacted]
Isolation of ERC-1265744 resistant mutants of HIV-1 GSK Document Number RH2007/00210/00 (E-265744-EB-002-R)	Human MT-2, HeLa-CD4 and M8166 cells	In vitro	No	GSK and [redacted]
Anti-HIV activity of S-265744 sodium against Raltegravir resistant HIV-1 strains GSK Document Number 2013N166662_00 (S-265744-EB-007-R)	Human HeLa CD4 cells	In vitro	No	GSK and [redacted]
Anti-HIV activity of S-265744 sodium against reverse transcriptase inhibitor resistant HIV-1 strains GSK Document Number 2013N166663_00(S-265744-EB-008-R)	Human HeLa CD4 cells	In vitro	No	GSK and [redacted]
Anti-HIV activity of S-265744 sodium against protease inhibitor resistant HIV-1 strains GSK Document Number 2013N166664_00 (S-265744-EB-009-R)	Human MT4 cells	In vitro	No	GSK and [redacted]
Isolation of S-265744 resistant mutants from integrase inhibitor resistant HIV-1 strains GSK Document Number 2013N166665_00 (S-265744-EB-010-R)	Human MT2 cells	In vitro	No	GSK and [redacted]

Module 2.7.2.4 Special Studies

Type of Study **Document Number** **Status**	**Species (Strain)/ Test System**	**Method of Administration**	**GLP**	**Testing Facility**
Evaluation for the susceptibility of S-265744 resistant HIV-1 strains isolated from in vitro passage study to S-265744 GSK Document Number 2013N166667_00 (S-265744-EB-012-N)	Human HeLa CD4 cells	In vitro	No	GSK and [redacted]
Anti-HIV activity of S-265744 in combination with other antiviral agents in MT-4 cells GSK Document Number 2013N166668_00 (S-265744-EB-013-N)	Human MT-4 cells	In vitro	No	GSK and [redacted]
Secondary Pharmacological Evaluation of the HIV Integrase Inhibitor GSK1265744Q in radioligand binding and enzyme assays and isolated tissue assays GSK Document Number RH2007/00209/00	Recombinant HIV integrase	In vitro	No	GSK
GSK1265744 against Non-HIV Viruses 2019N395410_00		In vitro	No	[redacted]
Anti-HIV activity against raltegravir-resistant strains GSK Document Number RH2008/00143/00		In vitro	No	GSK and [redacted]
Anti-HIV activity of GSK1349572 against raltegravir-resistant HIV-1 strains GSK Document Number RH2007/00115/00		In vitro	No	GSK and [redacted]

4.1.1. Mechanism of Action

CAB inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

The antiviral mechanism of CAB on HIV replication was investigated [GSK Document Number RH2010/00019/00, GSK Document Number RH2007/00210/00, GSK Document Number 2013N166667_00, GSK Document Number RH2007/00209/00] using quantitative PCR, in vitro passage, and direct binding dissociation studies. CAB demonstrated equivalent potency against two nonnucleoside inhibitor resistant, two nucleoside inhibitor resistant and two protease inhibitor resistant HIV-1 mutant clones (one with three and one with six mutations) compared with the wild type strain [GSK Document Number 2013N166663_00, GSK Document Number 2013N166664_00]. In addition, passage studies with CAB selected mutations within the integrase enzyme; some of those mutations recreated as site-direct mutant HIV virus conferred moderate levels of CAB resistance when compared to wild type viurs [GSK Document Number RH2007/00210/00].

4.1.2. In Vitro Antiviral Activity against Wild-type HIV-1 Strains in PBMC, MT4 and CIP4 Cell Lines

CAB activity against Ba-L HIV-1 in PBMCs, HIV-1 strain IIIB in MT4 cells and pseudotyped HIV-1 in cell line derived from 293T cells (CIP4) cells was examined [GSK Document Number RH2007/00068/00].

For PBMC assays, cells were stimulated with phytohemagglutinin and interleukin-2 and infected with HIV-1 strain BaL or HIV-1 strain NL432. Following incubation with CAB for 4 or 7 days, the antiviral activity was assayed by reverse transcriptase (RT) activity resulting in effective dose 50 (EC_{50}s) of 0.22 nM (BaL) and 0.53 nM (NL432). For MT-4 assays, cells were infected with HIV-1 strain IIIB and incubated with CAB for 4 or 5 days followed by cell viability analyses with CellTiter-Glo or MTT resulting in EC_{50}s of 0.57 and 2.1 nM, respectively (Table 2). For pseudotyped HIV (PHIV) assays, the infected cells were incubated with CAB for 2 days and when assayed for cell viability by Steady Glo gave an EC_{50} of 0.74 nM.

Table 2 Antiviral Activity of CAB in PBMC, MT4, or CIP4 cells

Cells/Cell lines	Virus	CAB Geometric mean EC_{50} (nM)	95% CI	N
PBMC	Ba-L	0.22	0.14-0.34	11
MT-4	HIV-1^{IIIB}	0.57	0.39-0.83	21
CIP4	PHIV vector	0.74	0.54-1.0	15

Data Source: RH2007/00068/00 Table 1, Table 2, and Table 3;

4.1.3. Effect of Human Serum and Serum Proteins

The effect of HSA (20 or 40 mg/mL), α_1-acid glycoprotein (AAG) (2 mg/mL) (Table 3) and human serum (extrapolated up to 100%) on the antiviral activity of CAB was evaluated in the PHIV or MT-4 assay systems. HSA was the predominant CAB binding component compared with AAG. Maximum fold shift observed with MT-4 assays performed at GSK [GSK Document Number RH2007/00068/00] and extrapolated to 100% human serum provided a mean consensus 660-fold shift in the EC_{50} values for CAB [and a resulting PA-EC_{50} of 101 nM for PBMCs in 100% serum [GSK Document Number RH2007/00068/00, Table 8].

Table 3 The Effect of Serum Proteins on Antiviral Activity of CAB in HIV-1 IIIB-Infected MT4 Cells

Serum Protein	Geometric Mean EC_{50}	95% Confidence Interval	Potency Shift	N
40 mg/mL HSA	220 nM	180 – 270 nM	390-fold	14
2 mg/mL AAG	0.33 nM	0.20 – 18 nM	0.57-fold	6

Data Source: RH2007/00068/00 Table 4 and Table 5

4.1.4. Antiviral Activity in Combination with other Antiviral Agents

CAB was tested for antiviral activity in combination with currently approved antiviral drugs [GSK Document Number 2013N166668_00]. In vitro combination studies identify antagonism of antiviral activity indicating that certain drugs should not be used clinically in combination. In this regard, the in vitro combination data support the conclusion that the antiviral activity of CAB is compatible with RPV, 3TC, TDF, and FTC.

The in vitro anti-HIV-1 activity of CAB was studied in checkerboard format in combination with representative anti-HIV drugs (RPV, 3TC, TDF, and FTC), in MT-4 cells with HIV-1 strain IIIB (Table 4). All were additive or weakly synergistic with CAB.

Table 4 Inhibition of HIV-1_{IIIB} by CAB in Combination with Other Marketed Anti-HIV Agents in MT-4 cells

Compound	Deviation from Additivity		Interaction with CAB
	Average	SD	
RPV	-0.068	0.031	Additive
3TC	-0.127	0.041	Weak Synergy
TDF	-0.145	0.040	Weak Synergy
FTC	-0.103	0.026	Weak Synergy
CAB	-0.053	0.037	Additive

Data Source: 2013N166668_00, Table 1

4.1.5. Evaluation of Cytotoxicity in Antiviral Assays

Cytotoxicity assays with CAB were conducted in parallel with the antiviral assays [GSK Document Number RH2007/00068/00, GSK Document Number RH2007/00034/00]. Overall the cytotoxicities measured in these assays were distinct from the antiviral potencies and provided selectivity ratios from 6300-fold to 22,000-fold indicating that the observed antiviral activity of CAB was not due to cytotoxicity.

4.1.6. Evaluation of Cytotoxicity in Human Cell Lines and Peripheral Blood Mononuclear Cells

Cytotoxicity assays were conducted in proliferating human leukemic and lymphomic cell lines and PHA stimulated and unstimulated human PBMCs from the same donors, with resulting cell cytotoxicity (CC) IC_{50}s for CAB in proliferating IM-9, U-937, MT-4 and Molt-4 cells of 6.4, 5.0, 9.2 and 13 μM, respectively and in unstimulated and stimulated PBMCs of 120 μM and 42 μM, respectively [GSK Document Number RH2007/00034/00] (Table 5). When compared to the antiviral activity of CAB IC_{50} of 1.3 nM in PBMCs the selectivity index for antiviral activity was >10,000.

Table 5 Cytotoxicity Assay Results in PBMCs and B and T Cells

Cells/Cell lines	CAB CC_{50} (μM)	95% CI	Flavopiridol CC_{50} (μM)	95% CI
IM-9 (n=4)	6.4	4-10	0.019	0.012-0.030
U-937 (n=4)	5.0	3.4–7.3	0.035	0.024-0.050
MT-4 (n=4)	9.2	4.5-19	0.13	0.062-0.26
Molt-4 (n=4)	13	11-17	0.16	0.13-0.21
Stimulated PBMCs (n=8)	42	29-61	0.36	0.25-0.53
Unstimulated PBMCs (n=8)	120	53-280	0.29	0.15-0.56

Data Source:RH2007/00034/00 Table 1

4.1.7. Susceptibility of Multiple Subtype B Clinical Isolates of HIV-1

CAB activity against site directed mutant strains and clinical isolates with integrase resistance mutations was evaluated at MBI using the Integrase PhenoSense assay [GSK Document Number RH2007/00092/01].

The susceptibility of 13 clinically diverse HIV-1 subtype B isolates to integrase inhibition by CAB was tested with MBI PhenoSense assay. The mean IC_{50} for viral replication of the clinical isolate based viruses was 1.3 nM (range 1.0 to 1.6 nM) (Table 6).

Table 6 Activity of CAB against a Panel of HIV-1 Subtype B Clinical Isolates

Virus	EC_{50} (nM)
ASJM 108	1.5
ASM 34	1.4
ASM 42	1.3
NIH 57	1.5
NIH 660	1.0
NIH 657	1.4
NIH 714	1.4
NIH 727	1.3
CV 110	1.1
CV 154	1.2
CV 163	1.2
CV 243	1.1
CV 281	1.1
HIV-1 IIIB	1.1
HXB2	1.6
NL4-3	1.4
Isolate mean	1.3
Isolate Median	1.3
Isolate standard deviation	0.2
Isolate range	1.0-1.6
Laboratory virus mean	1.4
Laboratory virus median	1.4
Laboratory virus standard deviation	0.2
Laboratory virus range	1.1-1.6
Data Source: RH2007/00092/01 Table 1	

4.1.8. Susceptibility of a Panel of HIV-1 and HIV-2 Isolates in PBMCs and Monocyte Derived Macrophages

The antiviral activity of CAB was tested against a panel of HIV-1 isolates (3 in each group of M subtypes A, B, C, D, E, F and G, and 3 group O isolates) (Table 7) and 4 HIV-2 isolates in PBMC assays [GSK Document Number RH2008/00133/00] (Table 8).

CAB was highly active with broad activity against all HIV-1 (geometric mean EC_{50} of 0.26 nM and range of 0.02 to 1.06 nM) and HIV-2 (geometric mean EC_{50} of 0.12 nM and range of 0.10 to 0.14 nM) isolates tested. In the monocyte-derived macrophage assays using 4 Subtype B isolates, the geometric mean EC_{50} was 0.92 nM and values ranged from 0.29 to 1.64 nM (Table 9).

Mean EC_{50}s for each of these categories are summarized in Table 10.

Table 7 Activity of CAB against Group M and O HIV-1 in PBMCs

HIV-1 Isolate	Envelope Subtype	EC_{50} (nM)
92RW009	A	0.13
92UG037	A	0.09
92UG029	A	0.71
92BR014	B	0.50
JR-CSF	B	0.05
92TH026	B	0.02
Ba-L	B	<0.10
Ba-L	B	0.17
92BR025	C	0.12
93IN101	C	<0.10
93IN101	C	0.22
93MW959	C	0.13
92UG001	D	0.34
92UG024	D	0.55
92UG046	D	0.24
93TH073	E	0.16
CMU08	E	0.36
CMU06	E	0.37
93BR019	F	0.16
93BR020	F	0.07
93BR029	F	<0.10
93BR029	F	0.06
JV1083	G	0.43
RU132	G	0.16
G3	G	0.06
BCF01	O	0.30
BCF02	O	0.55
BCF03	O	1.06

Data Source:RH2008/00133/00 Table 3

Table 8 Activity of CAB against HIV-2 Isolates in PBMCs

HIV-2 Isolate	EC_{50} (nM)
CDC 310319	0.11
CDC 310342	0.14
CEC 310342	0.12
CBL 20	0.10

Data Source:RH2008/00133/00 Table 4

Table 9 Activity of CAB against Subtype B Isolates in Macrophages

HIV-1 Isolate	EC_{50} (nM)
Ada	0.29
Ba-L	1.64
92BR014	1.36
92TH026	0.38

Data Source: RH2008/00133/00 Table 5

Table 10 Mean Activity of CAB against Broad Subtypes and HIV-2 in PBMCs, and Subtype B Isolates in Macrophages

Virus	Mean EC_{50} (nM)
Subtype A	0.31
Subtype B	0.17
Subtype C	0.14
Subtype D	0.38
Subtype E	0.30
Subtype F	0.10
Subtype G	0.22
Group O	0.64
HIV-2	0.12
Subtype B in Macrophages	0.92

Data Source: RH2008/00133/00 Table 3, Table 4, Table 5, Table 7, and Table 8

4.1.9. Activity against non-HIV Viruses

CAB was evaluated for antiviral activity against a panel of 11 non-HIV viruses (Table 11, Table 12, Table 13). In general, CAB did not exhibit significant antiviral activity in this panel [GSK Document Number 2019N395410_00]. Some activity was observed against rhinovirus (EC_{50} = 12.6 μM), (Table 11).

Table 11 Activity of CAB against non-HIV Viruses in Cytoprotection Assays

Virus	High Concentration (μM)	EC_{50} (μM)	TC_{50} (μM)
HSV-2	100	>100	>100
Influenza A	100	>100	>100
Human Parainfluenza	100	>100	>100
Measles Virus (Morilli virus)	100	>100	>100
Coxsackie A Virus	100	>100	>100
Coxsackie B Virus	100	>100	>100
Venezuelan Equine Encephalopathy virus	100	>100	>100
Polio Virus	100	>100	>100
Rhinovirus	100	12.6	>100

Data Source: 2019N395410_00 Table 4

Table 12 Activity of CAB against Hepatitis B Virus (Taqman Assay)

Virus	High Concentration (μM)	EC_{50} (μM)	TC_{50} (μM)
HBV	100	>100	>100

Data Source: 2019N395410_00 Table 4

Table 13 Activity of CAB against VZV in a Plaque Reduction Assay

Virus	High Concentration (μM)	EC_{50} (μM)	TC_{50} (μM)
VZV	400	202	>400

Data Source: 2019N395410_00 Table 4

4.1.10. Isolation of CAB Resistant HIV-1 Mutants

Selection of resistant mutants during in vitro passage of virus in the presence of drug may provide insight into the resistance mutations selected in vivo. Resistant mutants were isolated during passage of wild type virus or virus with RAL resistant mutants.

4.1.10.1. Isolation from Wild type HIV-1 Strain IIIB

Virus cultures were derived by co-culturing MT-2 cells with Molt-4 cells persistently infected with HIV-1 strain IIIB [GSK Document Number RH2007/00210/00]. This strain has ~40% T124A polymorphism in integrase in viral stocks used for passage [Kobayashi, 2011]. The culture media from the co-cultures, including resuspended co-cultured cells, was used for initiating passage of resistant variants. Every 3 or 4 days the cells were examined for apparent cytopathic effects and supernatants were used to infect new MT-2 cells in the presence of increasing CAB concentrations (up to 5-fold). Infected cell DNA was prepared and HIV proviral DNA sequence was determined.

At selected intervals (14, 28, 42, 56, 70, 84, 98 and 112 days), susceptibility to CAB was measured using the supernatant from passaged cells (briefly expanded in fresh M8166 cells) in assays using HeLa-CD4 cells carrying a reporter β-galactosidase gene. Viruses with >10-fold decrease in susceptibility to CAB were not observed during the 112 day passage: The following IN mutations emerged after passaging wild type HIV-1 (with T124A polymorphism) in the presence of CAB: Q146L (FC range 1.3-4.6), S153Y (FC range 3.6-8.4), S153F (FC range 6.3-6.4), and I162M (FC=2.8) As noted above, the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility to CAB. These data are consistent with direct targeting of the HIV-1 integrase in cells and provide a relative fold resistance level for virus with these substitutions (Table 14).

Table 14 Passage with HIV IIIB

Days of Culture	Amino Acid Substitution	CAB Fold Change
14	T124A	1.2-1.9
28	T124A	1.4-5.5
42	T124A	<0.88-4.0
56	T124A	1.1-4.6
	Q146L	3.3
	S153Y	4.7
	T124A, S153F	6.4
70	T124A	1.1-3.8
	Q146L	1.3
	S153Y	2.8-3.0
	T124A, S153Y	3.6
84	T124A	1.3-5.7
	Q146L	2.9
	S153Y	4.3-5.1
	T124A, S153Y	8.4
	T124A, I162M	2.8
98	T124A	1.3-5.2
	Q146L	3.9
	S153Y	4.7-6.0
	T124A, S153F	6.3
112	T124A	1.1-7.4
	Q146L	4.6
	S153Y	5.1-5.6
	T124A, S153Y	6.6

Data Source: RH2007/00210/00 Table 1

4.1.10.2. Isolation from Wild Type NL-432 and Site Directed Mutant INI Resistant HIV-1 Strain NL432

Wild type HIV-1 NL432 and molecular clones with single amino acid substitutions (E92Q, Q148H, Q148K, Q148R, and N155H) within the IN open reading frame were passaged sequentially under increasing concentration of CAB for up to 56 days [GSK

Document Number 2013N166665_00]. Passaged virus populations were analyzed for genotypic changes on Days 14, 28, 42 and 56, and for phenotypic fold change (FC) on Day 56 samples (Table 15).

Starting with mutants at IN position 148 (H, K, or R), the following additional mutations emerged after passaging with CAB: G56S, V72I, L74M, V75A, T122N, E138K, G140S, G149A, and M154I. CAB FC for various combinations of these mutations with Q148H/K/R ranged from 2.2 to 410, relative to that observed for NL432.

Table 15 Passage of NL-432 and Single Mutants with CAB

Initial Virus / Single Mutant	CAB Initial Conc. / Final Conc (nM)	Days of Culture	Amino Acid Substitution	CAB Fold Change of Passaged Virus Pools
NL-432	6.4 / 160	56	No mutation	0.85-1.3
	32	56	No replication	
	160	56	No replication	
Q148K	6.4 / 160	14	Q148K	
		28	E138K, Q148K	
		42	E138K, Q148K	
		56	E138K, Q148K	89-260
	32 / 160	14	E138K, Q148K	
		28	E138K, Q148K	
		42	E138K, Q148K	
		56	E138K, Q148K	53-190
			V72I, E138K, Q148K	410
	160	56	No replication	
Q148R	6.4 / 160	14	Q148R	
		28	Q148R E138K, Q148R	
		42	L74M, Q148R E138K, Q148R	-
		56	L74M, Q148R	
			E138K, Q148R	3.0-11
	32	56	No replication	
	160	56	No replication	
Q148H	6.4 / 160	14	G140S, Q148H	
		28	G140S, Q148H	
		42	G140S, Q148H E138K, G140S, Q148H L74M, V75A, G140S, Q148H	2.0 17 21 - 160
	32 / 160	28	G140S, Q148H	
		42	G140S, Q148H G140S G148H, G149A	

Initial Virus / Single Mutant	CAB Initial Conc. / Final Conc (nM)	Days of Culture	Amino Acid Substitution	CAB Fold Change of Passaged Virus Pools
			C56S, G140S, G148H, G149A	
		56	T122N, G140S, Q148H G140S, Q148H, M154I G56S, G140S, Q148H, G149A	16 2.2 55 - 130
	160	56	No replication	
N155H	6.4 / 6.4	14	N155H	
		28	N155H	
		42	N155H	
		56	N155H	1.1 – 2.0
	32		No replication	
	160		No replication	
E92Q	6.4 / 6.4	14	E92Q	
		28	E92Q	
		42	E92Q	
		56	E92Q	0.52 – 0.77
	32		No replication	
	160		No replication	

Data Source: 2013N166665_00 Table 1

Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM CAB and increasing to 160 nM CAB selected for no substitutions in the IN region by Day 56 (FC=0.85-1.3). Virus could not be replicated during passage of wild type HIV-1 NL432 in the presence of 32 or 160 nM CAB.

Passage of the Q148K mutant in the presence of 6.4 nM CAB selected for E138K, Q148K (FC=89-260) on Day 28 and was present throughout the remaining passages up to 160 nM CAB with no additional substitutions selected up to Day 56. Passage of the Q148K mutant in the presence of 32 nM CAB selected for E138K, Q148K (FC=53-190) on Day 14. Virus with V72I, E138K, Q148K (FC=410) was also isolated at Day 56.

Passage of the Q148R mutant selected E138K, Q148R and L74M, Q148R (FC=3-11) on Days 28 and 42, respectively, in the presence of 6.4 nM CAB, increasing to 160 nM CAB. Virus could not be replicated from the Q148R mutant passaged at 32 and 160 nM.

Passage of Q148H in the presence of 6.4 nM CAB selected G140S, Q148H (FC=2) on Day 14 and a mixture of G140S, Q148H (FC=2), E138K, G140S, Q148H (FC=17) and L74M, V75A, G140S, Q148H (FC=21-160) by Day 42. Passage of the Q148H mutant in the presence of 32 nM CAB selected for G140S, Q148H by Day 28 and T122N, G140, Q148H (FC=16), G140S, Q148H, M154I (FC=2.2) and G56S, G140S, Q148H, G149A (FC=55-130) by Day 56.

Passage of the E92Q or N155H mutant viruses in the presence of CAB did not lead to additional substitutions

4.1.11. Comparative Assessment of Resistance

Comparative susceptibilities to CAB, DTG and RAL were obtained from 60 RAL resistant site directed HIV-1 mutants.

4.1.11.1. Forty-two Integrase Inhibitor Resistant HIV-1 Strains

HIV-1 viruses (25 with single mutations, Table 16, and Table 17 with two or more mutations,) were produced from wildtype virus NL-432 using site directed mutagenesis. CAB, DTG and RAL susceptibilities were tested in HeLa-CD4 cell assay carrying a reporter β-galactosidase gene driven by HIV-1 LTR [GSK Document Number RH2007/00213/00, GSK Document Number RH2007/00115/00, GSK Document Number RH2008/00143/00, , GSK Document 2013N167276_00). CAB showed anti-HIV activity (susceptibility) with fold change (FC) <5 against 22 of 25 INI-resistant mutant viruses with single mutations; for DTG there were 24/25 mutant viruses with FC <5. While both CAB and DTG had >5-FC with G118R, only CAB had >5 FC with Q148K and Q148R. F121Y and T124A caused no increase in FC for either CAB or DTG. N155H resulted in 1.7 FC to CAB and 0.99 FC to DTG (Table 16).

Among the multiple mutants, the highest FC for CAB was observed with mutants containing Q148K or Q148R. E138K, Q148H gave just 0.92 FC to CAB but E138K, Q148K gave 81 FC to CAB. G140C, Q148R and G140S, Q148R gave 22 and 12 FC to CAB, respectively. While N155H did not alter susceptibility to CAB, N155H, Q148R gave 61 FC to CAB (Table 17).

The following IN mutations were associated with a CAB FC ≥2.5: T66K; G118R; Q148K/R; T66K, L74M; E92Q, N155H; E138K, Q148K/R; G140C/S, Q148H/K/R; T97A, N155H; L74M, N155H and Q148R, N155H.

Table 16 Fold Change (FC) of CAB, DTG and RAL against INI-Resistance Single Mutant Viruses by HeLa-CD4 Assay

Virus	CAB FC (SD)	DTG FC (SD)	RAL FC (SD)
Wild type (NL432)	1.0 (IC_{50}=1.6 nM, SD=0.27)	1.0 (IC_{50}=2.1 nM, SD=0.36)	1.0 (IC_{50}=6.1 nM, SD=0.89)
T66A	0.31 (0.03)	0.26 (0.01)	0.61 (0.09)
T66I	0.33 (0.08)	0.26 (0.09)	0.51 (0.10
T66K	2.7 (0.44)	2.3 (0.35)	9.6 (1.3)
E92I	1.8 (0.21)	1.5 (0.19)	2.1 (0.62)
E92Q	1.5 (0.11)	1.6 (0.12)	3.5 (1.4)
E92V	1.5 (0.15)	1.3 (0.20)	1.4 (0.18)
G118R	8.9 (0.86)	10 (4.7)	7.2 (1.5)
G118S	1.1 (0.35)	1.1 (0.21)	1.2 (0.30)
F121Y	1.0 (0.28)	0.81 (0.12)	6.1 (1.3)
T124A	0.97 (0.15)	0.95 (0.19)	0.82 (0.08)
G140S	0.81 (0.11)	0.86 (0.30)	1.1 (0.22)
Y143C	1.1 (0.29)	0.95 (0.26	3.2 (0.57)
Y143H	1.1 (0.21)	0.89 (0.11)	1.8 (0.38)
Y143R	1.4 (0.22)	1.4 (0.29)	16 (3.9)
P145S	0.43 (0.03)	0.49 (0.08)	0.87 (0.20)
Q146R	1.7 (0.25)	1.6 (0.17)	1.2 (0.26)
Q148H	0.86 (0.12)	0.97 (0.67)	13 (5.0)
Q148K	5.6 (0.61)	1.1 (0.19)	83 (6.6)
Q148R	5.1 (1.8)	1.2 (0.21)	47 (9.3)
I151L	2.5 (0.48)	3.6 (3.6)	8.4 (4.7)
S153Y	2.0 (0.63)	2.5 (1.1)	1.3 (0.19)
M154I	0.97 (0.10)	0.93 (0.27)	0.82 (0.18)
N155H	1.7 (0.18)	0.99 (0.094)	8.4 (1.8)
N155S	1.5 (0.29)	1.4 (0.36)	6.2 (1.9)
N155T	1.5 (0.26)	1.9 (0.32)	5.2 (2.0)

Data Source:RH2007/00213/00 Table 1, RH2007/00115_00 Table 1, RH2008_00143 Table 1 Table 2

Table 17 Fold Change (FC) of CAB, DTG and RAL against INI-Resistance Multiple Mutant Viruses by HeLa-CD4 Assay

virus	CAB FC (SD)	DTG FC (SD)	RAL FC (SD)
Wild type (NL432)	1.0 (IC_{50}=1.6 nM, SD=0.27)	1.0 (IC_{50}=2.1 nM, SD=0.36)	1.0 (IC_{50}=6.1 nM, SD=0.89)
T66I, I74M	0.38 (0.11)	0.35 (0.08)	2.0 (0.81)
T66I, E92Q	1.0 (0.38)	1.2 (0.19)	18 (3.6)
T66K, L74M	6.3 (1.8)	3.5 (0.94)	40 (13)
L74M, N155H	2.5 (0.04)	0.91 (0.17)	28 (12)
E92Q, N155H	5.3 (2.8)	2.5 (1.2)	>130
T97A, N155H	2.9 (0.27)	1.1 (0.46)	26 (7.9)
V72I, F121Y, T125K	2.0 (0.61)	1.3 (0.54)	13 (7.1)
V72I, F121Y, T125K, I151V	1.6 (0.66)	1.2 (0.32)	7.0 (2.8)
F121Y, T125K	1.4 (0.55)	0.98 (0.35)	11 (0.49)
E138K, Q148H	0.92 (0.08	0.89 (0.24)	17 (5.9)
E138K, Q148K	81 (24)	19 (8.0)	330 (75)
E138K, Q148R	12 (3.4)	4.0 (1.1)	110 (37)
G140C, Q148R	22 (4.9)	4.9 (1.8)	200 (42)
G140S, Q148K	5.6 (2.5)	1.5 (0.10)	3.7 (1.3)
G140S, Q148R	12 (3.5)	8.4 (4.0)	200 (5.3)
G140S, Q148H	6.1 (0.75)	2.6 (1.4)	>130
Q148R, N155H	61 (28)	10 (1.4)	>140

Data Source: :RH2007/00213/00 Table 1, RH2007/00115_00, Table 1, RH2008/00143_00, Table 1, Table 2

4.1.11.2. Half-Life of Dissociation

Integrase:DNA duplexes were attached to Scintillation Proximity Assay imaging bead; incubated overnight with [^{3}H]-labeled CAB, DTG, RAL or EVG overnight to achieve maximum binding. Excess unlabeled INI was added to block re-binding of the released [^{3}H] INI. Binding kinetics of CAB showed a decreased dissociative half-life with Q148K and Q138R SDMs. The half-life is between that of DTG and RAL (Table 18) (Dudas et al.2015).

Table 18 Half-Life (Hours) of Dissociation for WT and SDM Integrases at 37°C

WT or SDM	CAB	DTG	RAL	EVG
WT	51	71	8.8	2.7
Q148H	6.3	5.2	0.2	0.2
Q148K	2.0	11	0.3	ND
Q148R	2.2	9.2	0.4	ND

4.2. Clinical Virology – CAB + RPV

The combination of CAB and RPV has been studied in 4 Phase IIb/III and one Phase IIIb clinical trials. Oral CAB in combination with oral RPV was studied in LATTE (LAI116482, Section 4.2.2.2) CAB + RPV LA were studied in LATTE-2 (200056, Section 4.2.2.1), ATLAS (201585, Section 4.2.1.1), FLAIR (201584, Section 4.2.1.2) and ATLAS-2M (207966, Section 4.2.1.4). High level conclusions are given below:

The only subject with PDVF and treatment emergent mutations on CAB + RPV LA in LATTE-2 had INI RAM Q148R (CAB FC=5.1) and NNRTI RAMs K103N, E138G, K238T (RPV FC=3.3).

Two of the three CVFs (3/308, 1%) on CAB + RPV in 201585 (ATLAS) had subtype A or A1 and IN substitution L74I at both Day 1 PBMC HIV-1 DNA and SVF HIV-1 RNA. The third CVF had Subtype AG with no L74I at either timepoint. All 3 CVFs in the CAB +RPV group had RPV resistance mutations at the E138 position at virologic failure timepoint. These RAMs were also present in the Baseline HIV-1 viral DNA for 2 of these 3 subjects. One of the CVFs in the CAB + RPV group had INI resistance mutation N155H - this subject had a history of RAL use.

The three CVFs on CAB + RPV in 201584 (FLAIR) with resistance data had either Subtype A or A1 with IN mutation L74I detected at Baseline and SVF. Three CVFs in the CAB+ RPV group had treatment emergent RPV and INI resistant mutations. All 3 had CAB resistance in vitro; 2 of the 3 had RPV resistance in vitro. A fourth subject with CVF (4/283, 1%) never received an injection and virology data at SVF was not produced.

In the FLAIR study, L74I was present in 54/243 (22%) of subjects with Baseline integrase genotypes in the CAB + RPV group, 3/54 (5.6%) of these subjects with L74I had CVF. 50/54 (93%) subjects in the CAB + RPV group with L74I had <50 c/mL HIV-1 RNA at Week 48 (Snapshot Analysis). L74I was more common in Subtype A, A1, and AG (84%, 63%, 30% respectively, for those subjects in the CAB + RPV group) than in Subtype B (7% in the CAB + RPV group). Exploratory subgroup analysis results suggest that the presence of the integrase L74I substitution does not appear to differentially impact the treatment effect Week 48 in primary or secondary endpoint outcomes for CAB- (CAB + RPV) or DTG- (DTG/ABC/3TC) containing regimens.

In the pooled ATLAS and FLAIR studies, there were 7 CVFs on CAB + RPV (7/591, 1.2%) and 7 CVFs on CAR (7/591, 1.2%). Four of the 7 CVFs on CAB + RPV had INI RAMs and 6/7 had RPV RAMs. Three of 7 subjects developed dual resistance to CAB and RPV. The seventh CVF (FLAIR) never received an injection and resistance testing was not performed.

CVF was uncommon in 207966 (ATLAS-2M) with 8/522 (1.3%) subjects in the Q8W arm and 2/523 (0.4%) subjects in the Q4W arm (one before and one after Week 24). RPV resistance-associated mutations were present at Baseline in PBMCs for 5/8 subjects in the Q8W arm and no subjects in the Q4W arm. One subject in the Q8W arm had INI mutation G140G/R at Baseline. 6/8 CVFs in the Q8W arm and 1/2 CVF in the Q4W arm had RPV resistance-associated mutations at the SVF timepoint. Two subjects had a

history of NNRTI use. 5/7 CVFs in the Q8W arm and both CVFs in the Q4W arm had INI resistance mutations at the virologic failure timepoint. Two subjects (1 subject in each arm) had a history of RAL use. INI polymorphism, L74I, was observed at Baseline in 5/8 CVFs in Q8W arm and no subjects in the Q4W arm. At the SVF timepoint, 4/7 CVFs had L74I in the Q8W arm and none had L74I in the Q4W arm.

4.2.1. Phase III Studies

4.2.1.1. 201585 (ATLAS)

Study Design: Study 201585 is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen. 618 adult HIV-1 infected patients who were on a stable ARV regimen containing 2 NRTIs plus an INI, NNRTI, or a PI were randomized 1:1 to continue CAR or were switched to the CAB + RPV regimen through 52 weeks. Following the Week 52 visit, eligible subjects were given the option to transition to study 207966 (ATLAS-2M, comparing CAB + RPV Q4W to CAB + RPV Q8W) or to continue within the study 201585 Extension Phase. This study will continue (Extension Phase) for up to at least 96 weeks.

4.2.1.1.1. Confirmed Virologic Failure

The proportion of subjects with CVF up to Week 48 was a pre-defined secondary endpoint. CVF is defined as indicated by two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. CVF through Week 48 was low in the study and was distributed evenly between the groups, with 7 subjects meeting CVF: 3 subjects (1% of total 308 subjects) in the CAB + RPV group and 4 subjects (1.3% of total 308 subjects) in the CAR group (Data Source: 201585 Week 48 CSR Table 2.21). The number of subjects meeting confirmed virologic failure criteria by visit was similar in both treatment groups (Table 19).

Table 19 Number of Subjects Meeting Confirmed Virologic Failure Criteria by Visit (Maintenance Phase)

SVF Timepoint- Confirmed	CAB + RPV (N=3/308)	CAR (N=4/308)
Week 8	1	0
Week 12	1	0
Week 20	0	2
Week 24	1	0
Week 32	0	1
Week 40	0	1
Week 48	0	0
Any Timepoint	3	4

Data Source: 201585 Week 48 CSR Listing 40.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

4.2.1.1.2. HIV-1 Viral Genotyping and Phenotyping

Plasma samples collected at the SVF timepoint, the first of the 2 consecutive time points with HIV-1 RNA ≥ 200 c/mL, were analyzed for on-treatment resistance using Monogram Biosciences PhenoSense GT, PhenoSense Integrase and GenoSeq Integrase testing methods for PR, RT and IN. However, since subjects entered the study virologically suppressed (<50 c/mL), HIV-1 Baseline resistance testing could not be conducted using plasma samples and was therefore carried out on PBMCs to retrospectively evaluate pre-existing resistance in subjects with CVF. The Monogram Biosciences GenoSure Archive assay provides HIV-1 PRO, RT, and IN genotype data from integrated HIV-1 proviral DNA but does not generate phenotypic data. Of note, resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing [Sharkey, 2005]. As such, HIV-1 DNA resistance testing is exploratory and its primary value is in showing whether resistance is present, and it is less definitive at showing that resistance is not present.

For the 3 CVF subjects in the CAB + RPV group, mutations at RT position, E138, were present in all 3 subjects at the time of SVF, with decreased susceptibility to RPV (FC=2.4, 3.7, 6.5 (BCO for RPV as determined by Monogram Biosciences = 2.0)). Mutations at this position were also present in Baseline HIV-1 DNA for 2 subjects. One subject also had INI substitution, L74I, present at both Baseline HIV-1 DNA and at SVF. Another subject had INI RAM, N155H, at SVF, which was not observed in Baseline HIV-1 DNA and resulted in reduced susceptibility to CAB (FC=2.7 (BCO for CAB as determined by Monogram Biosciences = 2.5)), but not to DTG (FC=1.15). In addition this subject had the INI substitution, L74I, at both Baseline and SVF. The third subject had an additional NNRTI mutation, V108I, which was also present in Baseline HIV-1 DNA and could contribute to the reduced susceptibility to RPV that was observed (FC=3.7). The three subjects with CVF had Subtypes A, A1, or AG. (Table 20). As subjects entered ATLAS suppressed, plasma RNA sequencing was not performed and Subtype at Day 1 is not available for non-CVFs.

There were 4 CVF subjects in the CAR group, with 1 subject presenting at SVF with NNRTI RAM, M230M/I, with no corresponding decrease in susceptibility for RT drugs tested. This mutation was not present in Baseline HIV-1 DNA. Another subject had NNRTI RAM, G190S, and NRTI RAM, M184V, at SVF with only NRTI RAM, M184V, present in Baseline HIV-1 DNA. The phenotypic assay (RT/PR) failed for this subject. This subject also had INI substitution, L74I, at both Baseline and SVF, with no decreased INI susceptibility. Another subject had the NRTI RAM, M184I, at SVF with reduced susceptibility to FTC (FC= >97.2), which was part of their cART. The remaining subject had no RAMs present at SVF and no decreased susceptibility to any drugs tested (Table 20). See virology case narratives in Section 4.2.1.1.3

No subjects met CVF criteria after Week 48.

Table 20 Phenotypic and Genotypic Analysis of CVF subjects

Subject	Study ARM (Study ART)	On-Treatment, RAMs (HIV-1 RNA) SVF Timepoint				Drugs with reduced sensitivity (FC) SVF Timepoint[a]	Baseline RAMs[b] (PBMC/HIV-1 DNA) (Day 1)		Virus Subtype	
		RT		PRO	IN		RT	IN	Day 1 (PBMC/HIV-1 DNA)	SVF
		NRTI	NNRTI							
[redacted]	LA-CAB/LA-RPV	none	E138A	none	L74I	RPV(2.4)	E138E/A	L74I	A1	A
[redacted]	LA-CAB/LA-RPV	none	E138E/K	none	N155H L74I	EFV(3.3) ETR(5.2) RPV(6.5) EVG(33) RAL(16) CAB(2.7)	none	L74I	A	A1
[redacted]	LA-CAB/LA-RPV	none	V108I E138K	N88N/S	none	EFV(4.2) ETR(5.8) RPV(3.7)	V108V/I E138K	none	AG	AG
[redacted]	cART (EFV+3TC+AZT)	M184V	G190S	none	L74I	Phenotypic assay failed for RT/PR	M184M/I	L74I	Complex	A1
[redacted]	cART (EVG/Cobi+FTC+TDF)	M184I	none	none	none	FTC(>97.2)	none	none	B	B
[redacted]	cART (EVG/Cobi+FTC+TAF)	none	none	none	none	none	none	none	B	B
[redacted]	cART (EVG/Cobi+FTC+TDF)	none	M230M/I	none	none	none	none	none	B	B

Data Source: 201585 Week 48 CSR Table 8.8

[a]Reduced sensitivity was determined from the Clinical cutoffs or biological cutoffs used in PhenoSense GT assay by Monogram Biosciences

[b] No PI RAM s were observed in Baseline PBMC vDNA

4.2.1.1.3. Virology Narratives for Confirmed Virologic Failures

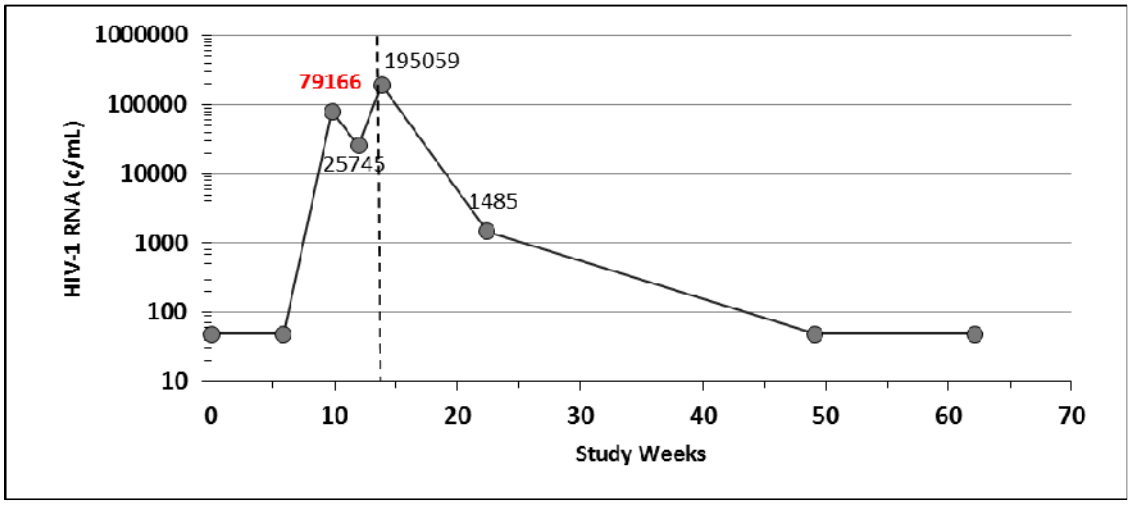
CAB + RPV group

For CAB PK, 201585 Week 48 CSR in-text Figure 9; for RPV PK, 201585 Week 48 CSR in-text Figure 10.

Subject [redacted]:

- CAB + RPV; female; Russia; BMI >15 to ≤25 kg/m^2
- Prior ART: lamivudine, ritonavir, lopinavir and zidovudine.
- SVF Week 8, HIV-1 RNA 79,166 c/mL; CVF Week 12, HIV-1 RNA 25,745 c/mL.
- Baseline PBMC vDNA had RPV resistance-associated mutation, E138E/A and INI substitution, L74I. Subtype A1.
- SVF plasma vRNA had RPV resistance-associated mutation, E138A and INI substitution, L74I. RPV FC= 2.4. CAB FC = 0.8. Subtype A.
- Prescribed lamivudine, ritonavir, lopinavir and zidovudine, and entered LTFU. Resuppression occurred at LTFU Month 9 visit.

Figure 1 Subject [redacted] HIV-1 Viral Load History

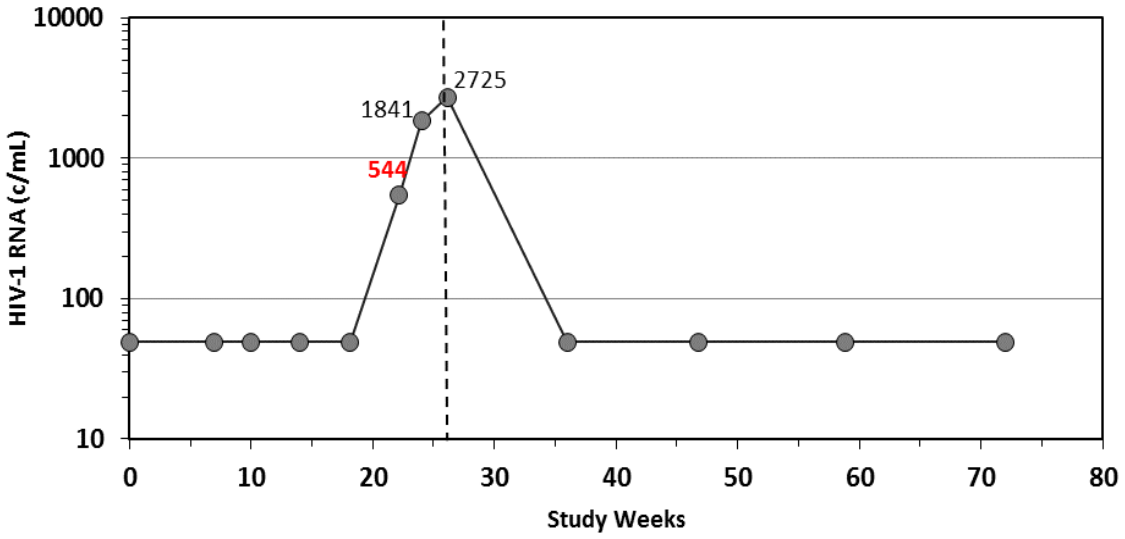


Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

Subject [redacted]:

- CAB + RPV; male; Russia; BMI >25 to ≤30 kg/m^2.
- Prior ART: emtricitabine, raltegravir, and tenofovir followed by abacavir, efavirenz and lamivudine.
- SVF Week 24, HIV-1 RNA 544 c/mL; CVF Week 24 Retest, HIV-1 VL 1841 c/mL.
- Baseline PBMC vDNA had INI substitution, L74I. Subtype A.
- SVF plasma vRNA had RPV resistance-associated mutation, E138E/K, RPV FC=6.5; INI substitutions L74I and N155H, CAB FC = 2.7. Subtype A1.
- Placed on atazanavir, lamivudine, and tenofovir, entered LTFU and was resuppressed at the LTFU Month 3 visit.

Figure 2 Subject [redacted] HIV-1 Viral Load History

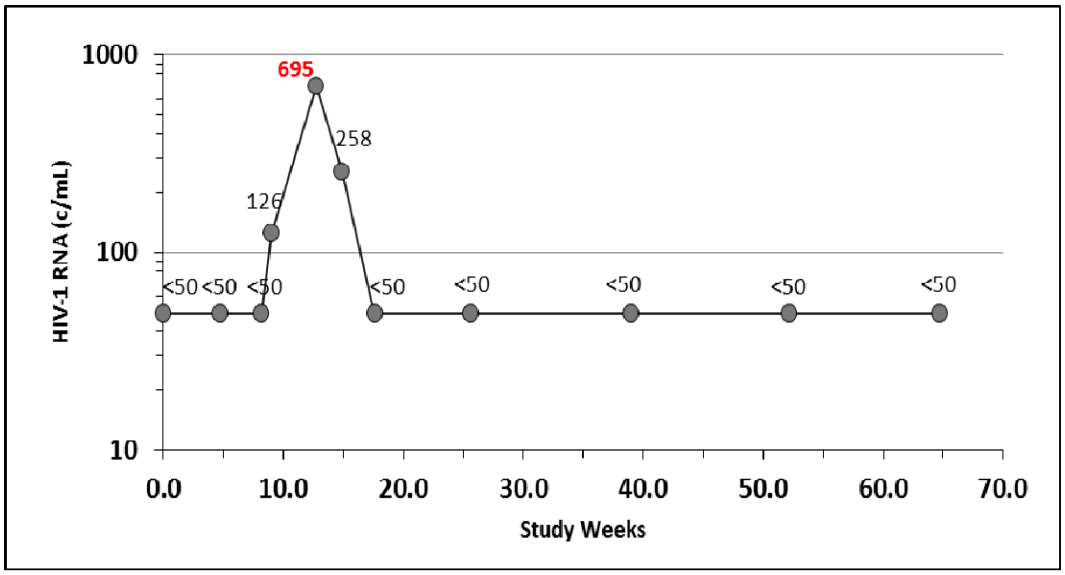


Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

Subject [redacted]:

- CAB +RPV; female; France; BMI >30 kg/m^2.
- Prior ART: lamivudine, nevirapine, zidovudine, and abacavir.
- SVF Week 12, HIV-1 RNA 695 c/mL; CVF Week 16, HIV-1 RNA 258 c/mL. SVF Week 8, HIV-1 RNA 372 c/mL, not confirmed.
- Baseline PBMC vDNA showed NNRTI resistance-associated mutation, V108V/I in addition to RPV RAM E138K. Subtype AG.
- SVF plasma vRNA had NNRTI resistance- associated mutation, V108I, in addition to RPV RAM E138K, RPV FC=3.7. CAB FC = 1.2. Subtype AG.
- Prescribed abacavir, lamivudine, ritonavir and darunavir and entered LTFU . Resuppressed at the LTFU Month 1 visit.

Figure 3 Subject [redacted] HIV-1 Viral Load History



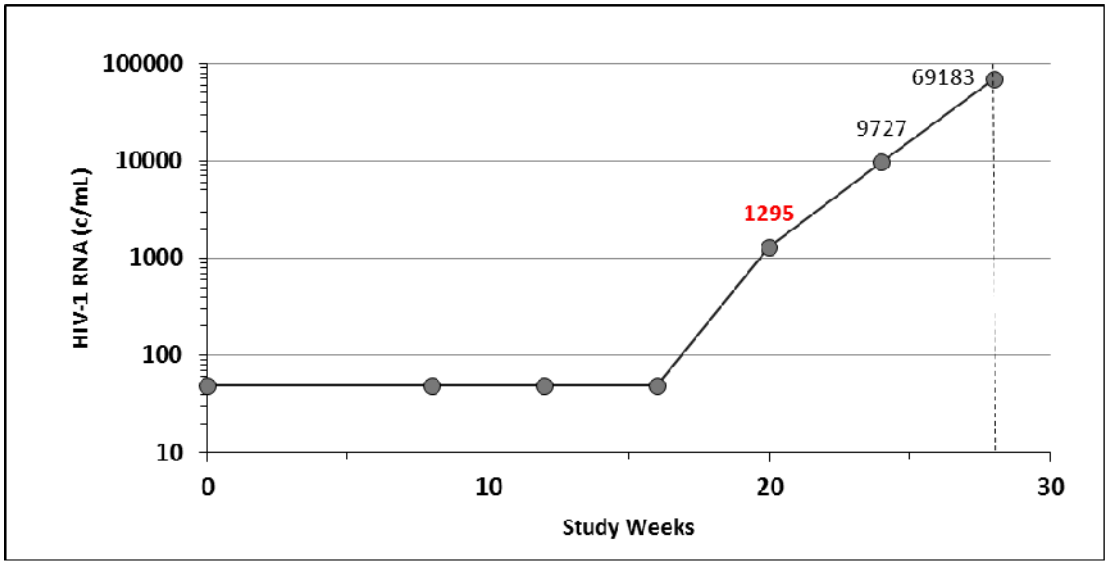
Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

CAR Group

Subject [redacted]:

- CAR; male; Russia; BMI >30 kg/m^2.
- Prior ART: efavirenz, lamivudine, and zidovudine which continued throughout the study.
- SVF Week 20, HIV-1 RNA 1295 c/mL; CVF Week 24, HIV-1 RNA of 9727 c/mL.
- Baseline PBMC vDNA had NRTI resistance-associated mutation, M184M/I and INI substitution, L74I. Subtype Complex.
- SVF plasma vRNA showed NNRTI resistance-associated mutation, G190S, NRTI resistance-associated mutation, M184V and INI substitution, L74I. RT/PR phenotype assay failed for this subject. Subtype A1.
- Subject withdrew from the study at Week 28, HIV-1 RNA 69,183 c/mL.

Figure 4 Subject [redacted] HIV-1 Viral Load History

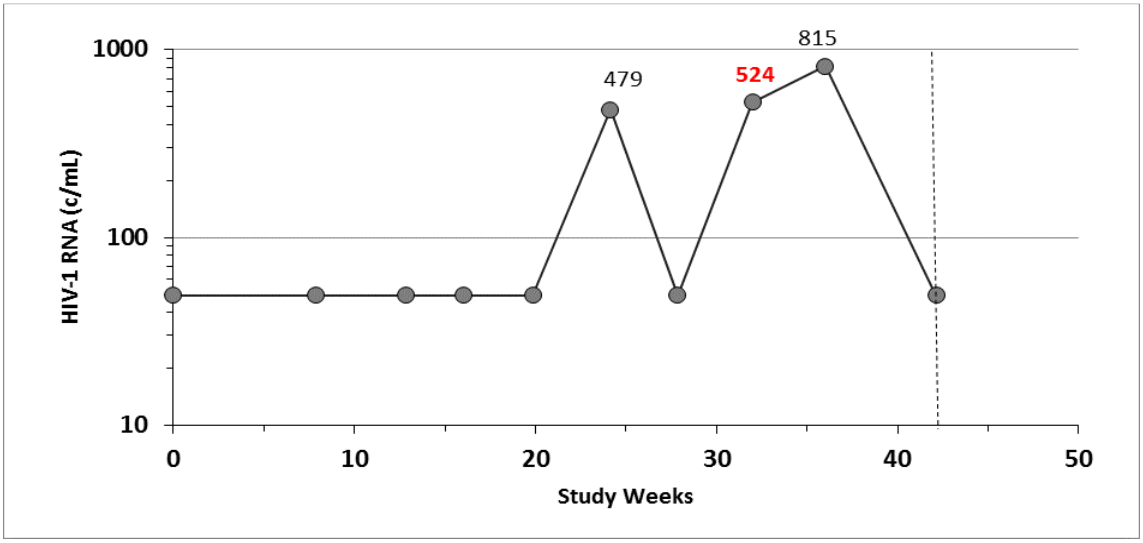


Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

Subject [redacted]:

- CAR; female; United States; BMI >15 to ≤25 kg/m^2.
- Prior ART: darunavir, ritonavir, tenofovir, and emtricitabine followed by elvitegravir, cobicistat, tenofovir and emtricitabine which continued throughout the study.
- SVF Week 32, HIV-1 RNA 524 c/mL; CVF Week 36, HIV-1 RNA 815 c/mL. SVF Week 24, HIV-1 RNA 479 c/mL, not confirmed.
- Baseline PBMC vDNA showed no resistance-associated mutations. Subtype B.
- SVF plasma vRNA showed NRTI resistance-associated mutation, M184I. Emtricitabine (FC >97.2). Subtype B.
- Resuppressed at Withdraw visit.

Figure 5 Subject [redacted] HIV-1 Viral Load History

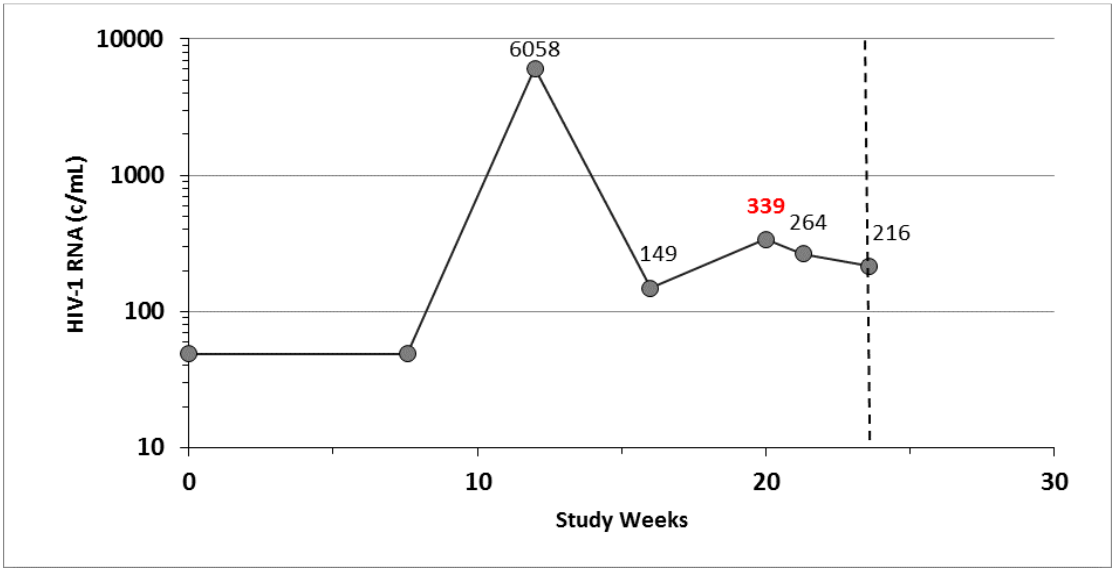


Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

Subject [redacted]:

- CAR; male; United States; BMI >15-≤25 kg/m^2.
- Prior ART: elvitegavir, cobicistat, tenofovir and emtricitabine followed by a regimen of elvitegavir, cobicistat, tenofovir alafenamide and emtricitabine which continued throughout the study.
- SVF Week 20, HIV-1 RNA 339 c/mL; CVF Week 20 Retest, HIV-1 RNA 264 c/mL. SVF Week 12, HIV-1 RNA 6058 c/mL; not confirmed.
- Baseline PBMC vDNA showed no resistance-associated mutations. Subtype B.
- SVF plasma vRNA had no resistance-associated mutations. Subtype B.
- Withdrew Week 24, HIV-1 RNA 216 c/mL.

Figure 6 Subject [redacted] HIV-1 Viral Load History

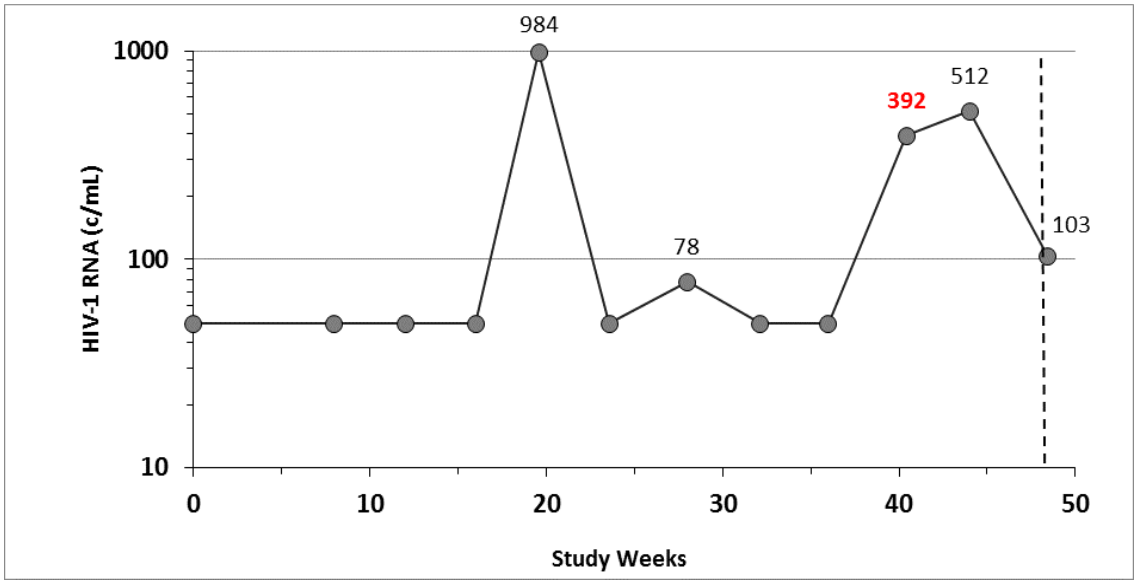


Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

Subject [redacted]:

- CAR; male; United States; BMI >30 kg/m^2.
- Prior/Study ART; elvitegavir, cobicistat, tenofovir and emtricitabine which continued throughout the study.
- SVF Week 40, HIV-1 RNA 392 c/mL; CVF Week 44, HIV-1 RNA 512 c/mL. SVF Week 20, HIV-1 RNA 984 c/mL; not confirmed. HIV-1 increased at Week 28, HIV-1 RNA to 78 c/mL.
- Baseline PBMC vDNA showed no resistance-associated mutations. Subtype B.
- SVF plasma vRNA had NNRTI resistance-associated mutation, M230M/I. No reduced drug susceptibility. Subtype B.
- Withdrew Week 48, HIV-1 RNA 103 c/mL.

Figure 7 Subject [redacted] HIV-1 Viral Load History



Note: The dotted vertical reference line indicates last IP on treatment study day.
Data Source: 201585 Week 48 CSR Listing 40

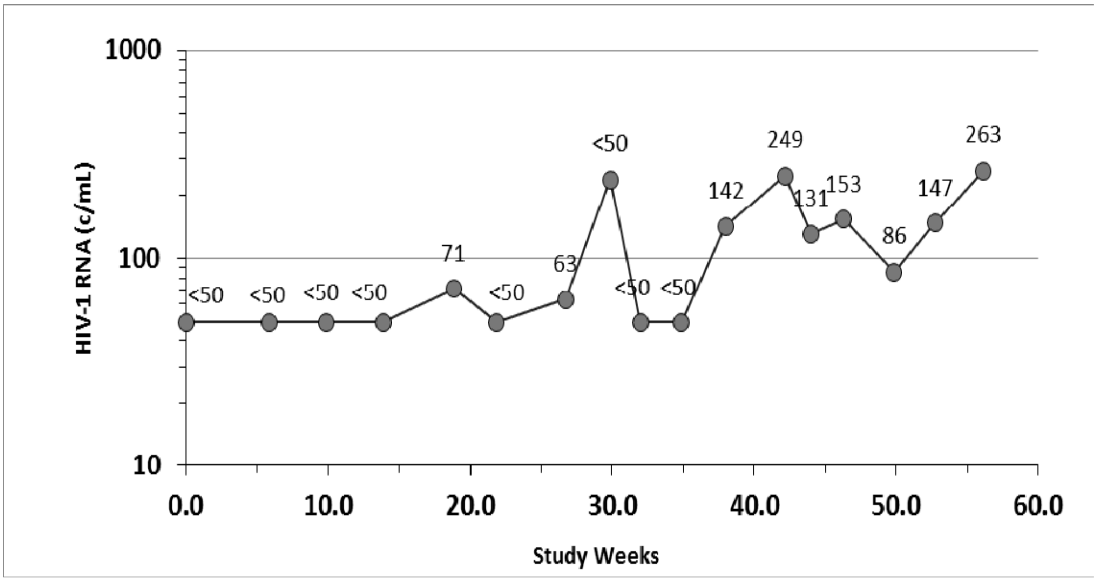
4.2.1.1.4. HIV-1 Exploratory Analysis

One subject in the CAB + RPV group reached SVF criteria twice during the Maintenance Phase, but virologic failure was never confirmed. HIV-1 PR, RT, and INI genotype and phenotype were determined on the last on-treatment isolate from this subject that had HIV-1 RNA ≥200 c/mL, regardless of no confirmatory HIV-1 RNA. Another subject that was randomized to the CAR arm and switched to CAB+RPV LA at Week 56b had multiple HIV-1 RNA blips (HIV-1 RNA ≥50 but <200 c/mL) starting at Week 44 and continuing until withdrawal at Week 92. HIV-1 RT, PR, and IN genotype and phenotype were determined on the Week 80 plasma sample.

Subject [redacted]:

- CAB + RPV; male; South Africa; BMI >30 kg/m^2.
- Prior ART: efavirenz, lamivudine, and tenofovir.
- SVF Week 28, HIV-1 RNA 239 c/mL and Week 40 HIV-1 RNA 249 c/mL; not confirmed. HIV-1 blips (VL≥50 but <200 c/mL), Week 16 (71 c/mL), Week 24 (63 c/mL), Week 36 (142 c/mL), Week 40 Retest (131 c/mL), Week 48 (86 c/mL) and Week 48 Retest (147 c/mL).
- Baseline PBMC vDNA had NRTI resistance associated mutation, K70K/R. Subtype B.
- Week 40 plasma vRNA. No INI primary mutations; no reduced INI sensitivity. RT/PR assays failed.
- Week 48 Retest. HIV-1 RNA of 263 c/mL. LTFU entered. HAART regimen of raltegravir, tenofovir, and emtricitabine switched to emtricitabine, tenofovir and efavirenz. The subject was considered a Snapshot Nonresponder at Week 48.

Figure 8 Subject [redacted] HIV-1 Viral Load History



Data Source: 201585 Week 48 CSR Listing 40

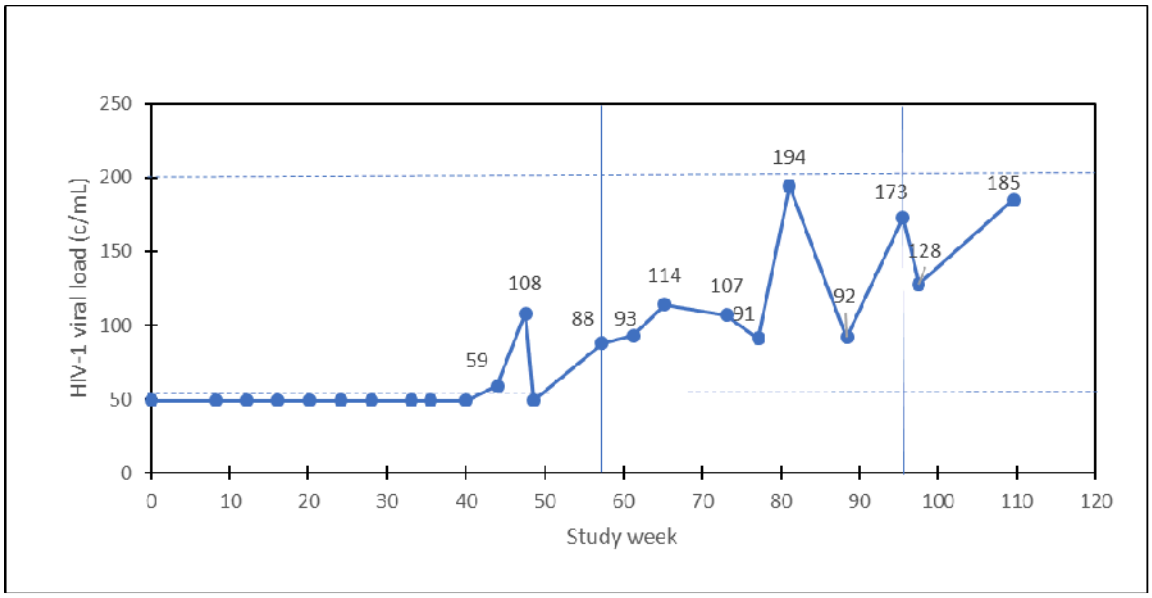
Subject [redacted]

Subject [redacted] had several HIV viral load blips (HIV VL ≥50 but <200 c/mL) starting at Week 44 and continuing until withdrawal at Week 92. This subject was a Week 48 Snapshot responder based on a Week 48 retest viral load of <50 c/mL. Subject was on CAR during maintenance phase and switched to LA CAB+RPV at Week 56B. HIV-1 RT, PR, and IN genotype and phenotype were determined on the Week 80 plasma sample and a RPV-resistance mutation, E138A was present. No Day 1 PBMC sample was available for sequencing.

- CAR in maintenance phase, started LA CAB+RPV at Week 56B; female; South African site; BMI >25 to 30 kg/m^2.
- Prior/Study ART: efavirenz, emtricitabine, and tenofovir; oral and LA CAB+RPV; CAB+RPV oral bridging (Extension phase).
- HIV-1 viral blips: Week 44 (59 c/mL), Week 48 (108 c/mL), Week 56B (88 c/mL), Week 60 (93 c/mL), Week 64 (114 c/mL), Week 72 (107 c/mL), Week 76 Retest (91 c/mL), Week 80 (194 c/mL), and Week 88 (92 c/mL).
- Week 80 plasma sample showed RPV-resistance mutation, E138A. RT and PR phenotype assay failed. No INI mutations or resistance observed. Subtype Complex.
- Withdrew Week 96 (VL- 173 c/mL). Placed on atazanavir, emtricitabine, and tenofovir and entered LTFU.

Data Source: Listings 129, 130, 133, 148; data on file.

Figure 9 Subject [redacted] HIV-1 Viral Load History



Lower horizontal dotted line represents HIV-1 viral load of 50 c/mL. Upper horizontal dotted line represents HIV-1 viral load of 200 c/mL. Left vertical line represents end of CAR and start of LA CAB+RPV therapy. Right vertical line represents withdraw time point and start of LTFU. Data Source: 2019N399072_00, Listing 133

At Baseline, 225/305 (74%) subjects in the CAB + RPV group and 217/302 (72%) subjects in the CAR group had plasma HIV-1 RNA <2 c/mL (Data Source: 201585 Week 48 CSR Table 2.34). At Week 48, 235/279 (84%) subjects in the CAB + RPV group and 225/292 (77%) subjects in the CAR group had plasma HIV-1 RNA <2 c/mL.

4.2.1.1.5. Discussion

Protocol defined CVF through Week 48 was rare (1%) in the study and was distributed evenly between the 2 treatment groups, with 7 subjects meeting CVF: 3 subjects in the CAB + RPV group and 4 subjects in the CAR group. In the CAB + RPV group, the 3 CVF subjects all had RPV RAMs at position E138 at the time of SVF leading to decreased virus susceptibility to RPV. RAMs at this position were also present in the HIV-1 viral DNA for 2 of the 3 subjects at Baseline. One subject also had INI substitution, L74I, present at both Baseline and at SVF. Another subject had prior exposure to RAL and had INI resistant mutation N155H at CVF. As this mutation causes high level resistance to RAL, but not dolutegravir or cabotegravir, it is likely the prior exposure to RAL is the source of N155H. A proviral DNA analysis of the Baseline sample did not detect the presence of N155H. This subject also had the INI substitution, L74I, present at both Baseline and SVF. Another CVF subject in the CAB + RPV group had NNRTI RAM, V108I which was present as a mixture of V108V/I in Baseline PBMC DNA and could contribute to the in vitro resistance seen to RPV. Comparison of the plasma HIV-1 RNA and PBMC HIV-1 DNA genotype results must be viewed with the caveat that resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing [Sharkey, 2005]. As such, HIV-1 DNA resistance testing is exploratory and its primary value is in showing whether resistance is present, and it is less definitive at showing that resistance is not present. Since all

subjects entered the study suppressed, only PBMC viral DNA could be genotyped at Baseline. No phenotype analysis is performed on virus isolated from PBMCs.

In the CAR group, 1 subject had the NRTI RAM, M184I, at virologic failure with a corresponding decrease in susceptibility to emtricitabine (FC>97.2) which was part of the subject's ART. The Baseline viral DNA for this subject did not have this RAM. Another subject had NRTI RAM, M184V, and NNRTI RAM, G190S, at virologic failure. The phenotypic assay failed for this subject. Baseline viral DNA did not have the G190S RAM, but did have the NRTI RAM, M184M/I, which usually emerges before M184V, but is outcompeted by M184V within several weeks [Keulen, 1997]. This subject also had the INI substitution, L74I, at Baseline and SVF, but no decrease in INI susceptibility was observed. One subject had the NNRTI RAM, M230M/I at virologic failure and did not have any decreased susceptibility to their study ART. Baseline viral DNA did not contain the M230M/I RAM. Another subject had no RAMs present either at virologic failure or in Baseline viral DNA.

4.2.1.1.6. Conclusions

- CVF was rare (1%), with 3 subjects in the CAB + RPV group and 4 subjects in the CAR group.
- All 3 CVFs in the CAB + RPV group had RPV resistance mutations at the virologic failure timepoint. These RAMS were also present in the Baseline HIV-1 viral DNA for 2 the of the 3 subjects. These 3 subjects had Subtypes A, A1, and AG.
- One of the CVFs in the CAB + RPV group had INI resistance mutation, N155H; this subject had a history of RAL use.
- No subjects met CVF criteria after Week 48

4.2.1.2. 201584 (FLAIR)

Study Design: Study 201584 is a 120-week Phase III, multi-phase, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study in HIV-1, ART-naïve adult subjects to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC. Subjects who had an HIV-1 RNA <50 c/mL at the Week -4 Visit were eligible to enter the Maintenance Phase. Eligible subjects were randomized (1:1) to receive either oral CAR (ABC/DTG/3TC or the alternative non-abacavir backbone) or oral CAB 30 mg + RPV 25 mg once daily for 4 weeks followed by IM CAB + RPV every 4 weeks thereafter. Subjects randomized to CAR during the Maintenance Phase will continue CAR for at least an additional 100 weeks, after which time they will be given the option to switch to the IM CAB + RPV arm in the Extension Phase or be withdrawn from the study.

4.2.1.2.1. Confirmed Virologic Failure

The proportion of subjects with CVF was a pre-defined secondary endpoint with CVF being defined as 2 consecutive HIV-1 RNAs ≥200 c/mL after prior suppression to

<200 c/mL. CVF through Week 100 was low in the study with 4 (1.4%) subjects meeting CVF in the CAB + RPV group and 4 (1.4%) subjects in the CAR group (Table 21) Since the Week 48 analysis [GSK Document Number 2017N345267_00], there was one additional CVF during the Maintenance Phase in the CAR group at Week 64 with no on treatment resistance mutations.

During the Extension Phase, there was a CVF in the CAB + RPV group at Week 108, details of which are provided in Section 4.2.1.2.3 (Data Source: 201584 Week 96 CSR Table 7.13).

Table 21 Number of Subjects Meeting CVF Criteria by Visit (Maintenance Phase) (CVF Population)

SVF Timepoint	CAB + RPV (N=4/283)	CAR (N=4/283)
Week 8	1	1
Week 12	0	1
Week 16	0	1
Week 20	1	0
Week 24	0	0
Week 28	1	0
Week 32	0	0
Week 40	0	0
Week 48	1	0
Week 64	0	1
Week 100	0	0
Any timepoint	4	4

Data Source: 201584 Week 96 CSR Listing 52
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

4.2.1.2.2. HIV-1 Viral Genotyping and Phenotyping

Plasma samples collected at the Induction Baseline (Week -20) and SVF timepoint were analyzed for on-treatment resistance using Monogram Biosciences PhenoSense GT, PhenoSense Integrase and GenoSeq Integrase testing methods for PR, RT and IN.

Among the total of 5 CVF subjects in the CAB + RPV group (Maintenance and Extension Phase), 1 subject with SVF at Week 20 had treatment emergent RPV RAM E138E/A/K/T, with 7.09 FC to RPV and treatment emergent INI RAM Q148R with 5.22 FC to CAB, 1 subject with SVF at Week 28 had treatment emergent RPV RAM mutation K101K/E/Q with 1.93 FC to RPV and INI RAM G140R with 6.72 FC to CAB (INI genotype and phenotype obtained at Week 24 as Week 28 sample did not yield IN results. Week 24 had RPV RAM K101E with 2.63 FC to RPV), 1 subject with SVF at Week 48 had treatment emergent RPV RAM E138K with 0.97 FC to RPV and treatment emergent INI RAM Q148R with 9.36 FC to CAB, 1 subject with oral CAB + RPV treatment interruption at Week 4a (result of positive pregnancy test later confirmed as false) who never received any CAB + RPV injections and therefore had no virology data generated, and 1 subject with SVF at Week 108 had NNRTI resistance mutations V106V/A, V108V/I, E138G, and M230L with 27 FC to RPV, 7.77 FC to EFV, and 19 FC to ETV.

This subject had IN resistance mutations N155H and R263K with 9 FC to CAB, 3.78 FC to DTG, and 17 FC to RAL.

Four CVF subjects had Subtype A1 and 1 had Subtype AG (See Table 22 for summary of subtypes.). None of the subjects with CVF had K103N at Baseline (only two subjects with K103N at screening were randomized to the CAB + RPV group; they both responded).

Table 22 Summary of Prevalence of HIV-1 Subtype (ITT-E Population)

HIV-1 Subtype	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)
A	46 (16)	36 (13)
A/B	1 (<1)	0
A1	8 (3)	4 (1)
AE	1 (<1)	6 (2)
AG	10 (4)	16 (6)
B	174 (61)	174 (61)
B/C	1 (<1)	0
BC	0	3 (1)
BF	2 (<1)	2 (<1)
BG	1 (<1)	0
C	18 (6)	20 (7)
Complex	1 (<1)	3 (1)
CPX	3 (1)	3 (1)
D	0	4 (1)
F	5 (2)	5 (2)
F2	3 (1)	0
G	2 (<1)	1 (<1)
Missing	7 (2)	6 (2)

Data Source:201584 Week 48 CSR Table 1.43
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

There were 4 CVF subjects in the CAR group (SVF at Week 8, Week 12, Week 16, and Week 64), none of whom had any treatment emergent NRTI or INI RAMs (Table 23).

See Section 4.2.1.2.3 for subject narratives.

Table 23 Phenotypic and Genotypic Analysis of CVF subjects

Subject	Study Group	SVF Timepoint	NNRTI RAMs		INI RAMs		HIV Subtype at Baseline
			BASELINE (FC)	SVF (FC)	BASELINE (FC)	SVF (FC)	
Subject [redacted]	CAB + RPV	Week 28	V90I RPV (1.0)	V90I, K101E RPV (2.63) Week 24	L74I CAB (0.95)	L74I, G140R CAB (6.72) DTG (2.23) Week 24	A1
Subject [redacted]	CAB + RPV	Week 20	V179V/I RPV (1.06)	E138E/A/K/T RPV (7.09)	L74I CAB (0.67)	L74I, Q148R CAB (5.22) DTG (0.95)	A1
Subject [redacted]	CAB + RPV	Week 48	V179V/I RPV (0.43)	E138K RPV (0.97)	L74I CAB (0.69)	L74I, Q148R CAB (9.36) DTG (1.11)	A1
Subject [redacted]	CAB + RPV	Week 8	None	None	None	None	AG
Subject [redacted]	CAB + RPV	Week 108	None RPV (0.45)	V106V/A, V108V/I, E138G, M230L RPV (27) EFV (7.77) ETV (19)	L74I CAB (0.86)	N155H, R263K CAB (9.0) DTG (3.78) RAL (17)	A1
Subject [redacted]	CAR	Week 12	V179I RPV (0.54)	V179V/I RPV (0.49)	L74I CAB (0.79)	L74I CAB (0.74) DTG (0.75)	A1
Subject [redacted]	CAR	Week 16	None RPV (0.43)	None RPV (0.33)	None CAB (0.93)	None CAB (0.87) DTG (0.81)	B
Subject [redacted]	CAR	Week 8	None RPV (0.39)	None RPV (0. 44)	None CAB (0.68)	None CAB (0.69)	B

Subject	Study Group	SVF Timepoint	NNRTI RAMs		INI RAMs		HIV Subtype at Baseline
			BASELINE (FC)	SVF (FC)	BASELINE (FC)	SVF (FC)	
						DTG (0.74)	
Subject [redacted]	CAR	Week 64	None RPV (0.62)	Could not be generated	L74I CAB (0.72)	L74I CAB (0.84)	Complex

Data Source: 201584 Week 96 CSR Table 7.12 and Table 7.13

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

4.2.1.2.3. Virology Narratives for Confirmed Virologic Failures

CAB + RPV Group

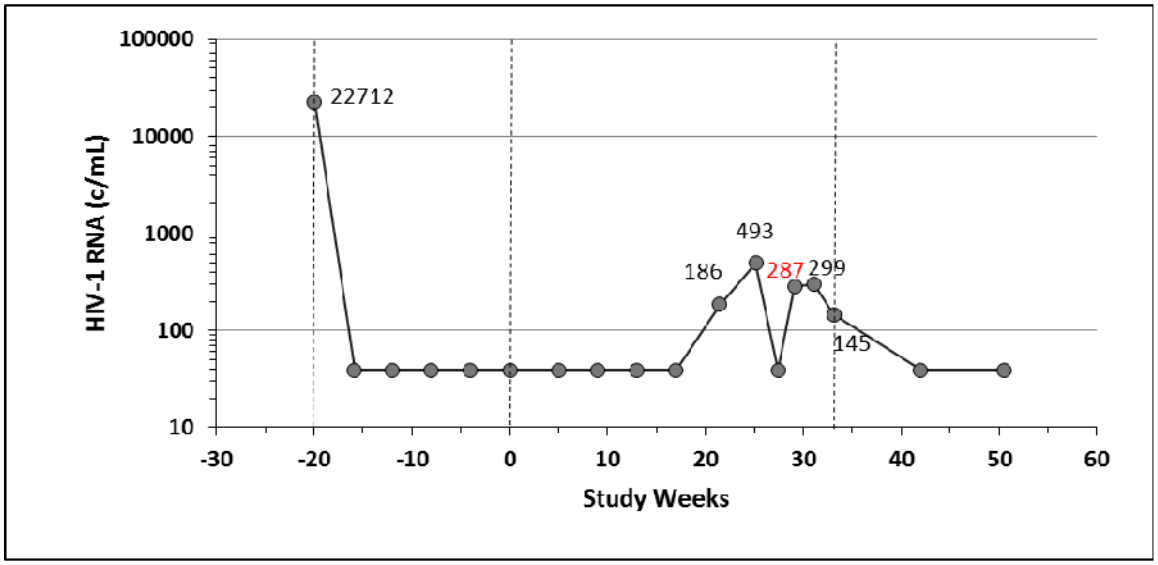
For CAB PK, 201584 Week 48 CSR in-text Figure 13; for RPV PK, 201584 Week 48 CSR in-text Figure 14.

Subject [redacted]

Male. Russia. BMI >30 kg/m^2. Used 1 ½ inch needle. Baseline; 22712 c/mL HIV-1 RNA SVF Week 28; 287 c/mL HIV-1 RNA, Confirmatory HIV-1 RNA 299 c/mL. Subtype A1

- Baseline RT had NNRTI minor mutation V90I with full susceptibility to all NNRTIs. Baseline IN had L74I with susceptibility to CAB, DTG, RAL, and EVG.
- Week 28 had RPV resistance mutation K101K/E/Q in addition to V90I with 1.93 FC sto RPV, 22 FC to nevirapine, and 4.48 FC to efavirenz. Week 28 (287 c/mL HIV-1 RNA) IN geno type and IN phenotype could not be generated. Therefore, Week 24 plasma was sent for Virology analyses
- Week 24 (SVF-which was not confirmed, 493 c/mL HIV-1 RNA) had NNRTI resistance mutation K101E, in addition to V90I, with 2.63 FC to RPV, 39 FC to nevirapine, 2.71 FC to etravirine, and 4.79 FC to efavirenz. Week 24 IN had L74I plus G140R with 25 FC to EVG, 25 FC to RAL, 6.72 FC to CAB and 2.23 FC to DTG. The IN RC for this virus was too low to quantitate. Repeat assays on additional Week 24 samples did not generate IN genotype or phenotype.

Figure 10 Subject [redacted] HIV-1 Viral Load History



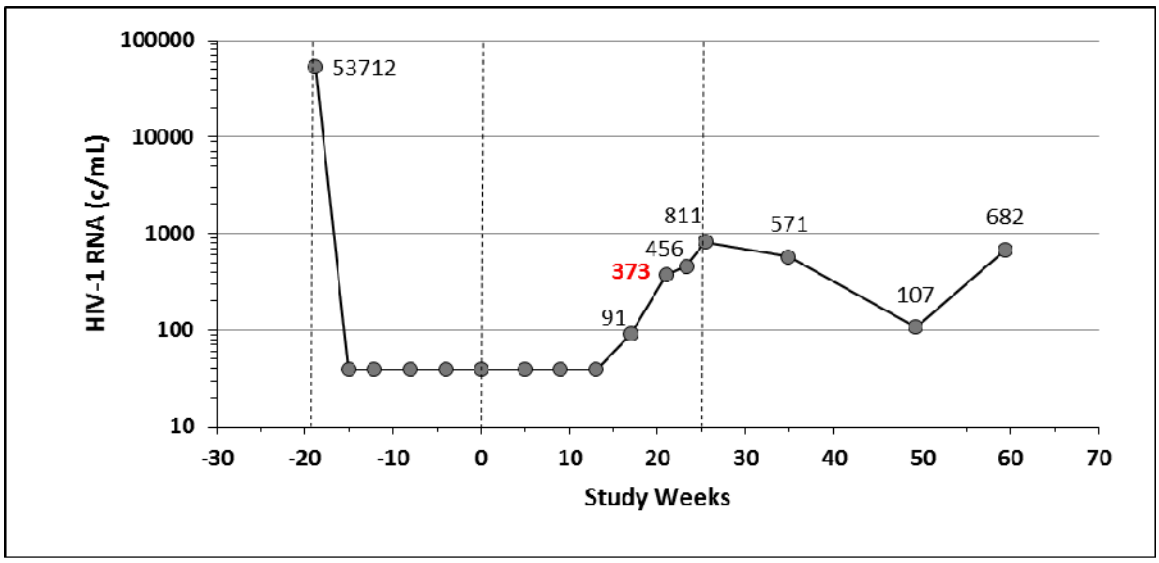
Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical

reference line indicates last on-treatment study day, i.e. min (max (day of last IP injection dose+35 days, day of last oral CAB+RPV+1), day of LTFU HAART start date)
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

- Female. Russia. BMI >30 kg/m^2. Used 1 ½ inch needle. Baseline 53712 c/mL HIV-1 RNA, SVF Week 20 373 c/mL HIV-1 RNA, Confirmatory HIV-1 RNA 456 c/mL. Subtype A1.
- Baseline had NNRTI mutation V179V/I with no resistance to any NNRTI. Baseline IN had L74I and was susceptible to all Integrase inhibitors.
- Week 20 PSGT had RPV resistance mutation E138E/A/K/T with 7.09 FC in IC50 to RPV and either high level or partial resistance to all NNRTIs. The Week 20 IN geno had Q148R in addition to the L74I which was present at Baseline. This virus was fully susceptible to DTG but had 57, 20, and 5.22 FC in IC50 to EVG, RAL, and CAB, respectively. The IN RC for this virus was 34%.

Figure 11 Subject [redacted] HIV-1 Viral Load History



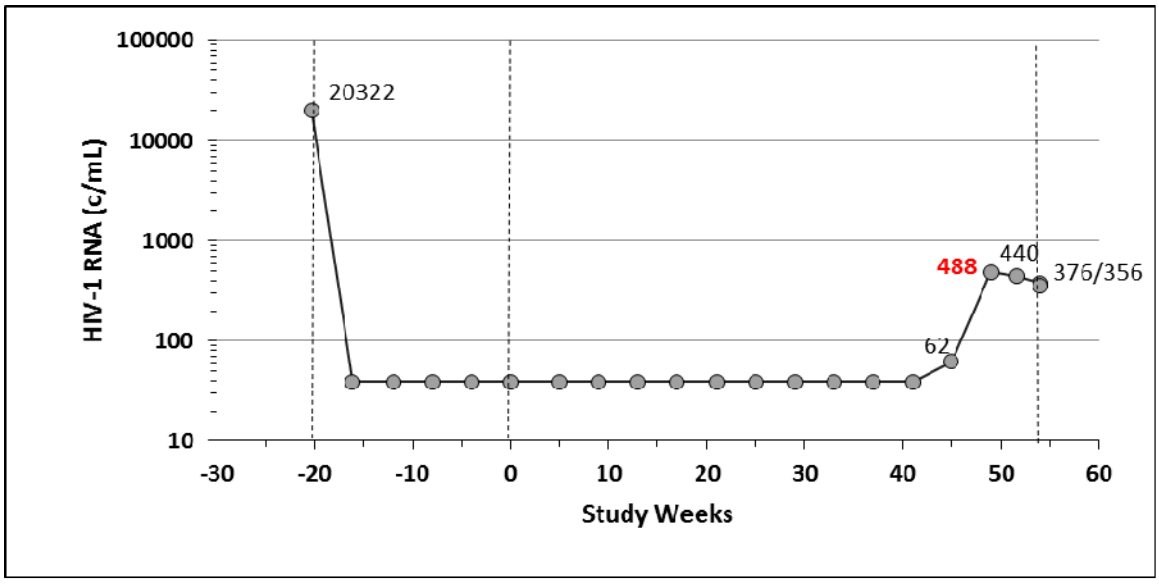
Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical reference line indicates last on-treatment study day, i.e. min (max (day of last IP injection dose+35 days, day of last oral CAB+RPV+1), day of LTFU HAART start date)
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

- Female. Russia. BMI >30 kg/m^2. Used 1 ½ inch needle. Baseline 20322 c/mL HIV-1 RNA, SVF Week 48: 488 c/mL HIV-1 RNA, Confirmatory HIV-1 RNA 440 c/mL. Subtype A1.

- Baseline had V179V/I with full susceptibility to all NNRTIs. Baseline IN had L74I, with full susceptibility to all INIs.
- At Week 48, V179V/I was no longer present, but E138K was. There was no in vitro resistance to any NNRTI (RPV FC = 0.97). The Week 48 IN had treatment emergent INI mutation Q148R with 9.36 FC to CAB, 30 FC to RAL, 100 FC to EVG, and 1.11 FC to DTG. The IN RT for this virus was 38%.

Figure 12 Subject [redacted] HIV-1 Viral Load History

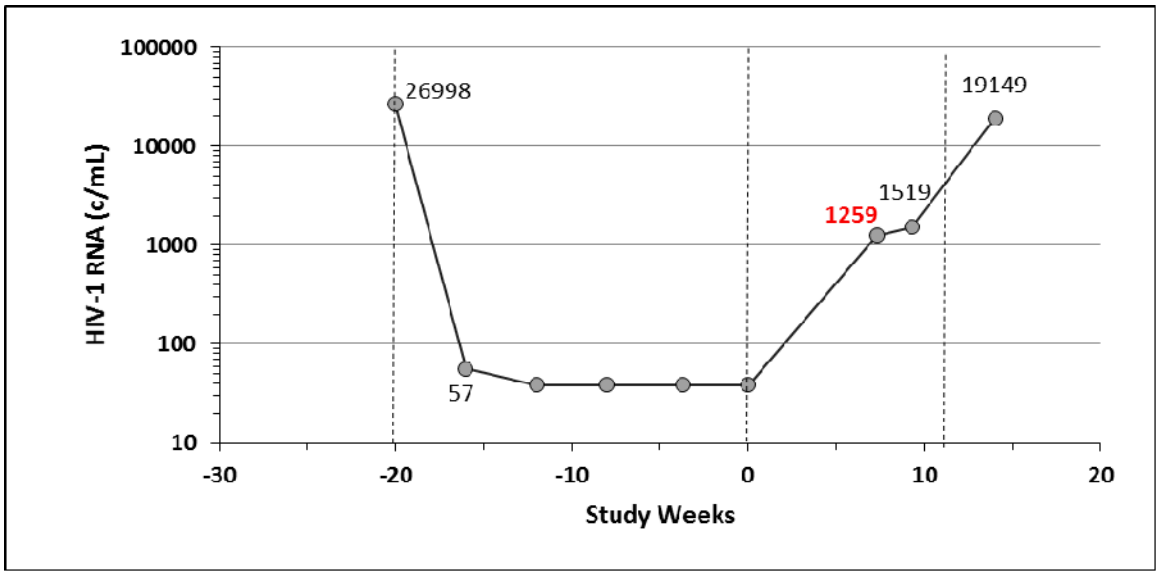


Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical reference line indicates last on-treatment study day, i.e. min (max (day of last IP injection dose+35 days, day of last oral CAB+RPV+1), day of LTFU HAART start date)
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

- Female. Russia. BMI >15 to ≤25 kg/m^2. Baseline 26998 c/mL HIV-1 RNA. SVF Week 8 retest 1259 c/mL HIV-1 RNA. Confirmatory HIV-1 RNA 1519 c/mL. Subtype AG.
- Subject was thought to be pregnant and never received an injection. Virology data was not generated. Subject did not enter long term follow-up.

Figure 13 Subject [redacted] HIV-1 Viral Load History



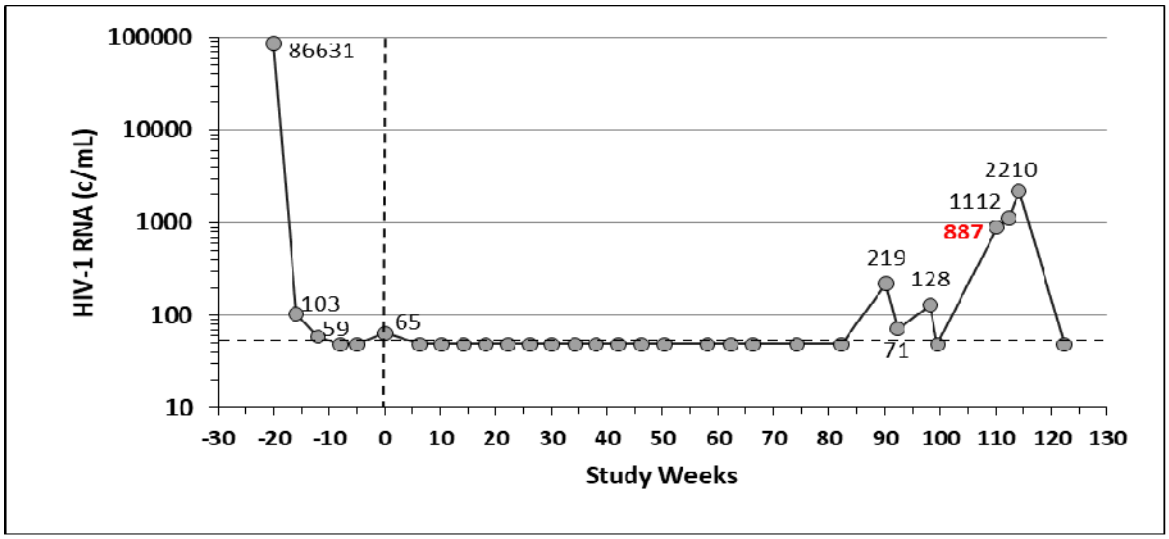
Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical reference line indicates last on-treatment study day, i.e. min (max (day of last IP injection dose+35 days, day of last oral CAB+RPV+1), day of LTFU HAART start date)
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

Subject [redacted] is Male, from Russia. BMI >30 kg/m^2. Used 1½ inch needle. Baseline; 86631 c/mL HIV-1 RNA. The Week 108 visit had 887 c/mL HIV-1 RNA (SVF). The confirmatory visit had 1112 c/mL HIV-1 RNA. The subject had detectable HIV-1 RNA at Week 88 and 96. Subtype A1. IN polymorphism L74I present at Baseline and Week 108.

- Baseline RT had no NNRTI mutations with full susceptibility to all NNRTIs. Baseline IN had L74I with susceptibility to CAB, DTG, RAL, and EVG.
- Week 108 had NNRTI resistance mutations V106V/A, V108V/I, E138G, and M230L with 27 FC to RPV, 7.77 FC to EFV, and 19 FC to ETV. Week 108 had IN resistance mutations N155H and R263K with 9 FC to CAB, 3.78 FC to DTG, and 17 FC to RAL.
- Subject was switched to TDF/FTC and EFV and entered the LTFU Phase of the study. Plasma HIV-1 RNA was 46 c/mL at the LTFU Month 3 visit.

Figure 14 Subject [redacted] HIV-1 Viral Load History



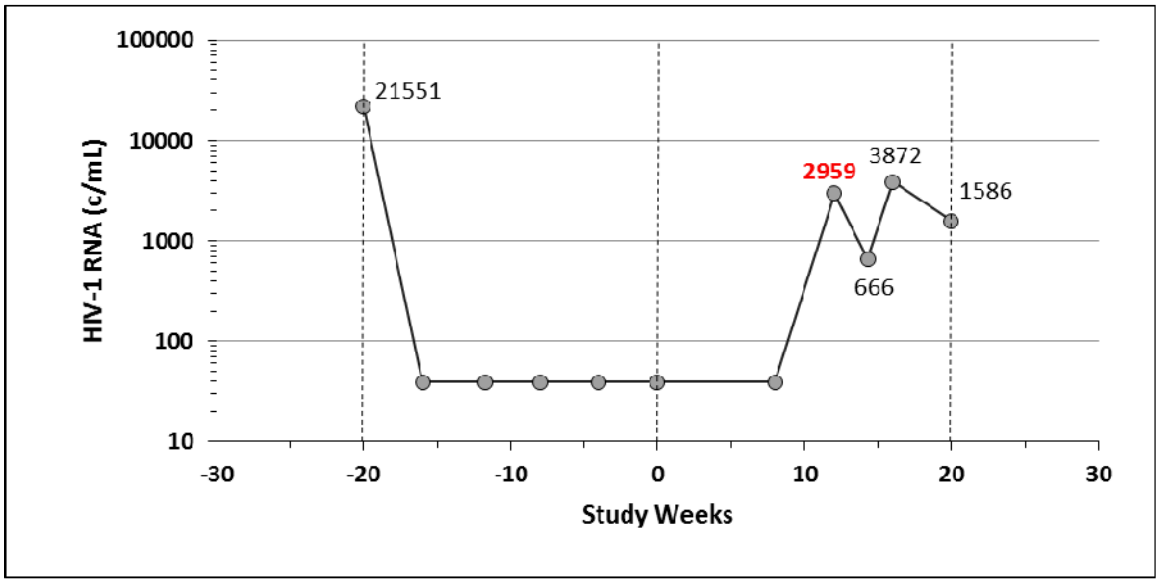
Data Source: 201584 Week 48 CSR Listing 45

CAR Group

Subject [redacted]

- Female. Russia. BMI >15 to ≤25 kg/m^2. Baseline 21551 c/mL HIV-1 RNA. Week 12; 2959 c/mL HIV-1 RNA, Confirmatory HIV-1 RNA 666 c/mL HIV-1 RNA. Subtype A1.
- This subject had V179I at Baseline and Week 12 without resistance to any NNRTI. IN had L74I and I203M at both Baseline and Week 12 with no increase in FC to any integrase inhibitor.

Figure 15 Subject [redacted] HIV-1 Viral Load History

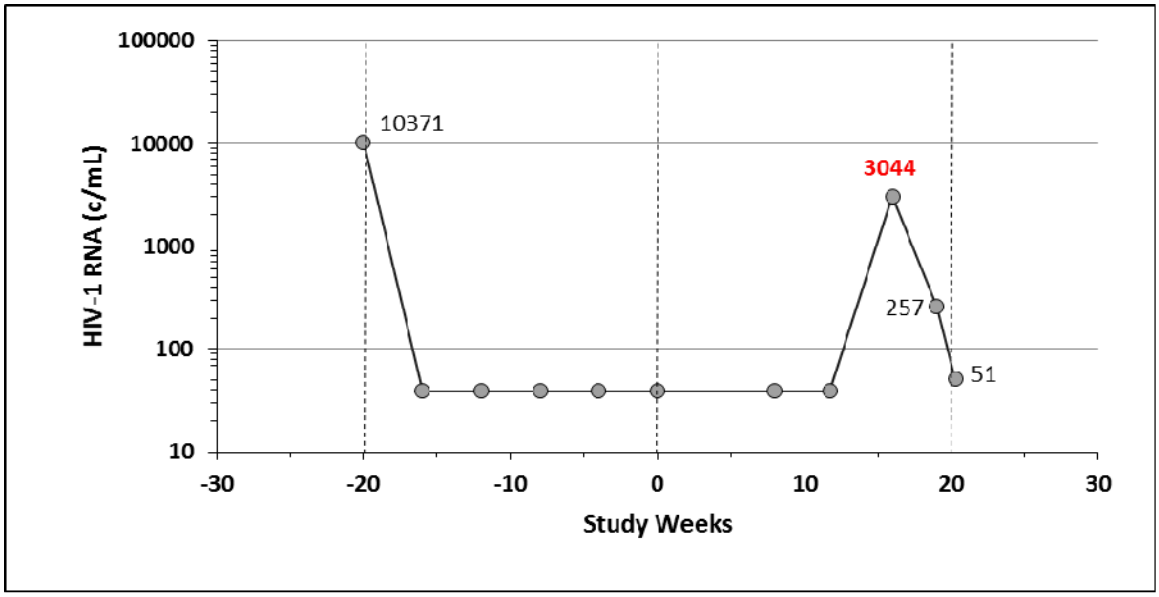


Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical reference line indicates last Maintenance phase on-treatment study day of ABC/DTG/3TC, i.e. day of last ABC/DTG/3TC dose + 1
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

- Male. Spain. BMI >15 to ≤25 kg/m^2. Baseline 10371 c/mL HIV-1 RNA. SVF Week 16; 3044 c/mL HIV-1 RNA, Confirmatory HIV-1 RNA 257 c/mL. Subtype B.
- This subject had no treatment-emergent mutations in RT or integrase. Additionally, there are no changes in phenotype NNRTI or IN between Baseline and Week 16.

Figure 16 Subject [redacted] **HIV-1 Viral Load History**

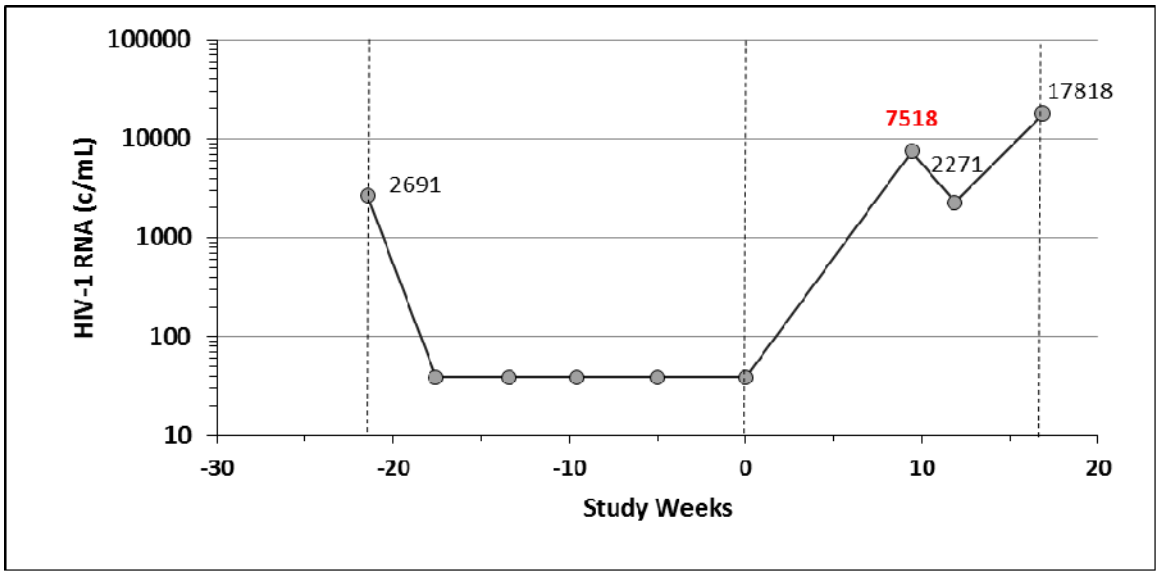


Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical reference line indicates last Maintenance phase on-treatment study day of ABC/DTG/3TC, i.e. day of last ABC/DTG/3TC dose + 1
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

- Male. US. BMI >15 to ≤25 kg/m^2. Baseline 2691 c/mL HIV-1 RNA. SVF Week 8; 7518 c/mL HIV-1 RNA, Confirmatory HIV-1 RNA 2271 c/mL. Subtype B.
- There were no treatment emergent mutations in RT or IN. Additionally, there were no changes in phenotype NNRTI or IN between Baseline and Week 8.

Figure 17 Subject [redacted] HIV-1 Viral Load History

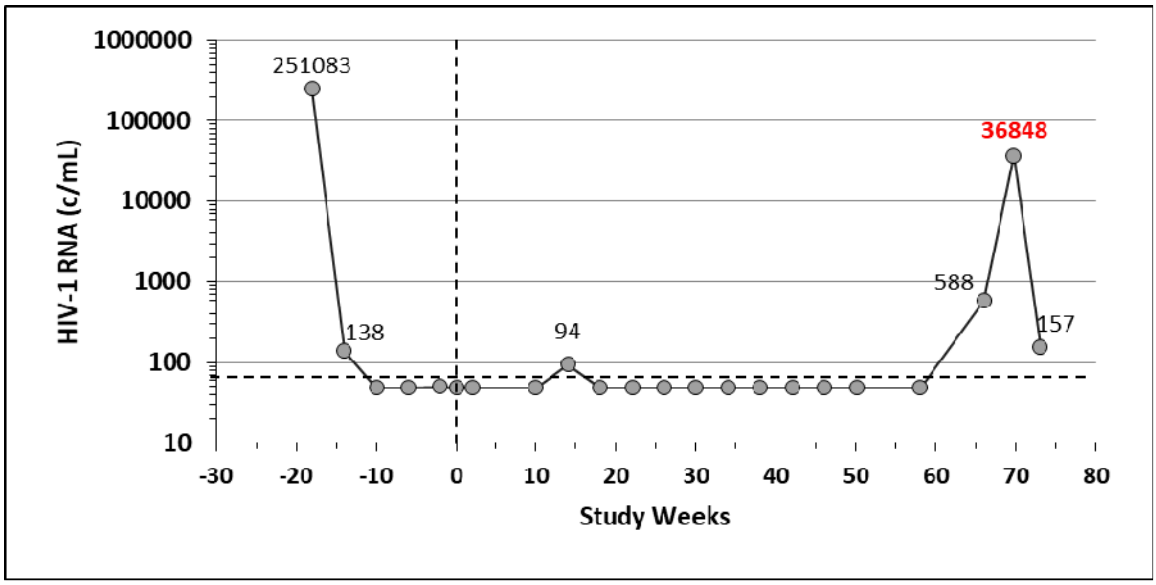


Note: The first vertical line indicates start of induction phase investigational product (ABC/DTG/3TC). The second vertical line indicates start of Maintenance phase investigational product (oral CAB + oral RPV). The third vertical reference line indicates last Maintenance phase on-treatment study day of ABC/DTG/3TC, i.e. day of last ABC/DTG/3TC dose + 1
Data Source: 201584 Week 48 CSR Listing 45

Subject [redacted]

Subject [redacted] was in the CAR group, had 251083 c/mL HIV-1 RNA at Baseline, had a single blip of 94 c/mL HIV-1 RNA at Week 12, but had <50 c/mL HIV-1 RNA at every visit post Week 12 until Week 64. The Week 64 visit had 588 c/mL HIV-1 RNA (SVF). The confirmatory visit had 36,848 c/mL HIV-1. PSGT at Week 64 could not be generated. There were no treatment emergent IN mutations at Week 64. This subject, who is from Russia and is female, has Subtype A virus by Q2 and Complex Subtype by Monogram. IN polymorphism L74I was present at Baseline and at Week 64.

Figure 18 Subject [redacted] HIV-1 Viral Load History



Horizonal dotted line represents HIV-1 viral load of 50 c/mL. Vertical line represents start of LA CAB+RPV therapy.

4.2.1.2.4. HIV-1 Exploratory Analyses

One subject in the CAB + RPV group reached SVF at the Week 12 repeat visit with 231 c/mL HIV-1 RNA, but virologic failure was never confirmed (this subject had a viral load ≥50 copies/mL). This subject was receiving treatment for syphilis at time of Week 12 repeat and was withdrawn due to investigator-identified virologic failure and presence of IN T97A prior to enrollment in 201584. This subject had no treatment-emergent NRTI or NNRTI resistance mutations. This subject had IN mutation T97A at Baseline and at Week 12. This mutation did not cause increase in FC to DTG, RAL, EVG, or CAB at either Baseline or at Week 12.

At Maintenance Baseline (Day 1), 169/280 (60%) subjects in the CAB + RPV group and 160/283 (57%) subjects in the CAR group had plasma HIV-1 RNA <2 c/mL (Data Source: 201584 Week 48 CSR Table 2.50). At Week 48, 177/257 (69%) subjects in the CAB + RPV group and 193/260 (74%) subjects in the CAR group had plasma HIV-1 RNA <2 c/mL.

4.2.1.2.5. Discussion

CVF through Week 48 was low in the study and was similar between the 2 treatment groups, with 7 subjects meeting CVF: 4 subjects in the CAB + RPV group and 3 subjects in the CAR group. In the CAB + RPV group, 1 subject had CVF without receiving an injection and therefore virology data were not generated. The remaining 3 CVF subjects had treatment-emergent RPV RAMs at either position K101 or E138 that decreased virus susceptibility to RPV. These 3 subjects also had NNRTI substitutions V90I or V179I at Baseline that did not alter the susceptibility to RPV. While the single subject with the V90I substitution present at Baseline also had it at SVF, the V179I that was present at Baseline in 2 subjects was no longer present at SVF. All 3 subjects had the IN

substitution L74I at Baseline with no decrease in susceptibility to any INI. This substitution was also present at SVF, accompanied by G140R in 1 subject at Week 24 (see additional details below) and Q148R in 2 subjects. All 3 of these subjects had >5-fold decrease in susceptibility to CAB while retaining susceptibility to DTG. All 3 subjects were from Russia and had Subtype A1 virus.

Five additional subjects with subtype A1 (4/5 were from Russia) maintained viral suppression (2/5 with L74I). Site directed mutants were generated in subtype B NL4-3 and a consensus A1 IN sequence derived from the 3 CVF Baseline IN sequences. The L74I, G140R (FC 0.87 with subtype A1 vs 0.58 with subtype B) or L74I, Q148R (FC 4.1 with subtype A1 vs 4.4 with subtype B) sequences in the A1 sequence resulted in similar IC50 FC compared to subtype B background. Therefore, this preliminary in vitro virologic assessment did not indicate a differential sensitivity to CAB between subtype A1 and subtype B.

Week 28 IN Genotype and IN Phenotype could not be generated at the SVF timepoint for Subject [redacted] (viral load at Week 28 was just 287 c/mL HIV-1 RNA). Therefore, Week 24 (SVF, 493 c/mL) samples were sent to Monogram Biosciences. Week 24 PSGT had, in addition to V90I, K101E with 2.63 FC to RPV. The Week 24 IN Genotype had L74I (which was present at Baseline), and G140R which is not a commonly evaluated IN resistance mutation. The IN Phenotype showed resistance to EVG, RAL, and CAB (6.72 FC) with susceptibility (2.23 FC) to DTG. The RC for this virus was too low to quantitate. A repeat IN genotype and IN phenotype was requested from Monogram on another Week 24 sample. Unfortunately, the new aliquot would not amplify. Dobard (CROI 2018) demonstrated selection of G140R in SIV infected macaques treated with CAB [Dobard, 2018].

4.2.1.2.6. Conclusions

- CVF through Week 48 was rare in this study (1%); 4 subjects in the CAB + RPV group and 3 subjects in the CAR group.
- Three CVFs in the CAB+ RPV group had treatment emergent RPV and INI resistant mutations. All 3 had CAB resistance in vitro; 2 of the 3 had reduced in vitro RPV phenotypic susceptibility. All three were from Russia and had Subtype A1 virus; a total of 8 subjects with Subtype A1 were exposed to this regimen. The fourth CVF never received an injection and virology data were not generated.
- None of the 3 CVFs on CAR had treatment-emergent resistance mutations.

4.2.1.3. Integrase genotypes at Induction Baseline (Week -20) in FLAIR (201584)

4.2.1.3.1. Background

Subjects were excluded from Study 201584 if they had any evidence of primary resistance to NNRTIs (except for K103N which was allowed) according to plasma based screening data from the central laboratories (Q2 Solutions or Monogram), or any known resistance to INIs from historical resistance test results. Integrase genotype was not performed at Screening as current treatment guidelines do not advise integrase inhibitor resistance testing at ARV treatment initiation.

Three of the four subjects with CVF in the CAB + RPV group were from Russia, had Subtype A1 and had the Integrase substitution L74I at Baseline (Week -20) with no increase in Fold Change to CAB relative to wild type virus. To further characterize the potential role of L74I, we attempted to genotype Integrase at Baseline from the subjects enrolled in Study 201584 after all subjects met the Week 48 primary endpoint. This report [GSK Document Number 2019N407481_00] is a summary of those genotypes and associated treatment outcomes. Subjects from South Africa are not included due to the lag time in obtaining ethics committee approval and subject informed consent. Results from South Africa will be summarized when available.

4.2.1.3.2. Integrase Genotypes and HIV-1 Subtypes

Integrase genotypes at Induction Baseline were obtained on 243/283 (86%) subjects in the CAB + RPV group and 240/283 (85%) subjects in the CAR group. 54/243 (22%) subjects in the CAB + RPV group and 47/240 (20%) subjects in the CAR group had Integrase substitution L74I (Data Source: Table 7.15).

The majority of subjects from the Russian Federation had the L74I substitution, with 35/47 (74%) subjects in the CAB + RPV group and 29/36 (81%) of subjects in the CAR group. In contrast, just 3/37 (8%) subjects from the United States in the CAB + RPV group and 2/47 (4%) of the subjects in the CAR group had the L74I substitution (Table 24).

Table 24 Summary of the prevalence of L74I at Baseline (Week -20) by Country

Country	CAB + RPV (N=283) N with L74I/N genotyped (%)	CAR (N=283) N with L74I/N genotyped (%)
Canada	2/9 (22)	2/13 (15)
France	1/20 (5)	5/20 (25)
Germany	1/17 (6)	3/17 (18)
Italy	2/11 (18)	1/19 (5)
Japan	0/8	1/9 (11)
Netherlands	0/2	0/2
Russian Federation	35/47 (74)	29/36 (81)
Spain	9/77 (12)	4/68 (6)
United Kingdom	1/15 (7)	0/9
United States	3/37 (8)	2/47 (4)

Data Source: Post-hoc Table 7.16

HIV Subtype B was the most prevalent subtype with 165 (71%) subjects having Subtype B in the CAB + RPV group and 161 (67%) subjects having Subtype B in the CAR group. HIV Subtype A was the next most prevalent subtype with 38 (16%) subjects having Subtype A in the CAB + RPV group and 32 (13%) subjects having Subtype A in the CAR group. L74I was most commonly observed in Subtype A where it was present in 84% and 88% of subjects with this subtype in the CAB + RPV and CAR groups, respectively. With respect to subjects enrolled with Subtype A1, 63% of subjects in the CAB + RPV group had L74I while 75% of subjects in the CAR group had L74I. The L74I substitution was uncommon in Subtype B with just 7% in both treatment groups with Subtype B having L74I (Table 25).

Table 25 Summary of the prevalence of L74I at Baseline (Week -20) by Subtype

Subtype	CAB + RPV (N=283) N with L74I/N with subtype (%)	CAR (N=283) N with L74I/N with subtype (%)
Subtype A	32/38 (84)	28/32 (88)
Subtype A1	5/8 (63)	3/4 (75)
Subtype AE	0	0/3
Subtype AG	3/10 (30)	3/13 (23)
Subtype B	12/165 (7)	11/161 (7)
Subtype C	0/2	0/4
Subtype Missing	0/5	0/5
Subtype Other	2/15 (13)	2/18 (11)

Data Source: Post-hoc Table 7.17.

4.2.1.3.3. Efficacy Outcomes by Presence of Integrase Mutation L74I at Induction Baseline

Exploratory subgroup analysis results for the primary and secondary Snapshot endpoint proportions according to presence/absence of L74I mutation are presented in Table 26 and Table 27, respectively.

There were no statistically significant differences in treatment effect between the two groups in either subgroup (all 95% CIs contain 0). In addition, no meaningful difference in effect size was observed based on the presence/absence of L74I at Baseline.

A summary of Snapshot study outcomes is provided in Data Source: Post-hoc Table 2.56

Table 26 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 Snapshot Analysis (ITT-E Population)

L74I Mutation at Induction BL	Treatment	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Overall	CAB + RPV	6/283 (2.1)	-0.4 (-2.8, 2.1)
	CAR	7/283 (2.5)	
Yes	CAB + RPV	3/ 54 (5.6)	3.4 (-6.8, 13.5)
	CAR	1/ 47 (2.1)	
No	CAB + RPV	3/189 (1.6)	-1.5 (-5.3, 1.9)
	CAR	6/193 (3.1)	

Data Source: Post-hoc Table 2.54

a. Difference (unadjusted): proportion on CAB + RPV - proportion on CAR

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

Table 27 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 Snapshot Analysis (ITT-E Population)

L74I Mutation at Induction BL	Treatment	Number of HIV-1 RNA <50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Overall	CAB + RPV	265 / 283 (94)	0.4 (-3.7, 4.4)
	CAR	264 / 283 (93)	
Yes	CAB + RPV	50/ 54 (93%)	-1.0 (-12.7, 11.0)
	CAR	44/ 47 (94%)	
No	CAB + RPV	177/189 (94%)	0.4 (-4.9, 5.6)
	CAR	180/193 (93%)	

Data Source: Post-hoc Table 2.55

a. Difference (unadjusted): proportion on CAB + RPV - proportion on CAR

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

4.2.1.3.4. Discussion

L74I is a commonly observed polymorphism in Integrase, particularly in Subtype A. In the FLAIR study L74I was commonly observed at Baseline. An analysis of outcomes in the study indicates a high rate of success, in patients with pre-existing L74I, across both treatment groups (IM CAB + RPV and oral CAR of ABC/DTG/3TC). While 3 of the 4 CVFs in the CAB + RPV treatment group contained L74I, the totality of evidence does not suggest an association between the presence of L74I and virologic response.

4.2.1.3.5. CONCLUSIONS

- L74I was present in 22% (54/243) of subjects with Baseline integrase genotypes in the CAB + RPV group, three (5.6%) of these subjects with L74I had CVF. 50 (93%) subjects in the CAB + RPV group with L74I had <50 c/mL HIV-1 RNA at Week 48 (Snapshot Analysis).
- L74I is more common in the Russian Federation (74% of subjects in the CAB + RPV group) than in Canada, Italy, Spain, and the United States (22, 18, 12, and 8% respectively, for those subjects in the CAB + RPV group).
- L74I is more common in Subtype A, A1, and AG (84%, 63%, 30% respectively, for those subjects in the CAB + RPV group) than in Subtype B (7% in the CAB + RPV group). L74I was not observed in the six subjects with Subtype C.
- Exploratory subgroup analysis results suggest that the presence of the Integrase L74I substitution does not appear to differentially impact the treatment effect Week 48 in primary or secondary endpoint outcomes for CAB- (CAB + RPV) or DTG- (DTG/ABC/3TC) containing regimens.

4.2.1.4. Phase IIIb Study- 207966 (ATLAS-2M)

4.2.1.4.1. Study Design

Study 207966 is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of IM CAB + RPV Q8W compared to IM CAB + RPV Q4W in HIV-1 infected adult subjects.

The majority of subjects in study 207966 were enrolled from the ongoing 201585 Study with additional subjects on SOC included in order to support a targeted total sample size of approximately 1020 subjects.

All subjects completed a Screening Phase of up to 35 days prior to randomization. Eligible subjects were randomized (1:1) to receive either CAB + RPV Q8W or CAB + RPV Q4W for at least 100 weeks. Randomization was stratified by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks). Two groups of subjects were randomized:

<u>Group 1: Subjects randomized from current ART SOC therapy:</u>

Subjects randomized from current ART SOC therapy, including those enrolled to the CAR arm of Study 201585 (following completion of the Week 52 visit at minimum), received oral therapy with CAB 30 mg + RPV 25 mg once daily at Baseline (Day 1) for 28 days (±3 days) followed by IM CAB + RPV Q8W or IM CAB + RPV Q4W thereafter.

For subjects on SOC transitioning from Study 201585, eligibility for this study was determined once the final central lab results from Study 201585 were available and safety parameters had been reviewed.

Group 2: Subjects currently receiving IM CAB± RPV Q4W in Study 201585:

At Baseline (Day 1), subjects entering Study 207966 from Study 201585 and currently receiving IM CAB + RPV Q4W (including both those who were originally randomized to Q4W in the Maintenance Phase of Study 201585 and those who transitioned from SOC to the Q4W regimen within the Extension Phase of Study 201585) were randomized 1:1 to either continue IM CAB + RPV Q4W or transition to IM CAB + RPV Q8W.

4.2.1.4.2. Confirmed Virologic Failure

CVF was defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

CVF up to Week 48 was uncommon with 10 subjects meeting CVF criteria: 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Eight subjects met CVF criteria at or before the Week 24 timepoint (Table 28).

Table 28 Cumulative Proportion of Subjects Meeting CVF by Visit Up to Week 48 (Maintenance Phase) (ITT-E Population)

SVF Timepoint[a]	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Week 8	1 (0.2)	0
Week 16	4 (0.8)	1 (0.2)
Week 24	7 (1.3)[b]	1 (0.2)[c]
Week 32	7 (1.3)	2 (0.4)
Week 48	8 (1.5)	2 (0.4)

Data Source: GSK Document. Number. 2019N406358_01 Table 2.23.

a. First of the 2 consecutive HIV-1 RNA levels ≥200 c/mL
b. In the Week 24 analysis of the Q8W arm there were 6 CVFs at the Week 24 visit because one additional CVF was initially captured as 'insufficient viral response'
c. In the Week 24 analysis of the Q4W arm there were 2 CVFs at the Week 24 visit because one CVF was identified at Week 32 but was already included in the Week 24 analysis database.

Note: This summary is the proportion of CVFs up to the analysis visit.
Note: Only visits during which at least 1 new CVF occurs are shown.

4.2.1.4.3. HIV-1 Viral Genotyping and Phenotyping

Plasma samples collected at the SVF timepoint were analysed using MBI PhenoSense GT, PhenoSense Integrase and GenoSeq Integrase testing methods for PR, RT and IN. In addition, PBMCs at Baseline were analysed retrospectively to evaluate pre-existing resistance mutations in subjects with CVF. The MBI GenoSure Archive assay provides HIV-1 PR, RT, and IN genotype data from integrated HIV-1 proviral DNA but does not generate phenotypic data. Of note, resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing [Molina, 2018, Sharkey, 2005]. As such, HIV-1 DNA resistance testing is exploratory, and its primary value is in showing whether resistance is present. It is less definitive at showing that resistance is not present.

Four of the 8 CVF subjects in the Q8W arm transitioned from the oral CAR arm of Study 201585 into this study (Table 29). In the Q8W arm, 1 subject had no Baseline or SVF resistance mutations and no reduced drug susceptibility. At Baseline, 5 subjects had at least one RPV resistance-associated mutations present in vDNA from PBMCs, Y181C+H221Y; Y188Y/F/H/L; Y188L; E138A; and E138E/A, in addition to other major NNRTI resistance-associated mutations, K103N; V108V/I; and P225H. One subject had a major INSTI resistance-associated mutation at Baseline, G140G/R, and 5 subjects had either L74I or L74L/I, with 2 of these subjects having either T97T/A or G163G/R. Three subjects also presented with NRTI resistance-associated mutations and 1 of these subjects also had a PI resistance-associated mutation at Baseline.

At the SVF timepoint in the Q8W arm, 7 subjects had major NNRTI resistance-associated mutations with 2 of these subjects having an addition of K101E and 1 subject having an addition of E138E/K from Baseline to SVF timepoint. Six subjects had RPV resistance-associated mutations with 7 subjects presenting with reduced RPV susceptibility. RPV FC for these 7 subjects ranged from 2.4 to 15. Five of the 7 subjects with NNRTI resistance-associated mutations, also had INSTI resistance-associated mutations, N155H (2); Q148R; Q148Q/R+N155N/H (2). CAB FC for these subjects ranged from 1.8 to 9.1. The IN genotype and phenotype assay failed for one subject and CAB phenotype was unavailable for another. INSTI substitution, L74I, was seen in 4/8 subjects. All subjects remained sensitive to DTG and BIC. Three subjects had NRTI resistance-associated mutations that were also present at Baseline.

In the Q4W arm, neither subject had any RPV or INSTI resistance-associated mutations at Baseline. One subject had the NNRTI substitution, G190Q, in combination with the NNRTI polymorphism, V189I. These subjects also had NRTI resistance-associated mutations, M41L+ D67N+ L210W; or D67N, with 1 subject also having a PR mutation, V82T.

At the SVF timepoint in the Q4W arm, 1 of the 2 subjects had RPV resistance-associated mutations, K101E + M230L, while the other had the NNRTI substitution, G190Q, in combination with NNRTI polymorphisms V179I/V and V189I. RPV FC was 17 and >119.2, respectively. Both subjects had major INSTI resistance-associated mutations, either N155N/H or Q148R+E138E/K with CAB FC of 1.8 and 4.6, respectively. Both subjects remained susceptible to DTG and BIC. The subjects in the Q4W arm had the same NRTI mutations that were present at Baseline. One subject with PI mutation, V82T, also had an additional PI mutation, M46M/I, present at SVF that was not observed at Baseline. Results are shown in Table 29.

Among the 10 subjects with CVF (Q8W-8 subjects; Q4W-2 subjects), 4 carried HIV-1 subtype B, and 2 each had subtype A, A1 or C.

Table 29 Genotype and Phenotype Results from Day 1 and SVF Timepoints for CVF Subjects

Subject	Study Arm/ SVF Timepoint	On-Treatment, RAMs (HIV-1 RNA) SVF Timepoint				Drugs with Reduced Sensitivity (FC)[a]	Baseline RAMs (PBMC/HIV-1 DNA) (Day 1)				HIV-1 Subtype	
		RT		PR	IN	SVF Timepoint	RT		PR	IN	Day 1	SVF
		NRTI	NNRTI				NRTI	NNRTI				
Subject [redacted][bc]	Q8W Week 8	M184V	K103N A98G K238T[d]	none	none	FTC (>79.4) 3TC (>158.5) DLV (>116.6) EFV (>97.3) NVP (>199.3) *RPV (2.4)* *CAB (1.07)*[f]	L74L/V Y115Y/F M184M/V <u>Study 201585</u> L74L/V Y115Y/F M184V	A98A/G V108V/I V179V/I[d] **Y181**Y/**C H221**H/**Y** <u>Study 201585</u> A98G K103K/N V108V/I V179V/I[d] **Y181C H221Y** K238K/T[d]	none	none	C	Complex
Subject [redacted][b]	Q8W Week 16	none	none	none	none	*RPV (1.43)*[f] *CAB (0.63)*[f]	none	none	none	none	B	B
Subject [redacted]	Q8W Week 16	none	**Y188L**	none	Q148Q/R N155N/H	DLV (45) EFV (>110.96	none	**Y188**Y/F/ H/**L**	none	L74L/I[e] G140G/R	C	C

Subject	Study Arm/ SVF Timepoint	On-Treatment, RAMs (HIV-1 RNA) SVF Timepoint				Drugs with Reduced Sensitivity (FC)[a]	Baseline RAMs (PBMC/HIV-1 DNA) (Day 1)				HIV-1 Subtype	
		RT		PR	IN	SVF Timepoint	RT		PR	IN	Day 1	SVF
		NRTI	NNRTI				NRTI	NNRTI				
					L74I[e]	) ETR (3.5) NVP (>169.4) *RPV (6.8)* EVG (33) RAL (20) *CAB (2.63)*						
Subject [redacted]	Q8W Week 16	none	**K101E**	none	L74I[e] Q148R	DLV (8.97) EVF (6.3) ETR (4.3) NVP (27) *RPV (4.7)* EVG (60) RAL (31) *CAB (9.1)*	none	none	none	L74I[e]	Complex	A1
Subject [redacted]	Q8W Week 24	none	V179I[d] **Y188L** P225H	None	Assay failed	DLR (22) EFV (>115.4) ETR (4.2) NVP (>173.7) *RPV (15)*	none	V179I[d] **Y188L** P225H	none	L74I[e]	A1	A1
Subject [redacted]	Q8W Week 24	none	K103N **E138A**	none	N155H	DLV (>123.0) EFV (39) ETR (4.3)	none	K103N V108V/I **E138A**	none	none	B	B

Subject	Study Arm/ SVF Timepoint	On-Treatment, RAMs (HIV-1 RNA) SVF Timepoint				Drugs with Reduced Sensitivity (FC)[a]	Baseline RAMs (PBMC/HIV-1 DNA) (Day 1)				HIV-1 Subtype	
		RT					RT					
		NRTI	NNRTI	PR	IN	SVF Timepoint	NRTI	NNRTI	PR	IN	Day 1	SVF
						NVP (>192.5) *RPV (7.2)* EVG (25) RAL (11) *CAB (1.8)*[f]						
Subject [redacted][b]	Q8W Week 24	A62V	**K101E** **E138A**	none	L74I[e] T97A[e] N155H	DLV (7.99) NVP (22) *RPV (2.6)* EVG (96) RAL (74) *CAB (6.98)*	A62V Study 201585 A62V	**E138E/A** Study 201585 **E138E/A**	none	L74I[e] T97T/A[e] Study 201585 L74I[e] T97T/A[e]	A	A
Subject [redacted][bg]	Q8W Week 48	A62V	V90I **E138E**/K V179I[d]	none	L74I[e] Q148Q/R N155N/H	DLV (8.6) ETR (3.6) EVG (18) RAL (4.8) *RPV (4.2)* *no CAB data*	A62V Study 201585 A62V	V90I V179I[d] Study 201585 V90I V179V/I[d]	M46M/I	L74I[e] Study 201585 L74I[e] G163G/R[e]	A1	A
Subject [redacted][c]	Q4W Week 16	M41L D67N L210W	G190Q[d] V179V/I[d] V189I[d]	M46 M/I V82T	N155N/H	FTC (3.6) 3TC (5.4) TDF (2.2) AZT (5.4) EFV (>97.3)	M41L D67N L210W	G190Q[d] V189I[d]	V82T	none	B	B

Subject	Study Arm/ SVF Timepoint	On-Treatment, RAMs (HIV-1 RNA) SVF Timepoint				Drugs with Reduced Sensitivity (FC)[a]	Baseline RAMs (PBMC/HIV-1 DNA) (Day 1)				HIV-1 Subtype	
		RT					RT					
		NRTI	NNRTI	PR	IN	SVF Timepoint	NRTI	NNRTI	PR	IN	Day 1	SVF
						ETR (165) NVP (>199.3) DLV (>116.6) *RPV (>119.2)* NFV (7.5) RTV (5.6) EVG (16) RAL (4.8) *CAB (1.8)*[f]						
Subject [redacted]	Q4W Week 32	D67N	**K101E M230L**	none	Q148R E138E/K	AZT (3.9) DLV (>134.9) EFV (78) ETR (16) NVP (>189.6) *RPV (17)* EVG (>82.99) RAL (36) *CAB (4.6)*	D67N	none	none	none	B	B

Data Source: Table 7.8; GSK Document Number. 2018N370336_00

Note: Bolded genotypes are RPV resistance-associated mutations. RPV and CAB phenotype data is in italics.

a. Reduced sensitivity was determined from the Clinical cut-offs or biological cutoffs used in PhenoSense GT or PhenoSense Integrase assays by Monogram Biosciences. FC= Fold change in IC50 compared to wild type HIV-1 virus.

b. Subject transitioned from Study 201585.

c. Protocol deviator- [redacted]- Inclusion criteria 5_ 2nd regimen contained PI after NNRTI-based regimen; [redacted]- Exclusion criteria 11_Evidence of current CDC Stage 3 disease.

and exceeded the number of allowed prior ART changes.

d. NNRTI substitution is not considered a resistance-associated mutation according to IAS-USA 2019 [Wensing, 2019].
e. INSTI substitution is not considered a major resistance-associated mutation according to IAS-USA 2019.
f. Fold change is below biological cut-offs used in assays by Monogram Biosciences, ie 2.0 for RPV and 2.5 for CAB.
g. Phenotype and genotype data for the SVF timepoint is from the CVF (Week 48 Retest) timepoint.

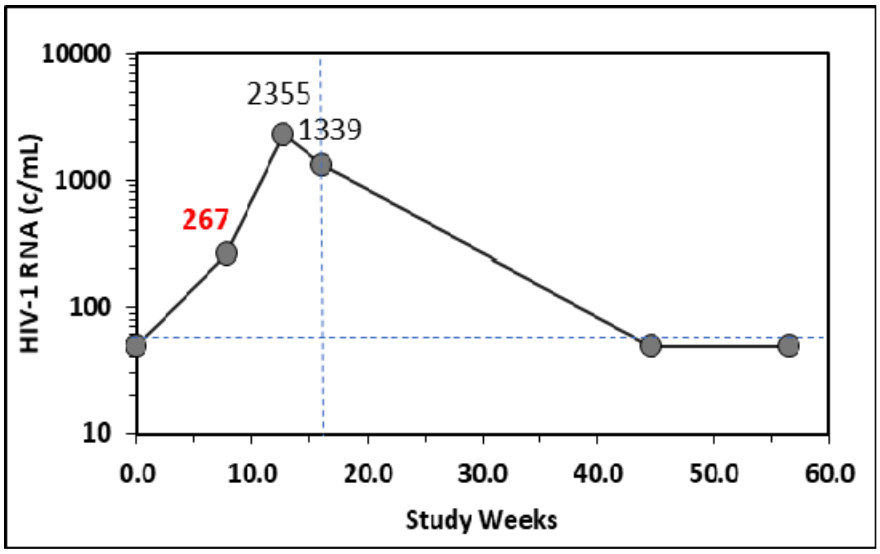
4.2.1.4.4. Virology Narratives for Confirmed Virologic Failures

CAB + RPV Q8W Group

Subject [redacted]

- Female; South Africa; BMI >30 kg/m2; 1.5" needle used.
- Failed inclusion criteria 5- Subject had 2nd regimen consisting of a PI after NNRTI regimen.
- Study 201585; Subject [redacted]; CAR arm. Switched to LA CAB + RPV at Week 52 while in Study 201585
- Prior ART: stavudine/lamivudine/nevirapine and emtricitabine/tenofovir disoproxil fumarate/atazanavir/ritonavir.
- SVF Week 8, HIV-1 RNA 267 c/mL; CVF Week 16, HIV-1 RNA 2355 c/mL.
- Study 201585 Baseline PBMC vDNA had NNRTI resistance-associated mutations K103K/N, V108V/I, Y181C, H221Y: NRTI resistance-associated mutations L74L/V and no INSTI resistance-associated mutations. Subtype C.
- Study 207966 Baseline PBMC vDNA had V108V/I, Y181Y/C, H221H/Y and no INSTI resistance-associated mutations. Subtype C.
- SVF plasma vRNA had NNRTI resistance-associated mutation, K103N, and no INSTI resistance-associated mutations. RPV FC= 2.4. CAB FC= 1.1. Subtype is Complex.
- Prescribed tenofovir disoproxil fumarate/emtricitabine/atazanavir/ritonavir at Week 16 in study 207966 and entered LTFU.
- Resuppressed by LTFU Month 9 visit.

Figure 19 Subject [redacted] HIV-1 Viral Load History

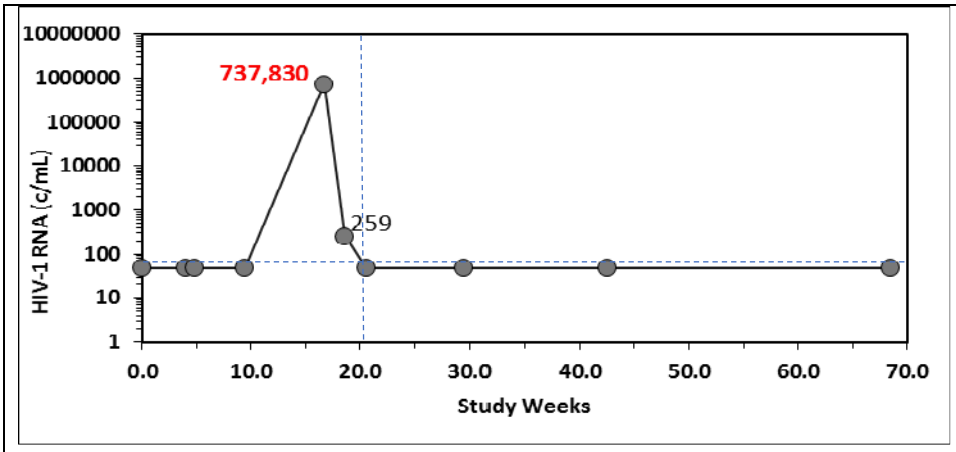


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Male; Spain; BMI ≤30 kg/m^2; 1.5" needle used.
- Study 201585; Subject [redacted]; CAR arm.
- Prior ART: efavirenz, emtricitabine, tenofovir disoproxil fumarate and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate.
- SVF Week 16, HIV-1 RNA 737,830 c/mL; CVF Week 16 Retest, HIV-1 RNA 259 c/mL.
- Study 207966 Baseline PBMC vDNA had no resistance-associated mutations. Subtype B.
- SVF plasma vRNA had no resistance-associated mutations and no reduced sensitivity to NNRTIs or INIs. Subtype B.
- Prescribed dolutegravir/abacavir/lamivudine at the Withdraw visit (Week 21 in study 207966). Was suppressed at this visit.
- Entered LTFU.

Figure 20 Subject [redacted] HIV-1 Viral Load History

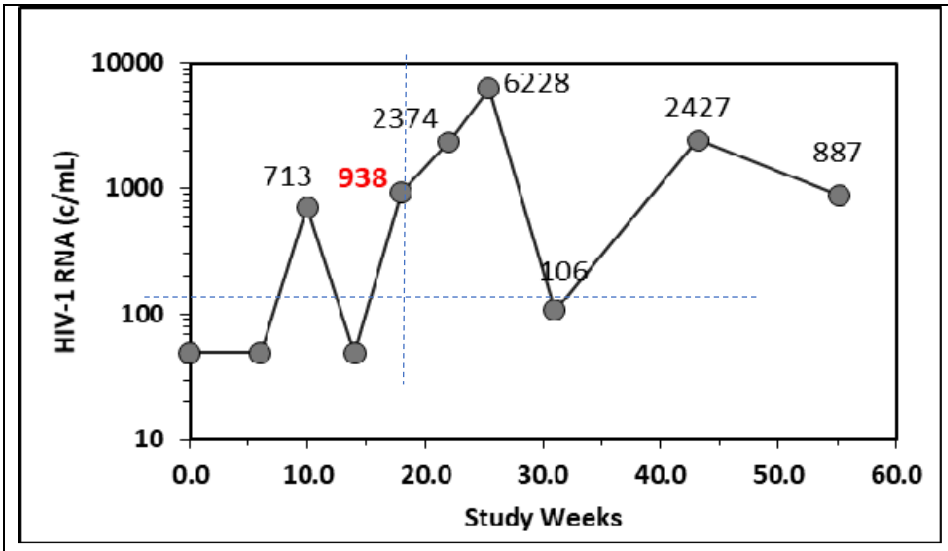


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Female; South Africa; BMI >30 kg/m^2; 1.5" needle used.
- Prior ART: efavirenz, emtricitabine, tenofovir disoproxil fumarate. Newly recruited to study 207966.
- SVF Week 10, HIV-1 RNA 713 c/mL was not confirmed.
- SVF Week 16, HIV-1 RNA 938 c/mL; CVF Week 24, HIV-1 RNA 2374 c/mL.
- Study 207966 Baseline PBMC vDNA had NNRTI resistance-associated mutation, Y188Y/F/H/L and INSTI resistance-associated mutation, G140G/R and INSTI polymorphism, L74I. Subtype C.
- SVF plasma vRNA had NNRTI resistance-associated mutation, Y188L and INSTI resistance-associated mutations, Q148Q/R and N155N/H and INSTI substitution, L74I. RPV FC= 6.8 and CAB FC=2.6. Subtype C.
- Prescribed lopinavir/ritonavir/emtricitabine/tenofovir disoproxil fumarate and discontinued study medication.
- Entered LTFU. Not resuppressed (LTFU Month 9).

Figure 21 Subject [redacted] HIV-1 Viral Load History

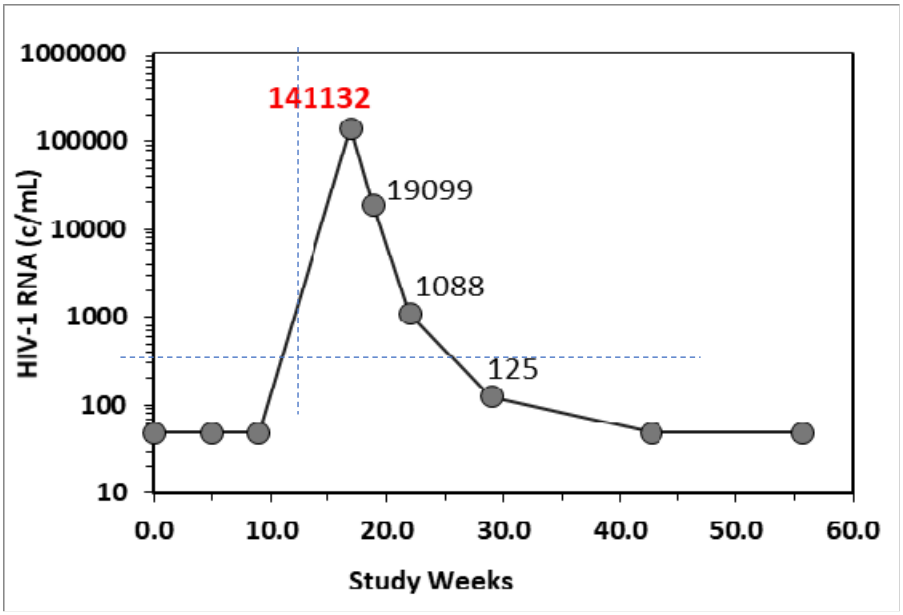


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Female; Russia; BMI >30 kg/m^2; 1.5" needle used.
- Prior ART: lopinavir, zidovudine, lamivudine, tenofovir disoproxil fumarate. Newly recruited to study 207966.
- SVF Week 16, HIV-1 RNA 141,132 c/mL; CVF Week 16 Retest, HIV-1 RNA 19,099 c/mL.
- Study 207966 Baseline PBMC vDNA had IN substitution, L74I. Subtype Complex.
- SVF plasma vRNA had RPV resistance-associated mutation, K101E, and INSTI resistance-associated mutation, Q148R and INSTI substitution, L74I. RPV FC= 4.7. CAB FC= 9.1. Subtype A1.
- Prescribed abacavir/lamivudine/atazanavir at Week 25 in study 207966 and discontinued study medication.
- Entered LTFU and was resuppressed at LTFU Month 6 visit.

Figure 22 Subject [redacted] HIV-1 Viral Load History

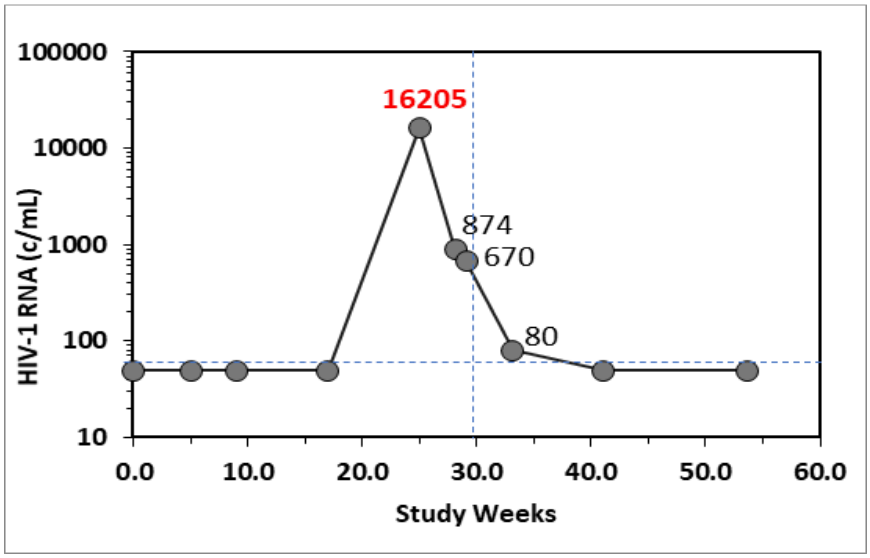


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Female; Canada; BMI >30 kg/m^2; 1.5'' needle used.
- Prior ART: abacavir/ lamivudine/darunavir; elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate; elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
- SVF Week 24, HIV-1 RNA 16,205 c/mL; CVF Week 32, HIV-1 RNA 874 c/mL.
- Study 207966 Baseline PBMC vDNA had NNRTI resistance-associated mutations, Y188L and P225H, and IN substitution, L74I. Subtype A1.
- SVF plasma vRNA had NNRTI resistance-associated mutations, Y188L and P225H. IN analysis failed. RPV FC=15. Subtype A1.
- Prescribed darunavir/cobicistat/emtricitabine/tenofovir alafenamide at Week 30 and withdrew from the study.
- Entered LTFU and was resuppressed at the LTFU Month 3 visit.

Figure 23 Subject [redacted] HIV-1 Viral Load History

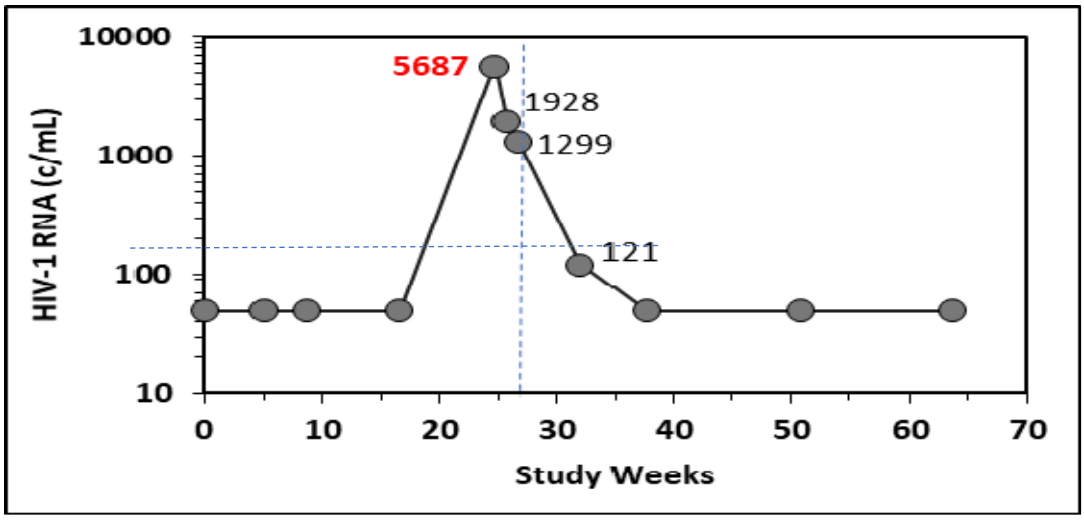


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Male; United States; BMI >30 kg/m^2; 1.5" needle used.
- Prior ART: dolutegravir/abacavir/lamiduvine.
- SVF Week 24, HIV-1 RNA 5687 c/mL; CVF Week 24, HIV-1 RNA 1928 c/mL.
- Study 207966 Baseline PBMC vDNA had NNRTI resistance-associated mutations, K103N, V108V/I and E138A. Subtype B.
- SVF plasma vRNA had NNRTI resistance-associated mutations, K103N and E138A and INSTI resistance-associated mutation, N155H. RPV FC= 7.2. CAB FC= 1.8. Subtype B.
- Prescribed darunavir/cobicistat/emtricitabine/tenofovir alafenamide at Week 27 and withdrew from study.
- Entered LTFU and after 8 weeks switched ART to dolutegravir/abacavir/lamivudine. Resuppressed at the LTFU Month 3 visit.

Figure 24 Subject [redacted] HIV-1 Viral Load History

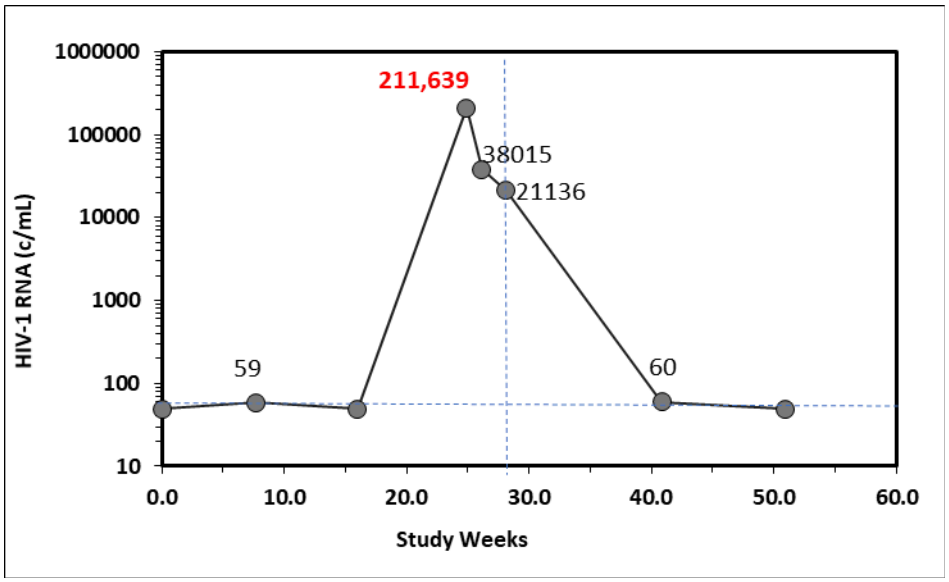


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Female; Russia; BMI ≥30 kg/m2; 1.5" needle used.
- Study 201585; Subject [redacted]; CAR arm. Switched to LA CAB + RPV while in Study 201585.
- Prior ART: emtricitabine/ tenofovir disoproxil fumarate; raltegravir/lamivudine/zidovudine.
- SVF Week 24, HIV-1 RNA 211,639 c/mL; CVF Week 24 retest, HIV-1 RNA 38,015 c/mL.
- Study 201585 and Study 207966 Baseline PBMC vDNA had RPV resistance-associated mutation, E138E/A. Subtype A.
- SVF plasma vRNA had RPV resistance-associated mutations, K101E and E138A, INSTI resistance-associated mutation, N155H, and IN substitutions, L74I and T97A. RPV FC=2.6 and CAB FC= 6.98. Subtype A.
- Started dolutegravir/abacavir/lamivudine at Week 28 and withdrew from study.
- Entered LTFU and was resuppressed at LTFU Month 6 visit.

Figure 25 Subject [redacted] HIV-1 Viral Load History

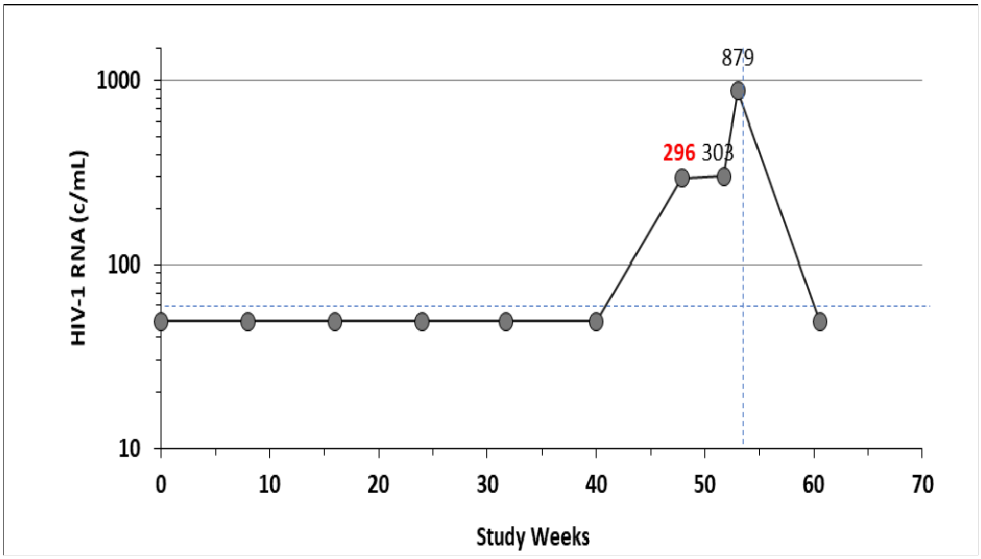


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Male; Russia; BMI <30 kg/m2; 1.5" needle used.
- Study 201585; Subject [redacted]; CAR arm. Switched to LA CAB + RPV while in Study 201585; <24 weeks of prior CAB + RPV exposure during Study 201585.
- Prior ART: lamivudine/lopinavir/ritonavir/zidovudine
- SVF Week 48, HIV-1 RNA 296 c/mL; CVF Week 48 Retest, HIV-1 RNA 303 c/mL.
- Study 201585 Baseline PBMC vDNA had no NNRTI resistance-associated mutations: no INSTI resistance-associated mutations; NRTI resistance associated mutation, A62V. Subtype A1.
- Study 207966 Baseline PBMC vDNA had NNRTI resistance-associated mutation, V90I; no INSTI resistance-associated mutations; NRTI resistance-associated mutation, A62V; PI resistance-associated mutation, M46M/I. Subtype A.
- CVF (Week 48 retest) plasma vRNA had RPV resistance-associated mutation, E138E/K; INSTI resistance-associated mutations, Q148Q/R + N155N/H. RPV FC=4.25 No CAB resistance data available. Subtype A.
- Prescribed lamivudine/r/lopinavir/zidovudine at Week 53.
- Entered LTFU and was resuppressed at LTFU Month 3 visit.

Figure 26 Subject [redacted] HIV-1 Viral Load History



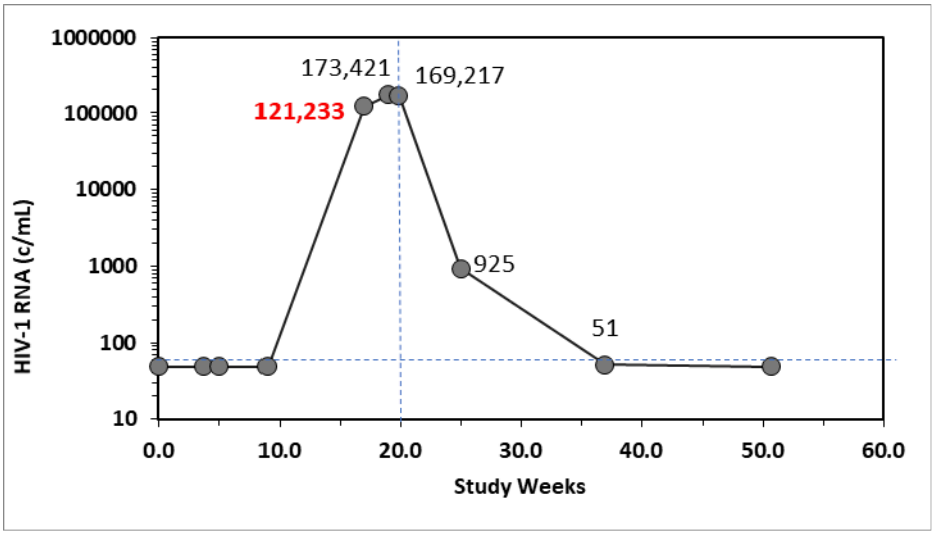
Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q8W: min(max(date of last IP injection dose + 63 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

CAB + RPV Q4W Group

Subject [redacted]

- Male; France; BMI ≤30 kg/m^2; 1.5" needle used.
- Failed exclusion criteria 11- evidence of current CDC Stage 3 disease-CD4$^+$ count <200 cells/µL present at Day 1 and exceeded the number of allowed prior ART changes.
- Prior ART: abacavir/lamivudine/zidovudine and enfuvirtide, maraviroc, raltegravir, and darunavir.
- SVF Week 16, HIV-1 RNA 121,233 c/mL; CVF Week 16 retest, HIV-1 RNA 173,421 c/mL.
- Study 207966 Baseline PBMC vDNA had no major NNRTI or INSTI resistance-associated mutations. Subtype B.
- SVF plasma vRNA had INSTI resistance-associated mutation, N155N/H. No reduced sensitivity to CAB (CAB FC=1.8). No major NNRTI resistance-associated mutation, but NNRTI substitutions, G190Q, V179V/I, V189I. RPV FC=>119.2 and CAB FC= 1.8. Subtype B.
- Prescribed darunavir/abacavir/lamivudine at Week 20 and withdrew from study.
- Entered LTFU and was resuppressed at Month 6 visit.

Figure 27 Subject [redacted] HIV-1 Viral Load History

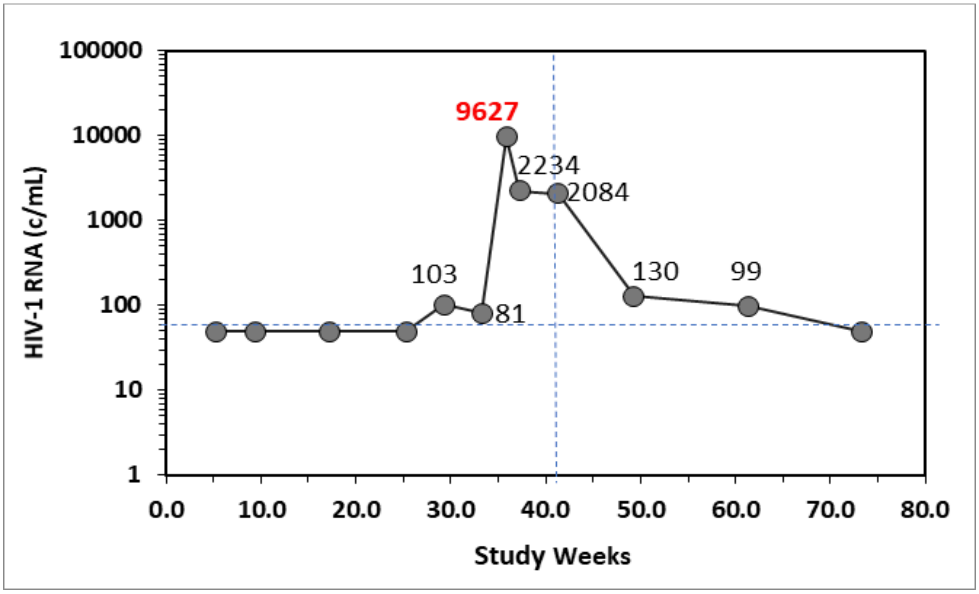


Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q4W: min(max(date of last IP injection dose + 35 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Male; United States; BMI ≤30 kg/m^2; 1.5'' needle used.
- Prior ART: darunavir/emtricitabine/tenofovir disoproxil fumarate, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, and elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide.
- SVF Week 32, HIV-1 RNA 9627 c/mL; CVF Week 32 retest, HIV-1 RNA 2234 c/mL.
- Study 207966 Baseline PBMC vDNA had no resistance-associated mutations. Subtype B.
- SVF plasma vRNA had NNRTI resistance-associated mutations, K101E and M230L, and INSTI resistance-associated mutations, Q148R and E138E/K. RPV FC=17 and CAB FC=4.6. Subtype B.
- Prescribed darunavir/cobicistat/emtricitabine/tenofovir alafenamide at Week 37 and withdrew from study.
- Entered LTFU and was resuppressed at LTFU Month 6 visit.

Figure 28 Subject [redacted] HIV-1 Viral Load History



Data Source: GSK Document Number. 2019N406358_01 Listing 40.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q4W: min(max(date of last IP injection dose + 35 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

4.2.1.4.5. HIV-1 Exploratory Analysis

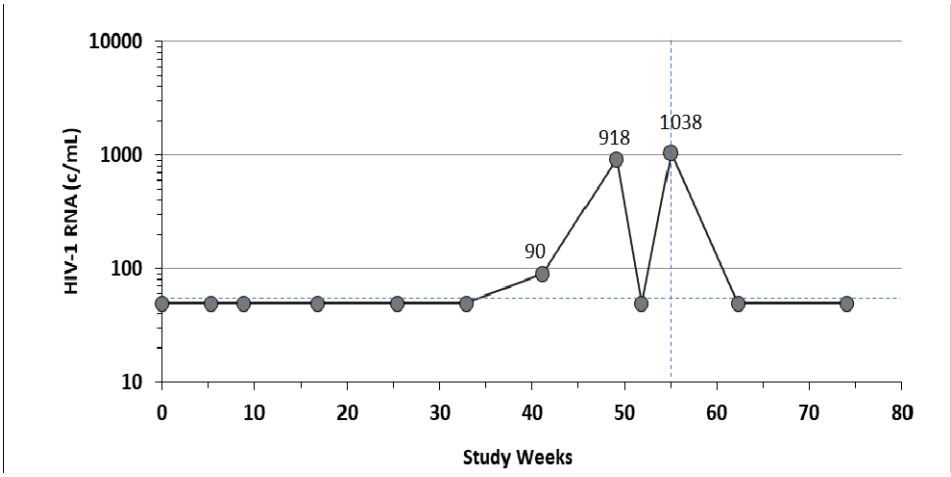
Subject [redacted] in the Q8W arm was suspected of having a superinfection because of their high HIV-1 viral load (737,830 c/mL) observed at SVF and subject-reported unprotected sexual encounters with multiple partners just prior to the Week 16 visit. Sequencing analysis was conducted on Baseline PBMC vDNA, SVF vRNA (Week 16), and CVF vRNA (Week 16 Retest) and the RT, PR and IN substitutions observed from the 3 timepoints were compared. Subject's VL decreased to 259 c/mL at the Week 16 Retest visit performed 14 days following the SVF (Week 16) visit. Based on the high degree of similarity between the Baseline, Week 16, and Week 16 Retest sequences and the rapid decline in VL between the Week 16 and Week 16 retest visits, a superinfection was not considered the cause for the high HIV-1 VL seen at the SVF timepoint.

Three subjects had SVF (i.e., HIV-RNA ≥200 c/mL) that was not confirmed. These subjects had genotype and phenotype analysis performed at either the SVF time point or last on-study time point with HIV RNA >50 c/mL. Baseline PBMC sequence analysis showed no resistance-associated mutations for one subject, INSTI mutations L74I + Q148Q/R for another and INSTI mutation T97T/A for the third subject. At the SVF or elevated VL time point, two subjects had RPV-resistance associated mutations, either K101E or E138K. The IN assay failed for 2 subjects and no INI-major resistance-associated mutations were observed for the third subject. Subtypes were A1 (n=1) and B (n=2).

Subject [redacted]:

- Q8W; Male; Spain; BMI 17.8 kg/m2; 1.5'' needle used.
- Prior ART: efavirenz/emtricitabine/tenofovir disoproxil fumarate, and rilpivirine/emtricitabine/tenofovir disoproxil fumarate.
- SVF Week 48, HIV-1 RNA 918 c/mL (not confirmed) and Withdraw-Week 56, HIV-1 RNA 1038 c/mL.
- Study 207966 Baseline PBMC vDNA had no NNRTI or INSTI resistance-associated mutations. Subtype A1.
- Week 48 SVF plasma vRNA had RPV resistance-associated mutation E138K. RPV FC=3.5. IN assay failed. Subtype A1.
- At Week 56 prescribed darunavir/cobicistat/emtricitabine/tenofovir alafenamide and entered LTFU. At LTFU Month 1 had HIV-1 RNA of <50 c/mL.

Figure 29 Subject [redacted] HIV-1 Viral Load History



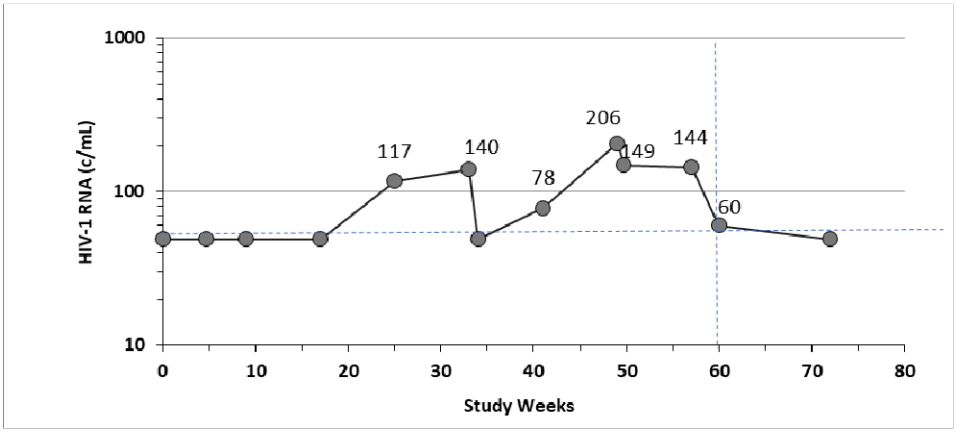
Data Source: GSK Document Number. 2019N406358_01 Listing 41.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q4W: min(max(date of last IP injection dose + 35 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Q8W; Male; United States; BMI 25.6 kg/m2. 1.5'' needle used.
- Prior ART: elvitegravir/cobicistat//emtricitabine/tenofovir disoproxil fumarate.
- SVF at Week 48, HIV-1 RNA 206 c/mL (not confirmed); HIV-1 viral load blips at Week 24 (117 c/mL), Week 32 (140 c/mL) Week 40 (78 c/mL), Week 48 (121 c/mL), Week 48 Retest (149 c/mL), Week 56 (144 c/mL) and Withdraw-Week 60 (60 c/mL).
- Study 207966 Baseline PBMC vDNA had INSTI resistance-associated mutation T97T/A. No NNRTI resistance-associated mutations were observed. Subtype B.

- SVF Week 48 plasma vRNA had no RPV-resistance associated mutations. IN sequencing assays failed. Subtype B.
- At Withdrawal, placed on bictegravir/tenofovir alafenamide/atazanavir/cobicistat and entered LTFU. LTFU Month 3 HIV RNA was <50 c/mL.

Figure 30 Subject [redacted] HIV-1 Viral Load History

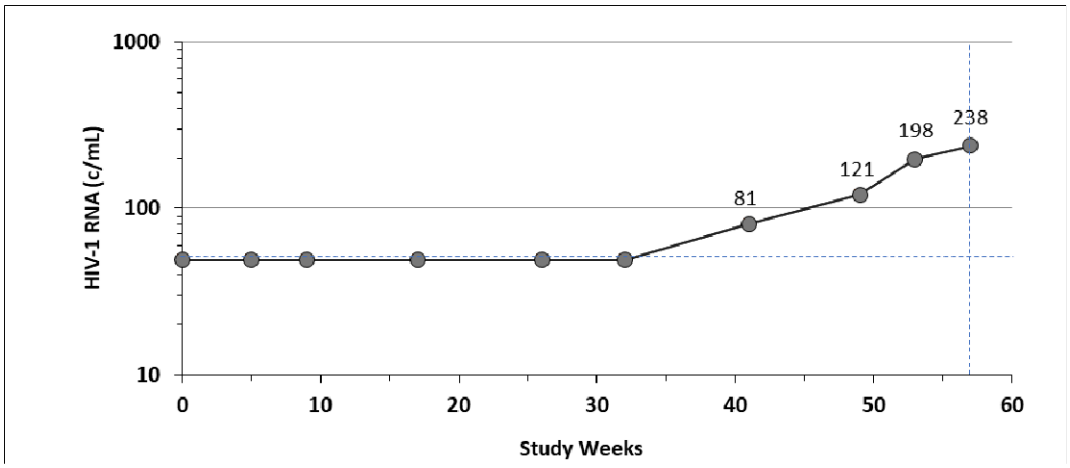


Data Source: GSK Document Number. 2019N406358_01 Listing 41.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q4W: min(max(date of last IP injection dose + 35 days, date of last oral CAB+RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Subject [redacted]

- Q4W; Male; United States; BMI >30 kg/m2. 1.5'' needle used.
- Prior ART: efavirenz/emtricitabine/tenofovir disoproxil fumarate, rilpivirine/emtricitabine/tenofovir disoproxil fumarate, and rilpivirine/emtricitabine/tenofovir alafenamide.
- SVF at Withdraw time point (Week 56), HIV-1 RNA 238 c/mL (not confirmed); HIV-1 viral load increased at Week 40 (81 c/mL), Week 48 (121 c/mL) and Week 48 Retest (198 c/mL).
- Study 207966 Baseline PBMC vDNA had INSTI resistance-associated mutation Q148Q/R and INSTI substitution L74I. No NNRTI resistance-associated mutations were observed. Subtype B.
- Week 48 Retest plasma vRNA contained RPV resistance-associated mutation K101E. RPV FC=3.9. IN genotype and phenotype analysis failed. Subtype B.
- At Withdrawal, placed on darunavir/cobicistat/emtricitabine/tenoovir alafenamide and entered LTFU.

Figure 31 Subject [redacted] HIV-1 Viral Load History



Data Source: GSK Document Number. 2019N406358_01 Listing 41.
Note: The dotted vertical line indicates the last on-treatment study day during the maintenance/extension phase. Q4W: min(max(date of last IP injection dose + 35 days, date of last oral CAB + RPV + 1 day), LTFU HAART start date). The horizonal dotted line represents HIV-1 VL 50 c/mL.

Data sources for virology narratives and exploratory virology narratives described in this report are GSK Document Number. 2019N406358_01 Listing 9, Listing 35, Listing 37, Listing 40, Listing 41, Table 7.8, Table 7.9.

4.2.1.4.6. Discussion

Among the 10 subjects with CVF (Q8W: 8 [1.5%] subjects; Q4W: 2 [0.4%] subjects), RPV resistance-associated mutations were seen in 5/10 CVFs in Baseline PBMCs and 7/10 CVFs at the SVF timepoint. RPV mutations that arose on treatment included K101E (2), K101E + M230L, and E138E/K. In vitro phenotypic resistance to RPV was observed in 9/10 CVFs at the SVF time point. Two subjects did not have any RPV resistance-associated mutations, but still had reduced susceptibility to RPV (FC=2.4 and >119.2). Both subjects had virus that harboured other NNRTI substitutions, but these substitutions were not expected to decrease sensitivity to RPV.

INSTI resistance-associated mutations occurred in 1/10 CVF subject in PBMCs at Baseline and 7/9 CVFs at the SVF timepoint. The INSTI mutation that was present at Baseline was G140G/R. This mutation was also reported in a FLAIR CVF subject at the SVF timepoint with an increased CAB FC=6.72 [GSK Document Number 2017N345267_00]. CAB mutations that arose on treatment were Q148R, Q148R + E138E/K, Q148Q/R + N155N/H (2), N155H (2), and N155N/H. CAB resistance (in vitro phenotypic analysis) was observed in 4/8 CVF subjects at the SVF timepoint. INSTI substitutions, L74I, T97T/A and G163G/R, were present in some subjects but do not reduce INSTI susceptibility by themselves. All subjects, with phenotype data at the SVF time point, retained susceptibility to dolutegravir and bictegravir.

CVF subjects in this study harboured Subtype A or A1 (n=4), B (n=4), and C (n=2) viruses. This is in contrast to the CVF subjects from the CAB LA +RPV LA group in

Study 201584 (FLAIR) and Study 201585 (ATLAS), where viral subtypes were either A, A1 or AG.

4.2.1.4.7. Conclusions

- CVFs were infrequent in the study with 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Virus subtypes observed in CVF subjects were A or A1 (n=4), B (n=4) or C (n=2).
- RPV resistance-associated mutations were found in 5/10 CVF subjects in Baseline PBMCs and 7/10 subjects at SVF time point.
- At the SVF time point, in vitro phenotypic resistance to RPV occurred in 9/10 CVF subjects.
- INSTI resistance-associated mutations were present in 1/10 subjects in Baseline PBMCs and 7/9 subjects at SVF time point.
- At the SVF time point, in vitro phenotypic CAB resistance occurred in 4/8 CVF subjects.
- INSTI substitution, L74I, was present in 5 subjects at Baseline and 4 subjects at the SVF time points.
- No dolutegravir or bictegravir resistance was observed in the CVF subjects.

4.2.1.5. Baseline PBMC HIV-1 DNA Analyses; 201585 (ATLAS)

Protocol Number and Title: 201585: A Phase III, randomized, multicenter, parallel-group, noninferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir (CAB LA) plus long acting rilpivirine (RPV LA) from current INI-, NNRTI-, or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed.

Study Design: 201585 (ATLAS) is a Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of a two drug regimen of CAB + RPV compared with maintenance of current ART (CAR). A total of 616 adult HIV-1 infected subjects who were on a stable ARV regimen containing 2 NRTIs plus an INSTI, NNRTI, or a PI were randomized 1:1 to continue CAR (n=308) or switched to the CAB + RPV regimen (n=308) through 52 weeks. The study continues with an Extension Phase up to at least 96 weeks. Subjects who discontinued CAR began oral therapy with CAB 30 mg + RPV 25 mg once daily for 4 weeks prior to administration of CAB + RPV every 4 weeks. At Week 52, eligible subjects on CAB + RPV (without meeting study defined withdrawal criteria and remained virologically suppressed: HIV-1 RNA <50 c/mL) could continue into the Extension Phase, transition into 207966 (ATLAS-2M), or withdraw from the study. Subjects who were randomized to continue CAR and successfully completed Week 48 were given the option at Week 52 to switch to the CAB + RPV group in the Extension Phase, transition to 207966, or withdraw from the study.

Subjects were excluded from Study 201585 if they had any evidence of primary resistance based on the presence of any major known INSTI or NNRTI resistance-associated mutation (RAM), except for K103N, International Antiviral Society (IAS-USA), [IAS–USA, 2019] by any historical resistance test result. Prior genotypic resistance testing was not required, but if available, had to be provided to GSK after screening and before randomization to provide direct evidence of no pre-existing exclusionary resistance mutations.

Peripheral blood mononuclear cell (PBMC) samples were collected at Day 1, Week 96, and Withdrawal, if applicable, for retrospective virologic analyses. PBMC DNA sequencing data was not available and not used for the purpose of screening individuals for study eligibility. These data were generated retrospectively for exploring the potential association between Baseline resistance and virologic outcome at Week 48. PBMC sequencing data must be interpreted with caution as detection of resistance mutations in PBMC DNA does not always correlate with clinically-observed drug resistance. Further, mutations that may be present in plasma HIV RNA may not always be observed, or may be observed at later time points, in PBMC DNA.

Confirmed Virologic Failure (CVF) (2 consecutive plasma HIV-1 RNA ≥200 c/mL) occurred in 3 subjects in the CAB + RPV group. Baseline PBMC HIV-1 proviral DNA sequencing showed that 2 of the 3 subjects s had the pre-existing RPV RAMs E138E/A and E138K, with one of these subjects also presenting with INSTI polymorphism L74I. The other subject had only the L74I polymorphism at Baseline. These 3 CVF subjects carried either HIV-1 Subtype A, A1, or AG. To understand the consequence of pre-existing NNRTI, RPV and/or INSTI RAMs, the presence of the L74I polymorphism, and subtype on CAB LA + RPV LA efficacy, HIV-1 proviral DNA from Baseline PBMCs was sequenced for all subjects with Baseline samples in both treatment groups. This report is a summary of those genotypes and associated treatment outcomes.

The objectives of this exploratory analysis are to:

- determine the prevalence of Baseline archived resistance mutations
- investigate the relationship between Baseline archived resistance and virologic outcome through Week 48

4.2.1.5.1. Methods

Source of Data

The Monogram Biosciences GenoSure Archive assay, a proviral DNA genotypic assay, was used to evaluate the presence of archived mutations in Baseline PBMCs. The assay provides HIV-1 PRO, RT, and IN genotype data from integrated HIV-1 proviral DNA but does not generate phenotypic data. Of note, resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing [Lee, 2012]; as such HIV-1 DNA resistance testing is exploratory. The assay's primary value is in showing the presence of archived resistance; thus, a HIV-1 mutation not detected in proviral DNA may still be present in plasma RNA.

Four subgroups of NNRTI and INSTI RAMs were pre-identified and are listed in Table 30. Protease genotype data are out of scope from this analysis.

Table 30 Mutations potentially associated with Resistance to INSTI or NNRTI

Class	Mutations
INSTI	Pre-specified INSTI mutations [1]: H51Y, T66A/I/K, L68V/I, L74I/M, E92Q/V/G, Q95K, T97A, G118R, F121Y, T124A, E138A/K/D/T, G140A/C/R/S, Y143C/H/R/K/S/G/A, P145S, Q146L/P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, G193E, S230R, R263K,
	IAS-USA major mutations associated with resistance to INSTI [2]: T66I, E92Q, G118R, F121Y, G140R, S147G, Q148H/K/R, Y143R/H/C, N155H, R263K
NNRTI	IAS-USA mutations associated with resistance to NNRTI [3]: V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M/T, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/S, H221Y, P225H, F227C/L/R, M230I/L, L234I
	IAS-USA major mutations associated with resistance to RPV [4]: L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L

Data Source: GSK Document Number 2019N40275_00 Table 1

[1] Mutations (T124A, Q146L) were added per FDA request for study 201584; mutations (H51Y, L74I, L68V/I, E92V, Q95K, E138D, Y143K/S/G/A, P145S, Q146P, V151I/L/A, N155S/T, E157Q, G163R/K, G193E, S230R) were identified during in vitro passage of DTG or seen in a previous DTG study in INSTI-experienced subjects (ING112574); all other mutations in this pre-specified list were identified per the IAS-USA mutations associated with resistance to Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir or Raltegravir [IAS–USA, 2019].

[2] IAS-USA major mutations associated with resistance to Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir or Raltegravir [IAS–USA, 2019].

[3]: IAS-USA mutations associated with resistance to Doravirine, Efavirenz, Etravirine, Nevirapine or Rilpivirine [IAS–USA, 2019].

[4] IAS-USA major mutations associated with resistance to RPV [IAS–USA, 2019]. These are identical to the ones mentioned in the EDURANT prescribing information, except for L100I, which is only mentioned in combination with K103N.

To investigate the potential impact of Baseline archived resistance on virologic outcome, the following efficacy endpoints at Week 48 (per the Snapshot algorithm) were assessed:

- The proportion of subjects with HIV-1-RNA ≥50 c/mL and
- The proportion of subjects with HIV-1-RNA <50 c/mL

The two endpoints were analyzed separately.

4.2.1.5.2. Study Population

Two analysis populations are defined as follows:

- Proviral DNA Resistance Population (PR):

This population is based on the Intention-to-Treat Exposed (ITT-E) population for whom Baseline proviral DNA genotypic data are available. This population was the primary population for the analyses described in this document.

- Proviral DNA Resistance Censored Population (PRC):

This population was defined to assess the effect of Baseline resistance on outcome without confounding factors (e.g. early discontinuation because of adverse events). Therefore, subjects who discontinued study treatment prior to Week 48 while last on-treatment HIV-1 RNA was <50 c/mL were excluded from this PRC. The rule for exclusion of subjects is in line with FDA's guidance document for clinical resistance analysis (i.e. Guidance for Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry, 2015). The PRC population was used for the efficacy sensitivity analyses.

4.2.1.5.3. Method of analysis

The prevalence of archived mutations at Baseline were summarized by study treatment group and overall. Within each group, similar tabulations were created by Baseline subgroups (geographic region, duration of prior INSTI /NNRTI use, prior INSTI/NNRTI treatment, Baseline third agent class and virus subtype).

The proportion of subjects with HIV-1 RNA ≥ 50 c/mL at Week 48 (Snapshot algorithm) was compared across the pre-specified INSTI mutations (major mutations vs non-major prespecified vs other) as well as across NNRTI mutations (resistance to RPV vs resistance to other NNRTIs) using Fisher's Exact Test (p-values were presented for the test within the CAB + RPV treatment group). The similar analysis was also performed for the proportion of subjects with HIV-1 RNA < 50 c/mL at Week 48. The proportion of subjects with HIV-1 RNA ≥ or <50 c/mL at Week 48 were also calculated by the presence or absence of individual mutations; no formal testing was done for individual mutations, except L74I.

Virologic outcomes are classified at Week 48 by the Snapshot algorithm. Subjects who are classified as "no virologic data" for Week 48 by Snapshot algorithm are excluded from the PRC population for the efficacy sensitivity analysis.

4.2.1.5.4. RESULTS

Prevalence of archived INSTI and NNRTI RAMs and HIV-1 subtype distribution at Baseline

Of the 616 Intent-to-Treat Exposed (ITT-e) subjects in ATLAS, genotypes from Baseline PBMCs were available for 530 subjects; 257/308 (83%) participants in the CAB + RPV group and 273/308 (89%) subjects in the CAR group, which constitutes the PR population for the efficacy analysis. In the PRC population, 241/257 (94%) (CAB LA+RPV LA) and 265/273 (97%) subjects (CAR) remained after excluding subjects who had no virologic data at Week 48 (i.e. discontinued study treatment prior to Week 48 while last on-treatment HIV-1 RNA was <50 c/mL (Source data: GSK Document Number 2019N420275_00 Table 2.11). This population is used for the efficacy sensitivity analysis.

The most common NNRTI and INSTI mutations observed and their prevalence at Baseline in the CAB +RPV group are shown in Table 31

At Baseline, in the CAB + RPV group (N=257), 164 (64%) of the subjects harbored virus with pre-specified INSTI mutations, with 5 (2%) having major INSTI RAMs T66T/I, G140G/R (n=3), and S147S/G. Other pre-specified INSTI mutations at Integrase positions L74, T124, V151, E157, or G193 were present in 2-35% of the PR population.

IAS-USA NNRTI RAMs were present in 67/257 (26%) subjects at Baseline with 11 (4%) presenting with RPV RAMs, K101K/E, E138A (n=2), E138E/A (n=4), E138E/K, E138K, Y181Y/C, and H221H/Y. Mutations at reverse transcriptase codons V90, K103, V106, E138, and V189 were the most common NNRTI RAMs observed (range 2-7%).

No subject presented with both pre-specified INSTI and IAS-USA NNRTI mutations at Baseline.

In the CAR arm, the prevalence of INSTI and NNRTI mutations at Baseline was very similar to those observed in CAB + RPV group, as shown in Table 31.

Table 31 Summary of NNRTI and INSTI-individual mutations in Baseline PBMCs (PR Population)

	CAB + RPV (n=257) n (%)	CAR (n=273) n (%)
Pre-specified INSTI	164 (64)	173 (63)
Major INSTI	5 (2)	8 (3)
Other pre-specified INSTI	159 (62)	165 (60)
Pre-specified INSTI (codons with prevalence ≥2%)		
L74I	42 (16)	57 (21)
L74L/I/M	4 (2)	0
T124A	89 (35)	80 (29)
T124T/A	6 (2)	12 (4)
V151V/I	4 (2)	7 (3)
E157Q	9 (4)	7 (3)
G193E	17 (7)	14 (7)
IAS-USA NNRTI	67 (26)	66 (24)
IAS-USA RPV	11 (4)	23 (8)
Other IAS-USA NNRTI	56 (22)	43 (16)
NNRTI (codons with prevalence ≥2%)		
V90I	19 (7)	4 (1)
K103N	4 (2)	6 (2)
K103K/N	7 (3)	3 (1)
V106I	4 (2)	5 (2)
E138A	2 (<1)	6 (2)
E138E/A	4 (2)	5 (2)
E138E/K	1 (<1)	1 (<1)
E138K	1 (<1)	0
E138E/A/K/T	0	1 (<1)
E138E/G	0	1 (<1)

	CAB + RPV (n=257) n (%)	CAR (n=273) n (%)
V189V/I	7 (3)	7 (3)

Mixtures and other mutations at these codons and for other RPV RAMs are available in Data Source: GSK Document Number 2019N420275_00 Table 1.1, Table 1.3.

Mixtures and single mutations found at codon 138 are listed individually (even though prevalence of some are <2%), since these are RPV RAMs. Source Data: GSK Document Number 2019N420275_00 Table 1.1, Table 1.3, Table 1.4

Subtype B was the most prevalent subtype observed in the study with 327/530 (62%) of the overall subjects presenting with this subtype and 162/257 (63%) in the CAB + RPV group. In Russia Federation, Subtypes A (23%) and A1 (35%) were the most prevalent while in subjects in South Africa, Subtype C (84%) was the most prevalent (Table 32).

A similar pattern/distribution by region was observed in the CAR group (as shown in Source Data GSK Document Number 2019N420275_00: Table 1.5).

Table 32 Prevalence of Subtype at Baseline by Geographic Region in CAB LA + RPV LA Group (PR Population)

Subtype	WCENA	Latin America	Russia Federation	East Asia	Oceania	Southern Africa	Total
n	155	16	40	10	11	25	257
A	1 (<1%)	_	9 (23%)	_	_	_	10 (4%)
A1	3 (2%)	_	14 (35%)	_	0	_	17 (7%)
AB	-	_	1 (3%)	_	_	_	1(<1%)
AE	5 (3%)	_	1 (3%)	_	1 (9%)	_	7 (3%)
AG	9 (6%)	_	1 (3%)	_	_	_	10 (4%)
B	128 (83%)	9 (56%)	5 (13%)	10 (100%)	10 (91%)	_	162 (63%)
BF	1 (<1%)	3 (19%)	_	_	_	_	4 (2%)
C	3 (2%)	_	_	_	_	21 (84%)	24 (9%)
COMPLEX	3 (2%)	4 (25%)	6 (15%)	_	_	4 (16%)	17 (7%)
F1	1 (<1%)	_	_	_	_	_	1(<1%)
G	1 (<1%)	_	3 (8%)	_	_	_	4 (2%)

Data Source: GSK Document Number 2019N420275_00 Table 1.5

In the CAB + RPV group, the prevalence of Baseline pre-specified INSTI mutations occurring at >5% by geographic regions is shown in Table 33. 70% (28/40) of the subjects from the Russian Federation had L74I. 76% (19/25) of subjects from South Africa had pre-specified INSTI mutations at the T124 position. There was no trend observed between the major INSTI, IAS-USA NNRTI, or RPV RAMs present and geographical region. (Source data: GSK Document Number 2019N420275_00 Table 1.61)

Similar findings exist for the CAR group. (Source data: GSK Document Number 2019N420275_00 Table 1.61)

Table 33 Prevalence of Pre-specified INSTI Individual Mutations at Baseline by Geographic Region (CAB LA + RPV LA group for PR population)

Mutations	Western & Central Europe & North America	Latin America	Russian Federation	East Asia	Oceania	Southern Africa	Total
n	155	16	40	10	11	25	257
L74I	12 (8%)	1 (6%)	28 (70%)			1 (4%)	42 (16%)
T124A	55 (35%)	4 (25%)	7 (18%)	1 (10%)	3 (27%)	19 (76%)	89 (35%)
G193E	10 (6%)	1 (6%)	1 (3%)	3 (30%)	2 (18%)		17 (7%)

Data Source: GSK Document Number 2019N420275_00 Table 1.61.

The pre-specified INSTI mutations present in ≥5% of subjects in the CAB + RPV group and their prevalence at Baseline by subtype were analyzed. L74I was the most common mutation found in Subtype A and A1 viruses compared to the other virus subtypes (Table 34).T124A was common in Subtype AE, AG, and C viruses. Mutations at position G193 were seen at <10% across all subtypes.

No data are presented for the IAS-USA NNRTI individual mutations present at Baseline since the number of mutations is low. There is no trend observed between the major INSTI, IAS-USA NNRTI, or RPV RAMs present and geographical regions (Source data GSK Document Number 2019N420275_00 Table 1.61)

Prevalence of pre-specified INSTI mutations and prevalence at Baseline by subtype in the CAR group is comparable to the CAB + RPV group (Source data: GSK Document Number 2019N420275_00 Table 1.68).

Table 34 Prevalence of Pre-specified INSTI Individual Mutations at Baseline by Subtype (CAB LA + RPV LA group)

Mutations	A	A1	AB	AE	AG	B	BF	C	CP	G	Total
n	10	17	1	7	10	162	4	24	17	4	257
L74I	9 (90%)	14 (82%)	1 (100%)	2 (29%)	-	8 (5%)	-	1 (4%)	7 (41%)	-	42 (16%)
T124A	-	3 (18%)	-	6 (86%)	8 (80%)	42 (26%)	2 (50%)	18 (75%)	6 (35%)	4 (100%)	89 (35%)
G193E	-	1 (6%)	-	-	-	15 (9%)	-	1(4%)	-	-	17 (7%)

Data Source: GSK Document Number 2019N420275_00 Table 1.68.

There was no association observed between the prevalence of Baseline INSTI or NNRTI mutations and Baseline characteristics (i.e. the duration of INSTIs or NNRTIs up to Baseline, the number of antiretrovirals (ART) taken prior to baseline, whether prior ART consisted of INSTIs or NNRTIs prior to Baseline regimen, or third agent class at Baseline). (Source data: GSK Document Number 2019N420275_00 Table 1.62, Table 1.63, Table 1.64, Table 1.65, Table 1.66, Table 1.67)

Baseline resistance in relation to virologic outcome at Week 48

In the PR population at Week 48, 236/257 (92%) of the subjects in the CAB + RPV group maintained virologic suppression (HIV-1 RNA <50 c/mL), 5/257 (2%) subjects had HIV-1 RNA >=50 c/mL and 16 had no virologic data.

For the INSTI class, 0/5 subjects with major INSTI RAMs, 5/159 (3%) with other (non-major) pre-specified INSTI RAMs and 0/93 without INSTI RAMs had HIV-1 RNA ≥50 c/mL at Week 48, respectively. The comparison across these three categories in relation to virologic outcome of 'HIV-1 RNA ≥50 c/mL' is not statistically significant (p=0.24). The proportions of subjects with HIV-1 RNA<50 c/mL were also compared across these 3 categories with no statistically significant differences observed (p=1.000) (Table 35).

For the NNRTI class, 2/11 (18%) subjects with RPV RAMs, 2/56 (4%) with other IAS-USA NNRTI RAMs and 1/190 (<1%) without IAS-USA NNRTI RAMs had HIV-1 RNA ≥50 c/mL at Week 48, respectively. The comparison across these three categories in relation to virologic outcome of 'HIV-1 RNA ≥50 c/mL' is statistically significant (p=0.003). The proportions of subjects with HIV-1 RNA<50 c/mL were also compared across these 3 categories with no statistically significant differences observed (p =0.118) (Table 35).

Outcomes were also tabulated for the subjects with either major baseline INSTI resistance or Baseline RPV resistance, which were observed in a total of 16 subjects. Among the 16 subjects with major Baseline INSTI or RPV RAMs (5/16 or 11/16 subjects, respectively), 2/16 participants (13%) had HIV-1 RNA ≥ 50 c/mL at Week 48 by the Snapshot algorithm. This is statistically significant (p=0.033) when compared to 3/241 subjects (1%) with no overall major resistance. Of the 16 subjects with major

Baseline INSTI or RPV resistance, 14 subjects (88%) maintained HIV-1 RNA <50 c/mL at Week 48, which compares similarly to 222/241 (92%) of subjects without major Baseline resistance (p-value= 0.628).

Similar findings were observed in PRC population (Source data: GSK Document Number 2019N420275_00 Table 2.11).

Table 35 Proportion of Virologic Outcome at Week 48 (Snapshot) by Resistance Class at Baseline (CAB LA + RPV LA group- PR population)

CAB LA + RPV LA **(N=257)**	**HIV-1 RNA ≥50 c/mL**	**HIV-1 RNA <50 c/mL**
Overall	5 /257 (2%)	236/257 (92%)
IAS-USA major mutations to INSTI	0/ 5	5/ 5(100%)
Other pre-specified INSTI	5/159 (3%)	146/159 (92%)
Other INSTI	0/ 93	85/ 93 (91%)
p-value	0.24	1.000
IAS-USA mutations to RPV	2/ 11 (18%)	9/ 11 (82%)
IAS-USA mutations to other NNRTI	2/ 56 (4%)	49/ 56 (88%)
Other NNRTI	1/190 (<1%)	178/190 (94%)
p-value	**0.003**	0.118
Overall Major Resistance[a]	2/ 16 (13%)	14/ 16 (88%)
No overall major resistance	3/241 (1%)	222/241 (92%)
p-value	**0.033**	0.628

Data Source: GSK Document Number 2019N420275_00 Table 2.9, Table 2.10.
Note: For each virologic endpoint (e.g. HIV-1 RNA ≥50), p values were derived by comparing across mutation subcategories using Fisher's Exact test.
a. At least one IAS-USA major mutation associated with resistance to RPV or to INSTI.

In the PR population, Baseline INSTI polymorphisms present among the 5 subjects with HIV-1 RNA ≥50 c/mL at Week 48 are shown in Table 36 and were observed at Integrase codons L74 and T124. Of the 42 subjects with L74I, 3/42 (7%) subjects had HIV-1 RNA ≥50 c/mL vs 2/206 (<1 %) with wild type (WT) + non-prespecified INSTI mutation. HIV-1 RNA <50 c/mL was observed for 37 (88%) subjects with mutations at position L74 vs 191/206 (93%) in those with that were WT at position L74. There were no subjects with major INSTI mutations at Baseline that had HIV-1 RNA ≥50 c/mL at Week 48.

Similar findings were observed in PRC population, with the proportion of subjects with HIV-1 RNA ≥50 c/mL being 2/193 (1%) in WT+ non pre-specified INSTI mutation vs 3/40 (8%) in L74I (Source data: GSK Document Number 2019N420275_00 Table 2.3).

Table 36 Proportion of Virologic Outcome at Week 48 by Baseline Pre-specified INSTI Mutations Present in Subjects with HIV-1 RNA ≥50 c/mL (CAB + RPV group – Snapshot analysis-PR population)

Mutation	≥50 c/mL	<50 c/mL
L74I	3/ 42 (7%)	37/ 42 (88%)
T124A	1/89 (1%)	84/89 (94%)

Note: Only displays codon at which at least one subject with mutations had HIV-1 VL ≥50 c/mL.
Data Source: GSK Document Number 2019N420275_00 Table 2.1.

Baseline IAS-USA NNRTI mutations observed in the 5 subjects with HIV-1 RNA ≥50 c/mL at Week 48 were present at RT codons, V90, V108, E138 and G190. The RPV RAMs seen in subjects with HIV-1 RNA ≥50 c/mL (Snapshot Week 48 analysis) were E138E/A and E138K. E138E/A was present in 4 subjects, 1 (25%) subject had HIV-1 RNA ≥50 c/mL and the other 3 (75%) subjects had HIV-1 RNA <50 c/mL at Week 48. Only 1 subject with E138K at Baseline had HIV-1 RNA ≥50 c/mL, while the other subject with E138K maintained viral suppression. There were 3 subjects that had either E138A (n=2) or E138E/K observed at Baseline and maintained viral suppression through Week 48 (Table 37).

Eleven RPV RAMs, K101K/E, E138A (n=2), E138E/A (n=4), E138E/K, E138K, Y181Y/C, and H221H/Y were present at Baseline with only mutations at position E138 being present in subjects with HIV-1 RNA ≥50 c/mL at Week 48. There were 10 subjects with either K103N or K103K/N at Baseline and all of these had HIV-1 RNA<50 c/mL at Week 48.

Similar findings were observed in the PRC population (Source data: GSK Document Number 2019N420275_00 Table 2.4).

Table 37 Proportion of Virologic Outcome at Week 48 by Baseline IAS-USA NNRTI Mutations Present in Subjects with HIV-1 RNA ≥50 c/mL (CAB + RPV Snapshot analysis PR population)

Mutation	≥50 c/mL	<50 c/mL
V90I	1/ 19 (5%)	17/19 (89%)
V108V/I	1/3 (33%)	2/3 (67%)
E138E/A	1/4 (25%)	3/4 (75%)
E138K	1/ 1 (100%)	0/1
G190G/E	1/2 (50%)	1/2 (50%)

Data Source; GSK Document Number 2019N420275 Table 2.2.
Note: Only displays codon at which at least one subject with mutations had HIV-1 RNA ≥50 c/mL. RPV RAMS are bolded.

Baseline PBMC sequencing data from the 5 subjects with HIV-1 RNA ≥50 c/mL showed INSTI and NNRTI mutations, L74I + V90I, L74I + E138E/A, L74I, T124T/A + G190G/E, and T124A + E138K + V108V/I. (Table 38). Of the NNRTI mutations, only E138E/A and E138K are RPV RAMs. None of the INSTI mutations are major INSTI RAMs. 3/5 subjects met CVF criteria, 3/5 subjects are from sites in the Russian Federation and 3/5 subjects carried Subtype A or A1.

Table 38 Pre-specified INSTI and IAS-USA NNRTI Baseline Substitutions for Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (CAB + RPV group - PR Population)

Subject	Pre-specified INSTI	IAS-USA NNRTI	Subtype	Geographical region
1	L74I	V90I	A	Russian Federation
2*	L74I	E138E/A	A1	Russian Federation
3*	L74I	-	A	Russian Federation
4	T124T/A	G190G/E	Complex	Southern Africa
5*	T124A	E138K, V108V/I	AG	WCENA

*Subjects met CVF criteria.
Data Source: GSK Document Number 2019N420275_00 Listing 1.

Pre-specified INSTI polymorphism, L74I, was present at Baseline in 16% of subjects from this study. Further characterization of the L74I polymorphism by geographical region vs virologic outcome to CAB + RPV (Table 39) showed 70% (28/40) of subjects from the Russian Federation that had HIV-1 RNA data at Week 48 harbored virus with L74I and 82% of these subjects had HIV-1 RNA < 50 c/mL.

Table 39 Proportion of Virologic Outcome at Week 48 by Baseline L74I Polymorphisms and Geographical Region (CAB LA + RPV group – Snapshot analysis- PR Population)

Region	**Russian Federation** (n=40)		**WCENA** (N=155)		**Latin America** (N=16)		**Southern Africa** (N=25)	
	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL
WT+ non pre-specified	0/ 10	8/ 10 (80%)	1/136 (<1%)	130/136 (96%)	0/ 15	14/ 15 (93%)	1/ 24 (4%)	23/ 24 (96%)

Region	**Russian Federation** (n=40)		**WCENA** (N=155)		**Latin America** (N=16)		**Southern Africa** (N=25)	
L74I	3/ 28 (11%)	23/28 (82%)	0/ 12	12/ 12 (100%)	0/ 1	1/ 1 (100%)	0/ 1	1/ 1 (100%)

Data Source: GSK Document Number 2019N420275_00 Table 2.5.

The prespecified INSTI polymorphism L74I was present in subjects with HIV-1 RNA >50 c/mL at Week 48 only in subjects that harbored Subtype A and A1 virus. The majority of the subjects having L74I and either Subtype A (67%) or Subtype A1 viruses (93%) at Baseline had HIV-1 RNA <50 c/mL at Week 48 (Table 40).

Table 40 Proportion of Virologic Outcome at Week 48 by Baseline L74I Polymorphisms and Virus Subtype (CAB LA + RPV group-Snapshot analysis- PR Population)

Subtype	**A (N=10))**		**A1 (N=17)**	
	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL
WT+ non pre-specified	0/ 0	0/ 0	0/ 1	1/ 1 (100%)
L74I	2/ 9 (22%)	6/ 9 (67%)	1/ 14 (7%)	13/14 (93%)

Data Source: GSK Document Number 2019N420275_00 Table 2.7.

Baseline PBMC sequencing showed INSTI polymorphism, L74I, present in 3/5 subjects with HIV-1 RNA ≥50 c/mL at Week 48 in this study. In another Phase III CAB +RPV study, FLAIR (201584), L74I was observed in 3/3 CVF subjects in Baseline plasma HIV-1 RNA. Comparison of outcome between subjects with Baseline L74I versus those without (ATLAS) was performed (Table 41). Of the 5 subjects with HIV-1 RNA ≥50 c/mL at Week 48, 3 presented with L74I and 2 did not. The association is significant (p=0.03) although the relevance is unclear.

Results were the same in PRC populations. (Source data: GSK Document Number 2019N420275_00 Table 2.3).

Table 41 Proportion of Virologic Outcome at Week 48 (Snapshot) in Subjects with L74I Polymorphism at Baseline (CAB LA + RPV group-Snapshot analysis - PR population)

		Week 48	
Codon	Subgroup	>=50 c/mL	<50 c/mL
L74	Wild type + non-prespecified INSTI mutation	2/206 (<1%)	191/206 (93%)

		Week 48	
Codon	Subgroup	>=50 c/mL	<50 c/mL
	L74I	3/ 42 (7%)	37/ 42 (88%)
	p-value	0.035	0.349

Note: For each virologic endpoint (e.g. HIV-1 RNA ≥50), p values were derived by comparing across mutation subcategories using Fisher's Exact test.
Data Source: GSK Document Number 2019N420275_00 Table 2.12.

4.2.1.5.5. Discussion

Within the ATLAS study, PBMC DNA sequencing data was generated retrospectively for exploratory analysis of potential associations between Baseline resistance and virologic outcome at Week 48. Proviral DNA information was not available and not used for the purpose of screening for study eligibility. Due to the investigational status of CAB and limited amount of resistance information available on the drug, the pre-specified INSTI mutations list was expanded and included a broad number of substitutions not usually implicated in INSTI resistance (i.e., polymorphisms L74I and T124A). At Baseline, 64% of subjects had at least one pre-specified INSTI substitution. IAS-USA NNRTI mutations (including RPV RAMs) were present in 25% of the subjects. Given the small number of subjects with HIV-1 RNA ≥ 50 c/mL at Week 48, a univariate analysis of Baseline mutations and Week 48 virologic outcome was performed. Additional analysis is planned with pooled data from all phase III CAB + RPV studies and will include other potential variables of interest.

The proportion of subjects with pre-existing major INSTI and RPV RAMs was low in the CAB + RPV group of the study, with 2% (5/257) and 4% (11/257) of the total, respectively. The low number of pre-existing major INSTI and RPV RAMs was expected since the subjects' historical genotype was reviewed during screening and subjects were excluded from the study if any known major INSTI or NNRTI RAMs, except for K103N, were present. No subjects with HIV-1 RNA ≥50 c/mL at Week 48 had the K103N RAM while 10 subjects had K103N or K103K/N at Baseline, as determined by PBMC DNA sequencing, and had a virologic outcome of <50 c/mL.

Baseline PBMC DNA sequencing showed only 5 major INSTI RAMs, T66T/I, G140G/R (n=3), and S147S/G; none of which were present in the 5 subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48. G140R, along with INSTI polymorphism L74I, was observed at virologic failure in 1 CVF subject in the FLAIR study (201584) and CAB susceptibility was reduced 6.7-fold [GSK Document Number 2017N345267_00]. L74I (n=3), T124T/A and T124A were present at Baseline in subjects with HIV-1 RNA>=50 c/mL. Mutations present at Integrase codons, L74, T124, V151, E157, and G193, that were observed at the highest prevalence at Baseline, are not associated with resistance to any of the INSTIs including cabotegravir.

Eleven RPV RAMs, K101K/E, E138A (n=2), E138E/A (n=4), E138E/K, E138K, Y181Y/C, and H221H/Y were present at Baseline. The only 2 RPV mutations present at Baseline in subjects with HIV-1 RNA ≥50 c/mL were E138E/A and E138K. The

remaining RPV RAMs at Baseline were reported in subjects with HIV-1 RNA <50 c/mL at Week 48. 3/8 subjects with E138 mutations also had additional IAS-USA NNRTI mutations at Baseline, V90I (n=2) and V108V/I. 1 of these 3 subjects had HIV-1 RNA ≥50 c/mL at Week 48. Of the reverse transcriptase codons, V90, K103, V106, E138, and V189, that were observed with the highest prevalence at Baseline, only the E138 codon has mutations associated with RPV resistance while the remailing codons are not implicated in resistance to RPV.

The statistically significant difference (p-value of 0.003) in Snapshot outcome (HIV-1 RNA ≥50 c/mL) observed in patients with RPV RAMs suggests that RPV mutations, namely at position E138, are potentially associated with non-response to CAB + RPV. However, with the small numbers of subjects harboring virus with E138A or E138K mutations or their mixtures and the univariate analysis of this study, it is difficult to assign a direct correlation of E138A with such a clinical outcome. ISA-USA mutations to other NNRTIs were present in 2/56 (4%) subjecs that had HIV-1 RNA ≥50 c/mL at Week 48.

The pre-specified INSTI substitution, L74I, is a common polymorphism seen particularly in participants with Subtype A virus. L74I was observed at Baseline in PBMCs from 2 (66%) ATLAS CVF subjects (GSK Document Number 2018N370336_00) and in plasma from 3 (75%) FLAIR (201584) CVF subjects [GSK Document Number 2017N345267_00] in the CAB LA + RPV LA group. In the FLAIR study, analysis of Baseline sequence indicated a high rate of success in subjects with pre-existing L741, and while a small number of CVFs also contained L74I, the totality of evidence did not suggest an association between the presence of L74I and treatment difference of CAB + RPV versus control arm [GSK Document Number 2019N407481_00]. The ATLAS study also has a high success rate (88%) in subjects with INSTI polymorphism L74I. A statistically significance difference (p-value of 0.035) does exist between subjects having HIV-1 RNA ≥ 50 c/mL at Week 48 in those containing L74I and those that do not. However, due to the univariate analysis of this study, it is difficult to conclude that there is a direct correlation between the presence of L74I and virologic outcome of HIV-1 RNA ≥ 50 c/mL at Week 48.

The impact of mutations at RT codon E138 and of the IN L74I polymorphism on virologic outcome will be further explored with pooled data from all Phase III CAB + RPV LA studies by including other factors (e.g. PK, L74I presence at Baseline, sex at birth, regimen, BMI) in the analysis model.

4.2.1.5.6. CONCLUSIONS

- Overall, the prevalence of pre-existing major INSTI and RPV RAMs was infrequent in the CAB + RPV group, comprising 6% of total mutations (2% major INSTI and 4% RPV RAMs). No major INSTI RAMs were present at Baseline in subjects with HIV-1 RNA ≥50 c/mL at Week 48. RPV RAMs were present at Baseline in 2/5 subjects with HIV-1 RNA ≥50 c/mL at Week 48.
- L74I was the most common INSTI mutation seen at Baseline in the Russian Federation (70% of subjects in the CAB + RPV group) and was the most

prevalent INSTI mutation at Baseline in Subtype A, A1, and AG (90%, 82%, 100% respectively).

- Subjects with the L74I polymorphism had a higher proportion with Snapshot HIV-1 RNA≥ 50 c/mL (3/42, 7%) at Week 48 than did subjects without L74I 2/206, <1%).
- The presence of E138 mutations in RT may potentially be associated with non-response to CAB + RPV. Of the most prevalent NNRTI mutations in the CAB + RPV group, only E138 mutations are associated with reduced RPV susceptibility. Mutations at RT position 138 were present in 2 (25%) subjects with HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot Analysis) and in 6 (75%) subjects with HIV-1 RNA <50 c/mL at Week 48.
- The results presented in this report are based on data using univariate analysis. The impact of mutations at codon E138 and of the L74I polymorphism on virologic outcome will be further explored with pooled data from all Phase III CAB + RPV studies by including other factors (e.g. PK, L74I presence at baseline, gender, regimen, BMI) in the analysis model.

4.2.1.6. Baseline PBMC HIV-1 DNA Analysis 207966 (ATLAS-2M)

Protocol Number and Title: 207966: A Phase IIIb, Randomized, Multicenter, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every 8 Weeks or Every 4 Weeks in HIV-1-infected Adults who are Virologically Suppressed – Study 207966 (ATLAS-2M) Week 48 CSR

Study Design: Study 207966 (ATLAS-2M) is an ongoing Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of Long-Acting (LA) CAB + RPV Q8W compared to CAB + RPV Q4W in HIV-1 infected adult subjects. A total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W-524 subjects; Q4W-525 subjects). This study recruited HIV-1 infected virologically suppressed (HIV-1 RNA <50 c/mL) subjects on stable ART including subjects who had completed, at minimum, Week 52 of Study 201585. The Week 48 endpoint is the primary analysis. The study continues with an Extension Phase up to at least 96 weeks. Subjects who discontinued current ART began oral therapy with CAB 30 mg + RPV 25 mg once daily for 4 weeks prior to administration of CAB + RPV every 4 or 8 weeks. Subjects entering Study 207966 from Study 201585 and currently receiving IM CAB + RPV Q4W (including both those who were originally randomized to Q4W in the Maintenance Phase of Study 201585 and those who transitioned from SOC to the Q4W regimen within the Extension Phase of Study 201585) were randomized 1:1 to either continue CAB + RPV Q4W or transition to CAB + RPV Q8W. Primary endpoint was Week 48 and secondary endpoint was Week 96. Any subject who received at least a single dose of CAB + RPV and discontinued the regimen for any reason entered a 52-week LTFU Phase. Subjects were to remain on suppressive HAART for at least 52 weeks after the last dose of CAB LA + RPV LA.

Subjects were excluded from ATLAS-2M if they had any evidence of primary resistance based on the presence of any major known INSTI or NNRTI resistance-associated mutation (RAM), except for K103N, International AIDS Society (IAS-USA), [IAS-USA, 2019] by any historical resistance test result. Prior genotypic resistance testing was not

required, but if available, had to be provided to GSK after screening and before randomization according to guidance in the SPM to provide direct evidence of no pre-existing exclusionary resistance mutations.

Peripheral blood mononuclear cell (PBMC) samples were collected at Day 1, Week 96, and Withdrawal, if applicable, for retrospective virologic analyses. PBMC DNA sequencing data was not available and not used for the purpose of screening individuals for study eligibility. These data were generated retrospectively for exploring the potential association between Baseline resistance and virologic outcome at Week 48. PBMC sequencing data must be interpreted with caution as detection of resistance mutations in PBMC DNA does not always correlate with clinically-observed drug resistance. Further, mutations that may be present in plasma HIV RNA may not always be observed, or may be observed at later time points, in PBMC DNA.

Confirmed Virologic Failure (CVF) (2 consecutive plasma HIV-1 RNA ≥200 c/mL) occurred in 10 subjects, 8 in the Q8W arm and 2 in the Q4W arm. Baseline PBMC HIV-1 proviral DNA sequencing showed that 5/10 subjects had pre-existing RPV RAMs (E138A, E138E/A, Y181C, Y188Y/F/H/L, Y188L, or H221H/Y) and 1/10 had a major pre-existing INSTI RAM (G140G/R). The INSTI polymorphism L74I was present in 5/10 subjects at Baseline. Subjects with CVF carried either HIV-1 Subtype A, A1, B, or C in this study. To understand the consequence of pre-existing NNRTI, RPV and/or INSTI RAMs, the presence of the L74I polymorphism, and subtype on CAB + RPV efficacy, HIV-1 proviral DNA from Baseline PBMCs was sequenced for all subjects with Baseline samples. In addition, the prevalence of NNRTI and INSTI RAMs and treatment outcomes were assessed by region. 427 subjects that transitioned from ATLAS had their ATLAS Baseline PBMC DNA sequenced and not their ATLAS-2M PBMC DNA. Four subjects (met CVF criteria) that transitioned from ATLAS had both ATLAS and ATLAS-2M Baseline PBMC DNA sequenced and their ATLAS Baseline PBMC data were used for analysis. This report is a summary of those genotypes and associated treatment outcomes.

The objectives of this exploratory analysis are to:

- determine the prevalence of Baseline archived resistance mutations
- investigate the relationship between Baseline archived resistance and virologic outcome through Week 48

4.2.1.6.1. Methods

Source of Data

The Monogram Biosciences GenoSure Archive assay, a proviral DNA genotypic assay, was used to evaluate the presence of archived mutations in Baseline PBMCs. The assay provides HIV-1 PRO, RT, and IN genotype data from integrated HIV-1 proviral DNA but does not generate phenotypic data. Of note, resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing [Lee, 2012]; as such HIV-1 DNA resistance testing is exploratory. The assay's primary value is in showing the presence of archived resistance; thus, a HIV-1 mutation not detected in proviral DNA may still be present in plasma RNA.

Four subgroups of NNRTI and INSTI RAMs were pre-identified and are listed in Table 42. Protease genotype data are out of scope from this analysis.

Table 42 Mutations potentially associated with Resistance to INSTI or NNRTI

Class	Mutations
INSTI	Pre-specified INSTI mutations [1]: H51Y, T66A/I/K, L68V/I, L74I/M, E92Q/V/G, Q95K, T97A, G118R, F121Y, T124A, E138A/K/D/T, G140A/C/R/S, Y143C/H/R/K/S/G/A, P145S, Q146L/P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, G193E, S230R, R263K,
	IAS-USA major mutations associated with resistance to INSTI [2]: T66I, E92Q, G118R, F121Y, G140R, S147G, Q148H/K/R, Y143R/H/C, N155H, R263K
NNRTI	IAS-USA mutations associated with resistance to NNRTI [3]: V90I, A98G, L100I, K101E/H/P, K103N/S, V106A/I/M/T, V108I, E138A/G/K/Q/R, V179D/F/L/T, Y181C/I/V, Y188C/H/L, G190A/E/S, H221Y, P225H, F227C/L/R, M230I/L, L234I
	IAS-USA major mutations associated with resistance to RPV [4]: *L100I, K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L*

[1] Mutations (T124A, Q146L) were added per FDA request for study 201584; mutations (H51Y, L74I, L68V/I, E92V, Q95K, E138D, Y143K/S/G/A, P145S, Q146P, V151I/L/A, N155S/T, E157Q, G163R/K, G193E, S230R) were identified during in vitro passage of DTG or seen in a previous DTG study in INSTI-experienced subjects (ING112574); all other mutations in this pre-specified list were identified per the IAS-USA mutations associated with resistance to Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir or Raltegravir [IAS–USA, 2019].

[2] IAS-USA major mutations associated with resistance to Bictegravir, Cabotegravir, Dolutegravir, Elvitegravir or Raltegravir [IAS–USA, 2019].

[3]: IAS-USA mutations associated with resistance to Doravirine, Efavirenz, Etravirine, Nevirapine or Rilpivirine [IAS–USA, 2019].

[4] IAS-USA major mutations associated with resistance to RPV [IAS–USA, 2019].

To investigate Baseline archived resistance in relation to virologic outcome, the efficacy endpoints at Week 48 (per the Snapshot algorithm) are:

- The proportion of subjects with HIV-1-RNA ≥50 c/mL and
- The proportion of subjects with HIV-1-RNA <50 c/mL

The two endpoints were analyzed separately.

4.2.1.6.2. Study Population:

Two analysis populations are defined as follows:

- Proviral DNA Resistance Population (PR):

  This population is based on the Intention-to-Treat Exposed (ITT-E) population for whom Baseline proviral DNA genotypic data are available. This population was the primary population for the analyses described in this document.

- Proviral DNA Resistance Censored Population (PRC):

  This population was defined to assess the effect of Baseline resistance on outcome without confounding factors (e.g. early discontinuation because of adverse events). Therefore, subjects who discontinued study treatment prior to Week 48 while last on-treatment HIV-1 RNA was <50 c/mL were excluded from this PRC. The rule for exclusion subjects is in line with FDA's guidance document for clinical resistance analysis (i.e. Guidance for Human Immunodeficiency Virus-1 Infection: Developing Antiretroviral Drugs for Treatment Guidance for Industry, 2015). The PRC population was used for the efficacy sensitivity analysis.

4.2.1.6.3. Method of analysis

The prevalence of archived mutations at Baseline were summarized by drug class or drug (RPV) and treatment group. Within each group, similar summaries were created by Baseline subgroups (geographic region, duration of prior INSTI /NNRTI use, prior INSTI/NNRTI treatment, Baseline third agent class).

The proportion of subjects with HIV-1 RNA ≥ 50 c/mL at Week 48 (Snapshot algorithm) was compared across the pre-specified INSTI mutations (major mutations vs non-major prespecified vs other) as well as across NNRTI mutations (resistance to RPV vs resistance to other NNRTIs) using Fisher's Exact Test (p-values were presented for the test within treatment groups). The similar analysis was also performed for the proportion of subjects with HIV-1 RNA < 50 c/mL at Week 48. The proportion of subjects with HIV-1 RNA ≥ or <50 c/mL at Week 48 were also calculated by the presence or absence of individual mutations. No formal testing was done for individual mutations, except L74I.

Virologic outcomes are classified at Week 48 by the Snapshot algorithm. Subjects who are classified as "no virologic data" for Week 48 per Snapshot algorithm are excluded from the PRC population for the efficacy sensitivity analysis.

4.2.1.6.4. RESULTS

Prevalence of archived INSTI and NNRTI RAMs at Baseline

Of the 1045 Intent-to-Treat Exposed (ITT-e) subjects in ATLAS-2M, genotypes from Baseline PBMCs were available for 882 subjects, 444/522 (85%) subjects in the Q8W group and 438/523 (84%) subjects in the Q4W group, which constitutes the PR population for the primary analysis.

Of the 882 subjects in the PR population, 427 (Q8W) and 417 subjects (Q4W) remained after excluding subjects who had no virologic data at Week 48 (i.e. discontinued study treatment prior to Week 48 while last on-treatment HIV-1 RNA was <50 c/mL), which constitutes the PRC population for the efficacy sensitivity analysis.

In the Q8W group (N=444) at Baseline, 265 (60%) subjects with pre-specified INSTI mutations were identified, with 10 (2%) subjects having major INSTI RAMs (Table 43). IAS-USA NNRTI RAMs were present in 85 (19%) subjects with 26 (6%) of these being RPV RAMs.

In the Q4W group (N=438), 270 (62%) subjects had pre-specified INSTI mutations that were observed at Baseline (Table 43) 14 (3%) of these subjects had major INSTI RAMs. 86 (20%) subjects were observed with IAS-USA NNRTI RAMs, of which 22 (5%) were RPV RAMs.

The prevalence of INSTI and NNRTI RAMs was well-balanced between the Q8W and Q4W groups.

Table 43 Prevalence of Resistance Classes at Baseline (PR Population)

	Q8W (N=444)	Q4W (N=438)	Total (N=882)
IAS USA Major INSTI	10 (2%)	14 (3%)	24 (3%)
Other pre-specified INSTI	255 (57%)	256 (58%)	511 (58%)
IAS USA RPV	26 (6%)	22 (5%)	48 (5%)
Other IAS USA NNRTI	59 (13%)	64 (15%)	123 (14%)
Overall Major Resistance (i.e. Major INSTI or IAS RPV)	34 (8%)	36 (8%)	70 (8%)
No Overall Major Class Resistance[a]	410 (92%)	402 (92%)	812 (92%)

a. At least one IAS-USA major mutation associated with resistance to either RPV or INSTI
Data Source: GSK Document Number 2019N420276_00 Table 1.4

The major INSTI RAMs present at Baseline in the Q8W and Q4W groups and their prevalence are shown in Table 44. The most common major INSTI RAM seen at

Baseline is G140G/R with 5 reported in the Q8W group and 6 in the Q4W group. No major INSTI RAM was present in >1% of the subjects.

Table 44 Major INSTI mutations Present at Baseline (PR Population)

	Q8W (N=444)	Q4W (N=438)	Total (N=882)
Major INSTI	n (%)	n (%)	n (%)
T66T/I	0	2 (<1)	2 (<1)
F121F/Y	0	1 (<1)	1 (<1)
G140G/E/K/R	0	1 (<1)	1 (<1)
G140G/R	5 (1)	6 (1)	11 (1)
S147S/G	1 (<1)	2 (<1)	3 (<1)
Q148Q/H	1 (<1)	0	1 (<1)
Q148Q/R	1 (<1)	1(<1)	2 (<1)
R263R/K	2 (<1)	1 (<1)	3 (<1)
Total	10 (2)	14 (3)	24 (3)

Data Source: GSK Document Number 2019N420276_00 Table 1.3

RPV RAMs observed at Baseline in both study groups are shown in Table 45. Mutations present at the E138 codon are the most prevalent mutations in both the Q8W and Q4W groups. This table represents the actual number of mutations present at Baseline. Four subjects have 2 mutations at Baseline as evidenced by the higher totals seen here than in Table 43, which measured the number of subjects with mutations not the individual mutations.

Table 45 Prevalence of Major NNRTI mutations at Baseline (PR Population)

	Q8W (N=444)	Q4W (N=438)	Total (N=882)
IAS-USA RPV	n (%)	n (%)	n (%)
K101K/E	1 (<1)	5 (1)	6 (<1)
E138A	6 (1)	7 (2)	13 (1)
E138E/A	5 (1)	4 (<1)	9 (1)
E138E/A/K/T	0	1 (<1)	1 (<1)
E138E/G	1 (<1)	1 (<1)	2 (<1)
E138E/K	2 (<1)	0	2 (<1)

	Q8W (N=444)	Q4W (N=438)	Total (N=882)
Y181C	2 (<1)	0	2 (<1)
Y181Y/C	0	2 (<1)	2 (<1)
Y188L	2 (<1)	0	2 (<1)
Y188Y/F/H/L	1 (<1)	0	1 (<1)
H221H/Y	4 (<1)	2 (<1)	6 (<1)
H221Y	1 (<1)	0	1 (<1)
M230M/I	0	2 (<1)	2 (<1)
M230M/L	2 (<1)	1 (<1)	3 (<1)
Total	27	25	52

Data Source: GSK Document Number 2019N420276_00 Table 1.3.

The pre-specified INSTI and IAS-USA NNRTI mutations at Baseline that were present at a prevalence ≥2% of the PR population are shown in Table 46 In both the Q8W and Q4W groups, mutations at Integrase positions L74, T124, V151, E157, and G193 were present in <1 to 30% of the PR population at Baseline (Table 46). These Integrase codons are not associated with resistance to any of the INSTIs, including cabotegravir.

Mutations at position V90 and K103 in the Reverse Transcriptase were present in ≥2% of the PR population in the Q8W group and mutations at positions, V90, K103, V106, E138 and V179 were observed in <1 to 3% of the PR population in the Q4W group. Of these, only the mutations at codon E138 are RPV RAMs.

Table 46 Prevalence of pre-specified INSTI and IAS NNRTI at Baseline (PR population)

	Q8W (N=444) n (%)	Q4W (N=438) n (%)	Overall n (%)
Pre-specified INSTI (codons with prevalence ≥2%)			
L74I	67 (15)	67 (15)	134 (15)
T124A	133 (30)	130 (30)	263 (30)
T124T/A	7 (2)	22 (5)	29 (3)
V151I	9 (2)	5 (1)	14 (2)
V151V/I	12 (3)	8 (2)	20 (2)
E157Q	11 (2)	11 (3)	22 (2)
G193E	24 (5)	33 (8)	57 (6)
G193G/E	3 (<1)	7 (2)	10 (1)
IAS-USA NNRTI (codons			

	Q8W (N=444) n (%)	Q4W (N=438) n (%)	Overall n (%)
with prevalence ≥2%)			
V90I	18 (4)	11 (3)	29 (3)
V90V/I	8 (2)	4 (<1)	12 (1)
K103N	10 (2)	7 (2)	17 (2)
K103K/N	3 (<1)	10 (2)	13 (1)
V106I	6 (1)	9 (2)	15 (2)
E138A	6 (1)	7 (2)	13 (1)
E138E/A	5 (1)	4 (<1)	9 (1)
E138E/A/K/T	0	1 (<1)	1 (<1)
E138E/G	1 (<1)	1 (<1)	2 (<1)
E138E/K	2 (<1)	0	2 (<1)
V179V/D	4 (<1)	7 (2)	11 (1)

Mixtures and other mutations at these codons are available in Source data: GSK Document Number 2019N420276_00 Table 1.1, Table 1.3. Mixtures and single mutations found at codon 138 are listed individually (even if prevalence is <2%), since these are RPV RAMs (Source Data: GSK Document Number 2019N420276_00 Table 1.3).

Subtype B was the most prevalent viral subtype observed in the study with 611/882 (69%) of the overall subjects presenting with this subtype and 309/444 (70%) and 302/438 (69%) in the Q8W and Q4W groups, respectively. Subtype B was the most common subtype observed in Western and Central Europe and North America, Latin America, East Asia and Oceania regions. In the Russian Federation, Subtype A1 (34 and 43%) was the most prevalent and in subjects in South Africa, Subtype C (97 and 88 %) was the most prevalent in Q8W and Q4W groups, respectively (Table 47).

Table 47 Prevalence of Subtype at Baseline by Geographic Region in CAB LA + RPV LA Group (PR Population)

Subtype	WCENA		Latin America		Russian Federation		East Asia		Oceania		South Africa		Total	
	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W
n	307	308	18	16	65	61	16	9	6	11	32	33	444	438
A	1 (<1%)	1 (<1%)	-	-	13 (20%)	8 (13%)	-	-	-	-	-	-	14 (3%)	9 (2%)
A1	7 (2%)	3 (<1%)	-	-	22 (34%)	26 (43%)	-	-	1 (17%)	1 (9%)	-	-	30 (7%)	30 (7%)
A2	1 (<1%)	-	-	-	-	-	-	-	-	-	-	-	1 (<1%)	0
AB	-	-	-	-	1 (2%)	2 (3%)	-	-	-	-	-	-	1 (<1%)	2(<1%)
AE	5 (2%)	5 (2%)	-	-	1 (2%)	1 (2%)	1 (6%)	-	-	-	-	-	7 (2%)	6 (1%)
AG	13 (4%)	8 (3%)	-	-	1 (2%)	-	-	-	-	-	-	-	14 (3%)	8 (2%)
B	262 (85%)	265 (86%)	13 (72%)	11 (69%)	14 (22%)	8 (13%)	15 (94%)	9 (100%)	5 (83%)	9 (82%)	-	-	309 (70%)	302 (69%)
BF	1 (<1%)	2 (<1%)	3 (17%)	3 (19%)	-	-	-	-	-	-	-	-	4 (1%)	5 (1%)
C	2 (<1%	7 (2%)	-	-	-	-	-	-	-	1 (9%)	31 (97%)	29 (88%)	33 (7%)	37 (8%)
CD	1 (<1%)	-	-	-	-	-	-	-	-	-	-	-	1 (<1%)	0
COMPLEX	5 (2%)	10 (3%)	2 (11%)	2 (13%)	12 (18%)	12 (20%)	-	-	-	-	1 (3%)	4 (12%)	20 (5%)	28 (6%)
D	3 (<1%)	3 (<1%)	-	-	-	-	-	-	-	-	-	-	3 (1%)	3 (1%)
F1	3 (<1%)	3 (<1%)	-	-	-	-	-	-	-	-	-	-	3 (1%)	3 (1%)
G	3 (<1%)	1 (<1%)	-	-	1 (2%)	4 (7%)	-	-	-	-	-	-	4(1%)	5 (1%)

Data Source: GSK Document Number 2019N420276_00 Table 1.5, Table 1.6, Table 1.13.

The prevalence by geographic regions of Baseline mutations occurring at >5% in the study population is shown in Table 48. INSTI polymorphism, L74I, was present most commonly in Russian Federation subjects with 69% of the subjects in the Q8W group and 79% in the Q4W group having L74I at Baseline. 78% and 61% of subjects from South Africa had INSTI mutations at the polymorphism, T124A position in the Q8W and Q4W groups, respectively.

No data are presented for IAS-USA NNRTI individual mutations present at Baseline since the number of mutations is low. There was no trend observed between the major INSTI, IAS-USA NNRTI, or RPV RAMs present and geographical region. (Source data: GSK Document Number 2019N420276_00 Table 1.6)

Table 48 Prevalence of Pre-specified INSTI Individual Mutations at Baseline by Geographic Region (CAB LA + RPV LA group for PR population)

Mutations	WCENA		Latin America		Russian Federation		East Asia		Oceania		Southern Africa		Total
	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W	
n	307	308	18	16	65	61	16	9	6	11	32	33	882
L74I	20 (7%)	13 (4%)	1 (6%)	1 (6%)	45 (69%)	48 (79%)	-	-	-	1 (9%)	1 (3%)	4 (12%)	134 (15%)
T124A	99 (32%)	91 (30%)	1 (6%)	9 (56%)	5 (8%)	6 (10%)	2 (13%)	-	1 (17%)	4 (36%)	25 (78%)	20 (61%)	263 (30%)
G193E	17 (6%)	24 (8%)	-	1 (6%)	3 (5%)	5 (8%)	1 (6%)	2 (22%)	3 (50%)	1 (9%)	-	-	58 (7%)

Data Source: GSK Document Number 2019N420276_00 Table 1.6.

Baseline pre-specified INSTI mutations or polymorphisms present in ≥5% of subjects and their prevalence by viral subtype were analyzed (Table 49). L74I was the most common polymorphism found in Subtype A and A1 viruses compared to the other virus subtypes. T124A was common in Subtype AE, AG, B, and C viruses. G193E was mainly seen in Subtype B.

No data are presented for IAS-USA NNRTI individual mutations present at Baseline, since the number of mutations is low. No trend was observed between IAS-USA NNRTI or RPV RAMs present and virus subtype. (Data Source: GSK Document Number 2019N420276_00 Table 1.13)

Table 49 Prevalence of Pre-specified INSTI Individual Mutations at Baseline by Subtype (PR Population)

	Pre-specified INSTI mutations					
Subtype	L74I		T124A		G193E	
	Q8W	Q4W	Q8W	Q4W	Q8W	Q4W
A	13 (93%)	7 (78%)	1 (7%)	1 (11%)	1 (7%)	2 (22%)
A1	24 (80%)	28 (93%)	7 (23%)	1 (3%)	1 (3%)	-
A2	-	-	1 (100%)	-	-	-
AB	1 (100%)	2 (100%)	-	-	-	-
AE	2 (29%)	-	5 (71%)	5 (83%)	-	-
AG	-	-	12 (86%)	7 (88%)	2 (14%)	-
B	13 (4%)	12 (4%)	71 (23%)	73 (24%)	20 (6%)	30 (10%)
BF	-	-	2 (50%)	4 (80%)	-	-
C	1 (3%)	4 (11%)	25 (76%)	21 (57%)	-	-
COMPLEX	12 (60%)	13 (46%)	3 (15%)	11 (39%)	-	1 (4%)
D	1 (33%)	1 (33%)	1 (33%)	1 (33%)	-	-
F1	-	-	2 (67%)	1 (33%)	-	-
G	-	-	3 (75%)	5 (100%)	-	-

Data Source: GSK Document Number 2019N420276_00 Table 1.13.

There was no association observed between the prevalence of Baseline INSTI or NNRTI mutations and other Baseline characteristics (i.e. the duration of INSTIs or NNRTIs up to Baseline, the number of antiretrovirals (ART) taken prior to Baseline, whether prior ART consisted of INSTIs or NNRTIs prior to Baseline regimen, or third agent class at Baseline). (Source data: GSK Document Number 2019N420276_00 Table 1.7, Table 1.8, Table 1.9, Table 1.10, Table 1.11, Table 1.12)

Baseline resistance in relation to virologic outcome at Week 48

In the Q8W group at Week 48, 418/444 (94%) of the subjects had HIV-1 RNA <50 c/mL, 9/444 (2%) subjects had HIV-1 RNA ≥50 c/mL and 17 had no virologic data.

In the Q4W group at Week 48, 412/438 (94%) of the subjects had HIV-1 RNA <50 c/mL, 5/438 (1%) subjects had HIV-1 RNA ≥50 c/mL and 21 had no virologic data.

For the INSTI resistance class, in both the Q8W and the Q4W groups, the proportion of subjects with major INSTI RAMs, with other pre-specified INSTI RAMs and without INSTI RAMs that had HIV-1 RNA ≥50 c/mL at Week 48 was determined (Table 50). The comparison across these three categories in relation to virologic outcome of HIV-1 RNA ≥50 c/mL is not statistically significant for either Q8W or Q4W groups (p=0.128 and p=0.159), respectively. The proportions of subjects with HIV-1 RNA<50 c/mL were similarly high across these three categories in both Q8W or Q4W groups (p=0.681 and p=0.743, respectively).

For the NNRTI class in the Q8W group, the comparison across the three categories, subjects with RPV RAMs, with other IAS-USA NNRTI RAMs and without IAS-USA NNRTI RAMs in relation to virologic outcome of 'HIV-1 RNA ≥50 c/mL' at Week 48 is statistically significant (p=<0.001). The subjects with RPV RAMs have a higher observed proportion of virologic outcome of 'HIV-1 RNA ≥50 c/mL' at Week 48. The proportion of subjects with HIV-1 RNA<50 c/mL were also compared across these 3 categories with statistically significant differences observed (p =0.013). The subjects with RPV RAMs have a lower observed proportion of virologic outcome of 'HIV-1 RNA <50 c/mL' at Week 48. For the Q4W group, comparison across the three categories in relation to virologic outcome of HIV-1 RNA ≥50 c/mL and HIV-1 RNA <50 c/mL were similar across these three categories (p=>0.999 and p=0.560), respectively.

Outcomes were also tabulated for the combination of Baseline major INSTI RAMs and/or Baseline RPV RAMs, which were observed in a total of 34 subjects (2/34 subjects had both major INSTI and RPV RAMs) in Q8W and 36 subjects (no subjects had both major INSTI and RPV RAMs) in Q4W. For the Q8W group, 5 subjects (13%) had HIV-1 RNA ≥ 50 c/mL at Week 48 compared to 4 /410 subjects (<1%) with no overall Baseline major resistance mutations (p<0.001). Of the 34 subjects with major Baseline INSTI and/or RPV RAMs, 29 subjects (85%) maintained HIV-1 RNA <50 c/mL at Week 48 compared to 389/410 (95%) of subjects without Baseline major resistance mutations (p=0.040).

For the Q4W group, 1/36 subjects (3%) with major Baseline INSTI and/or RPV RAMs had HIV-1 RNA ≥ 50 c/mL at Week 48 compared to 4/402 subjects (<1%) with no overall Baseline major resistance mutations (p=0.351). Of the 36 subjects with major Baseline INSTI and/or RPV RAMs, 35 subjects (97%) maintained HIV-1 RNA <50 c/mL at Week 48 compared to 377/402 (94%) of subjects without Baseline major resistance mutations (p=0.712).

Similar findings were observed in PRC population (Source data: GSK Document Number 2019N420276_00 Table 2.11).

Table 50 Proportion of Virologic Response at Week 48 by Resistance Class at Baseline (Snapshot analysis - PR population)

	Q8W		Q4W	
	HIV-1 RNA ≥50 c/mL	HIV-1 RNA <50 c/mL	HIV-1 RNA ≥50 c/mL	HIV-1 RNA <50 c/mL
Overall	9/444 (2%)	418/444 (94%)	5/438 (1%)	412/438 (94%)
IAS-USA major mutations to INSTI	1/10 (10%)	9/10 (90%)	1/14 (7%)	13/14 (93%)
Other pre-specified INSTI [2]	6/255 (2%)	240/255 (94%)	3/256 (1%)	240/256 (94%)
No pre-specified INSTI [3]	2/179 (1%)	169/179 (94%)	1/168 (<1%)	159/168 (95%)
p-value	0.128	0.681	0.159	0.743
IAS mutations to RPV	5/26 (19%)	21/26 (81%)	0/22	22/22 (100%)
IAS mutations to other NNRTI [4]	1/59 (2%)	58/59 (98%)	0/64	61/64 (95%)
No IAS mutations to NNRTI [5]	3/359 (<1%)	339/359 (94%)	5/352 (1%)	329/416 (93%)
p-value	**<0.001**	**0.013**	>0.999	0.560
Overall Major Resistance [1]	5/34 (15%)	29/34 (85%)	1/36 (3%)	35/36 (97%)
No overall major resistance	4/410 (<1%)	389/410 (95%)	4/402 (<1%)	377/402 (94%)
p-value	**<0.001**	**0.040**	0.351	0.712

Note: P-value based on Fisher's Exact test for the comparison of the percentages at Week 48 across subgroups (within treatment comparison). Statistically significant p-values are bolded.
[1] At least one IAS-USA major mutation associated with resistance to either RPV or to INSTI.
[2] Pre-specified INSTI mutations excluding IAS-USA major INSTI mutations.
[3] Any INSTI excluding pre-specified INSTI mutations.
[4] IAS-USA NNRTI mutations excluding IAS-USA major RPV mutations.
[5] Any NNRTI excluding IAS-USA NNRTI mutations.
Data Source: GSK Document Number 2019N420276_00 Table 2.9, Table 2.10.

In the PR population, Baseline PBMC sequencing data from the 14 subjects (9 from Q8W and 5 from Q4W) with HIV-1 RNA ≥50 c/mL are shown in Table 51. ATLAS Baseline PBMC vDNA sequence data from subjects that transitioned from ATLAS are also shown but are not included in the scope of this study. Of the INSTI mutations observed, only G140G/R and Q148Q/R are major INSTI RAMs. Of the IAS USA NNRTI mutations reported, E138A, Y181C, Y188L, and H221Y are RPV RAMs. There

were no subjects in the Q4W group with HIV-1 RNA ≥ 50 c/mL that had major IAS-USA NNRTI RAMs at Baseline. 9/14 subjects met CVF criteria, 3/14 subjects are from sites in the Russian Federation and 8/14 subjects carried Subtype B.

Table 51 Pre-specified INSTI and IAS NNRTI Baseline Substitutions for Subjects with HIV-1 RNA ≥ 50 copies/mL at Week 48 (Snapshot analysis - PR Population)

Subject	Treatment	Pre-specified INSTI	IAS-USA NNRTI	Subtype	Geographical region
1[a]	Q8W	L74I, T124A	**Y188L**, P225H	A1	WCENA
2[a]	Q8W	L74L/I, **G140G/R**	**Y188Y**/F/H/**L**	C	Southern Africa
3	Q8W	T97T/A	-	B	WCENA
4[a]	Q8W	-	K103N, V108V/I, **E138A**	B	WCENA
5[a]	Q8W	L74I	-	A1	EECA
6[ab]	Q8W	ATLAS-2M T124A ATLAS T124A	ATLAS-2M A98A/G, V108V/I, **Y181**Y/**C**, **H221**H/**Y** ATLAS A98G, K103K/N, V108V/I, **Y181C, H221Y**	C	Southern Africa
7[ab]	Q8W	ATLAS-2M L74I, T97T/A ATLAS L74I, T97T/A	ATLAS-2M **E138**E/**A** ATLAS E138E/A	A	EECA
8[ab]	Q8W	ATLAS-2M L74I ATLAS L74I, G163G/R	ATLAS-2M V90I ATLAS V90I	A	EECA
9	Q8W	-	-	B	WCENA

Subject	Treatment	Pre-specified INSTI	IAS-USA NNRTI	Subtype	Geographical region
10	Q4W	V151V/A	-	B	WCENA
11[a]	Q4W	-	-	B	WCENA
12[a]	Q4W	T124T/A	-	B	WCENA
13	Q4W	L74I, T124A, **Q148Q/R**	-	B	WCENA
14	Q4W	L74I	-	B	WCENA

Note: Bolded mutations are major INSTI or IAS-USA RPV mutations. Baseline PBMC DNA sequence analysis is from ATAS-2M unless otherwise specified.

a. Subject met CVF criteria

b. Subject transitioned from ATLAS (201585)

(Data Source: GSK Document Number 2019N420276_00 Listing 1)

Baseline INSTI polymorphisms and their prevalence observed in the 14 subjects with HIV-1 RNA ≥50 c/mL at Week 48 are shown in Table 52. In either Q8W and/ or Q4W groups, substitutions at Integrase codons L74, T97, T124, G140, Q148, and V151 were seen. In the Q8W group, only 1 major INSTI mutation was reported, G140G/R. In the Q4W group, the only major INSTI mutation was Q148Q/R.

Table 52 Virologic Response at Week 48 by Baseline INSTI Mutations Present in Subjects with HIV-1 RNA ≥50 c/mL (Snapshot Analysis - PR Population)

	Q8W (N=444)		Q4W (N=438)	
Pre-specified INSTI	**≥50 c/mL**	**<50 c/mL**	**≥50 c/mL**	**<50 c/mL**
L74I	4/67 (6%)	59/67 (88%)	2/67 (3%)	62/67 (93%)
L74L/I	1/6 (17%)	5/6 (83%)	0/3	3/3 (100%)-
T97T/A	2/8 (25%)	6/8 (75%)	0/5	4/5 (80%)-
T124A	2/133 (2%)	126/133 (95%)	1/130 (<1%)	122/130 (94%)
T124T/A	0/7	6/7 (86%)-	1/22 (5%)	21/22 (95%)
G140G/R	1/5 (20%)	4/5 (80%)	0/6	6/6 (100%)-
Q148Q/R	0/1	1/1 (100 %)-	1/1 (100%)	-
V151V/I	0/12	12/12 (100%)	1/8 (13%)	7/8 (88%)

Data Source: GSK Document Number 2019N420276_00 Table 2.1

Baseline IAS-USA NNRTI mutations and their prevalence observed in the 14 subjects with HIV-1 RNA ≥50 c/mL are shown in Table 53. The Baseline RPV RAMs seen in subjects with HIV-1 RNA ≥50 c/mL (Snapshot Week 48 analysis) were E138A, E138E/A, Y181C, Y188Y/F/H/L, Y188L, and H221H/Y. Overall 27 out of 30 (90%) subjects with Baseline K103N or K103K/N had HIV-1 RNA-1 <50 c/mL at Week 48. There were no Baseline IAS-USA NNRTI mutations seen in the Q4W group among subjects with HIV-1 RNA ≥50 c/mL.

Table 53 Virologic Response at Week 48 by Baseline IAS-USA NNRTIs Mutations Present in Subjects with HIV-1 RNA ≥50 c/mL (Snapshot analysis - PR Population)

	Q8W (N=444)	
IAS-USANNRTI	≥50 c/mL	<50 c/mL
V90I	1/18 (6%)	17/18 (94%)
A98G	1/5 (20%)	4/5 (80%)
K103K/N	1/3 (33%)	2/3 (67%)

	Q8W (N=444)	
K103N	1/10 (10%)	9/10 (90%)
V108V/I	2/3 (67%)	1/3 (33%)
E138A	1/6 (17%)	5/6 (83%)
E138E/**A**	1/5 (20%)	4/5 (80%)
Y181C	1/2 (50%)	1/2 (50%)
Y188L	1/2 (50%)	1/2 (50%)
Y188Y/F/H/**L**	1/1 (100%)	0/1
H221H/**Y**	0/4	4/4 (100%)
P225P/H	0/1	1/1 (100%)

Note: RPV RAMs are bolded.
Data Source: GSK Document Number 2019N420276_00 Table 2.2.

Characterization of INSTI polymorphism L74I in relationship to virologic outcome at Week 48

Pre-specified INSTI polymorphism, L74I, was present at Baseline in 15% of subjects in both the Q8W and the Q4W group of this study. L74I at Baseline was seen in 3/4, 2/3, and 5/10 CVF subjects in FLAIR, ATLAS, and ATLAS-2M, respectively [GSK Document Number 2017N345267_00; GSK Document Number 2018N370336_00; GSK Document Number 2019N406358_01]. Hence, further characterization of L74I present at Baseline in relationship to virologic response at Week 48 was warranted.

In the Q8W group, 4/67 (6%) subjects presenting with L74I at Baseline vs 4/359 (1%) in those without substitutions or with non-pre-specified substitutions at the L74 codon had HIV-1 RNA ≥50 c/mL at Week 48 Table 54. Comparison across these categories in relation to virologic outcome of HIV-1 RNA ≥50 c/mL was statistically significant (p=0.024). Comparison of these categories in relation to virologic outcome of HIV-1 RNA <50 c/mL was also statistically significant (p=0.041).

In the Q4W group, 2/67 (3%) subjects with L74I at Baseline vs 3/359 (<1%) subjects without substitutions or with non-pre-specified substitutions at the L74 codon had HIV-1 RNA ≥50 c/mL at Week 48. Comparison across these categories in relation to virologic outcome of HIV-1 RNA ≥50 c/mL was not statistically significant (p=0.177). Comparison of these categories in relation to virologic success was also not statistically significant (p=0.580).

Results were the same in PRC populations. (Source data: GSK Document Number 2019N420276_00 Table 2.13)

Table 54 Summary of Virologic response at Week 48 by Integrase L74I Subgroup at Baseline (Snapshot analysis - PR Population)

	Q8W		Q4W	
	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL
Wild type + non-prespecified	4/359 (1%)	342/359 (95%)	3/361 (<1%)	340/361 (94%)
L74I	4/67 (6%)	59/67 (88%)	2/67 (3%)	62/67 (93%)
p-value	**0.024**	**0.041**	0.177	0.580

Note: The L74I subgroups included in this table are all from the IN region. "Wild type + Non-prespecified" includes subjects who do not have any Baseline substitutions or who have Baseline non-prespecified substitutions at codon L74 in the IN region. Subjects with Baseline mixture of L74I or other pre-specified INSTI mutations at codon L74 in the IN region are excluded from the analysis.
Note: P-value is based on Fisher's Exact test for the comparison of the percentages at Week 48 across subgroups (within treatment comparison). The comparisons are performed for Plasma HIV-1 RNA ≥50 c/mL'and '<50 c/mL' separately.
Note: statistically significant p-values are bolded.
Data Source: GSK Document Number 2019N420276_00 Table 2.12.

Characterization of the INSTI polymorphism L74I by geographical region vs virologic response to CAB + RPV for the Q8W and Q4W groups is presented in Table 55. The majority of subjects with L74I in both Q8W and Q4W groups had HIV-1 RNA <50 c/mL Week 48 . In the Q8W group, 95% and 87% of subjects with L74I at Baseline and enrolled in WCENA or Russian Federation sites, respectively, had HIV-1 RNA <50 c/mL. In the Q4W group, 77% and 96% of subjects with L74I at Baseline and enrolled in a WCENA or Russian Federation site, respectively had HIV-1 RNA <50 c/mL.

Table 55 Proportion of Virologic Response at Week 48 by Baseline L74I Polymorphism and Geographical Region (Snapshot analysis - PR Population)

	L74I			
Region	**Q8W**		**Q4W**	
	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL
WCENA	1/20 (5%)	19/20 (95%)	2/13 (15%)	10/13 (77%)
Latin America	0/1	1/1 (100%)	0/1	1/1 (100%)
Russian Federation	3/45 (7%)	39/45 (87%)	0/48	46/48 (96%)
Oceania	-	-	0/1	1/1 (100%)
Southern African	0/1	0/1	0/4	4/4 (100%)

Data Source: GSK Document Number 2019N420276_00 Table 2.5.

The pre-specified INSTI polymorphism L74I was present in subjects with HIV-1 RNA >50 c/mL at Week 48 in subjects that harbored Subtype A, A1, B and COMPLEX virus. The majority of the subjects having L74I at Baseline and subtype A, A1, or COMPLEX (89/97; 92%) had HIV-1 RNA <50 c/mL at Week 48 (Table 56).

Table 56 Proportion of Virologic Response at Week 48 by Baseline L74 Polymorphisms and Virus Subtype (Snapshot analysis - PR population)

	L74I			
	Q8W		Q4W	
Subtype	≥50 c/mL	<50 c/mL	≥50 c/mL	<50 c/mL
A	1/13 (8%)	12/13 (92%)	0/7	6/7 (86%)
A1	2/24 (8%)	20/24 (83%)	0/28	27/28 (96%)
B	0/13	13/13 (100%)	2/12 (17%)	9/12 (75%)
COMPLEX	1/12 (8%)	11/12 (92%)	0/13	13/13 (100%)

Data Source: GSK Document Number 2019N420276_00 Table 2.7.

4.2.1.6.5. Discussion

Within the ATLAS-2M study, PBMC DNA sequencing data was generated retrospectively for exploratory analysis of potential associations between Baseline resistance and virologic outcome at Week 48. Proviral DNA information was not available and not used for the purpose of screening for study eligibility. Due to the investigational status of CAB and limited amount of resistance information available on the drug, the pre-specified INSTI mutations list was expanded and included a broad number of substitutions not usually implicated in INSTI resistance (i.e., polymorphisms L74I and T124A). Of the 1045 Intent-to-Treat Exposed (ITT-e) Subjects in ATLAS-2M, genotypes from Baseline PBMCs were available for 882 subjects, 444/522 (85%) subjects in the Q8W group and 438/523 (84%) subjects in the Q4W group. At Baseline, 60% of Q8W subjects and 62% of Q4W subjects had at least one pre-specified INSTI substitutions. IAS-USA NNRTI mutations (including RPV RAMs) were present in 19% and 20% of the Q8W and Q4W subjects, respectively. This study used univariate analysis and additional factors should be considered when investigating associations with virologic outcome data. Additional analysis is planned with pooled data from all Phase III CAB + RPV LA studies and will include other potential variables of interest.

The prevalence of pre-existing major INSTI and RPV RAMs was low in the study (Q8W- 2% and 6%, respectively and Q4W- 3% and 5% respectively). The low number of pre-existing major INSTI and RPV RAMs was expected since the subjects' historical genotype was reviewed during screening and subjects were excluded from the study if any known major INSTI or NNRTI RAMs, except for K103N, were present. K103N was observed in one subject with HIV-1 RNA ≥50 c/mL at Week 48, but this subject also had

the RPV RAM, E138A. Overall 15/17 (88%) subjects with Baseline K103N had HIV-1 RNA-1 <50 c/mL at Week 48 by Snapshot analysis, 1/17 (6%) had HIV-1 RNA ≥ 50 c/mL at Week 48 and 1/17 (6%) had no data in the Week 48 window. The prevalence of pre-specified INSTI mutations was 60% and 62% for Q8W and Q4W, respectively. IAS NNRTI mutations (including RPV RAMs) were present at 19%.and 20% for Q8W and Q4W, respectively. Baseline prevalence of resistance mutation classes were very similar to what was reported in ATLAS [GSK Document Number 2019N420275_00].

A total of 14 subjects had Snapshot HIV-1 RNA ≥50 c/mL at Week 48. Of the 9 subjects in the Q8W group with HIV-1 RNA ≥50 c/mL, Baseline PBMC vDNA sequencing showed major INSTI RAM, G140G/R, present in one CVF subject along with INSTI polymorphism, L74I. This mutation was not seen at the virologic failure time point for this subject. G140R, along with INSTI polymorphism L74I, was observed at virologic failure in 1 CVF subject in the FLAIR study (201584) and CAB susceptibility was reduced 6.7-fold [GSK Document Number 2017N345267_00].

In the Q4W group, major INSTI RAM, Q148Q/R, was seen at Baseline in one subject with HIV-1 RNA ≥50 c/mL at Week 48. This subject also presented with INSTI polymorphisms, L74I and T124A. At the virologic failure timepoint, Q148Q/R was not observed in this subject. Q148R, along with L74I, was seen at the time of virologic failure in 2 CVF subjects in FLAIR (CAB FC=5.2 and 9.4) and alone in 1 subject in LATTE-2 (200056) (CAB FC=5.1) [GSK Document Number 2017N345267_00; GSK Document Number 2016N273084_00].

In the Q8W group, RPV RAMs (E138A, E138E/A, Y181Y/C + H221H/Y, Y188L, and Y188Y/F/H/L) were present at Baseline in 5/9 subjects with HIV-1 RNA ≥50 c/mL at Week 48. IAS-USA NNRTI RAMs (V90I, A98G, K103N, V108V/I (n=2), and P225H) were also observed in subjects with HIV-1 RNA ≥50 c/mL at Week 48 in the presence or absence of RPV RAMs. All but Y181Y/C + H221H/Y were also observed at the virologic failure time point. Mutations at the E138 codon have been seen at virologic failure in CVF subjects from FLAIR, ATLAS, and LATTE-2 (RPV FC range from 1.0 to 7.1). No IAS-USA NNRTI or RPV RAMs were observed at Baseline in subjects with HIV-1 RNA ≥50 c/mL at Week 48 for the Q4W group.

Virus subtypes at Baseline in the CAB + RPV subjects with Snapshot HIV-1 ≥50 c/mL was one of the major differences between ATLAS-2M and the other 2 Phase III studies. FLAIR and ATLAS. Snapshot failures in FLAIR and ATLAS at Week 48 carried either Subtype A1 or AG virus, while the subjects with HIV-1 RNA ≥50 c/mL at Week 48 in this study carried Subtypes A, A1, B, or C virus at Baseline.

The p-value of <0.001 that is observed with the presence of RPV RAMs and in relation to Snapshot outcome of HIV-1 RNA ≥50 c/mL suggests when RPV mutations are present, they are potentially associated with a greater likelihood of having HIV-1 RNA ≥50 c/mL at Week 48 when administered CAB + RPV Q8W. This correlation was also seen in the ATLAS study. This does not seem to be the case for the Q4W group, as suggested by the p-value of >0.999 seen when RPV mutations are present in the Q4W group and the virologic outcome of HIV-1 RNA ≥50 c/mL at Week 48 is observed. However, with the

small numbers of subjects harboring virus with RPV RAMs, and the univariate analysis of these studies, it is difficult to assign a direct correlation with such a clinical outcome.

The pre-specified INSTI substitution, L74I, is a common polymorphism seen particularly in subjects with Subtype A and A1 virus (which is prevalent in Russian Federation) and has been observed both at Baseline and at virologic failure in subjects from CAB + RPV studies [GSK Document Number 2018N370336_00 and GSK Document Number 2017N345267_00]. There is a high number of subjects with HIV-1 RNA <50 c/mL (Q8W, 88% and Q4W, 93%) in subjects with INSTI polymorphism L74I. However, a statistically significant difference (p-value of 0.024) exists between subjects in the Q8W group having HIV-1 RNA ≥ 50 c/mL at Week 48 in those harbouring L74I virus and those that do not. This statistically significant difference also exists for the ATLAS study [GSK Document Number 2019N420275_00].

The results presented in this report are based on data using univariate analysis. The impact of RPV RAMs and of the L74I polymorphism on virologic outcome will be further explored with pooled data from all Phase III/IIIb CAB + RPV studies in a multivariable PK/PD analysis. In vitro site-directed mutagenesis studies will be used to assess the impact of L74I on INSTI mutations present in ATLAS-2M subjects at virologic failure.

4.2.1.6.6. CONCLUSIONS

- Overall, the prevalence of pre-existing major INSTI and RPV RAMs was infrequent and similar between the CAB + RPV Q8W and Q4W groups, with each group containing 8% of the total mutations. Major INSTI RAMs were present at Baseline in 1/9 and 1/5 subjects with HIV-1 RNA ≥50 c/mL at Week 48 in the Q8W and Q4W groups, respectively. RPV RAMs were present at Baseline in 5/9 and 0/5 subjects with HIV-1 RNA ≥50 c/mL at Week 48 in Q8W and Q4W groups, respectively.
- A higher proportion of Subjects with archived L74I have HIV-1 RNA ≥ 50 c/mL at Week 48, than do subjects without L74I. L74I was present in (15%) subjects at Baseline in both the Q8W (67/444) and the Q4W groups (67/438). 4 (6%) subjects in the Q8W group and 2 (3%) subjects in the Q4W group with L74I had HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot Analysis). 59 (88%) and 62 (93%) subjects with L74I had <50 c/mL HIV-1 RNA at Week 48 in the Q8W and Q4W groups, respectively.
- The presence of RPV RAMs at Baseline may potentially be associated with non-response to CAB + RPV in the Q8W group. Baseline RPV RAMs were present in 5 (19%) Q8W subjects and no Q4W subjects with HIV-1 RNA ≥50 c/mL Q8W at Week 48 (Snapshot Analysis) and in 21 (81%) Q8W subjects and 22 (100%) Q4W subjects with HIV-1 RNA <50 c/mL at Week 48.
- Virus subtypes at Baseline in the CAB + RPV subjects with Snapshot HIV-1 RNA ≥50 c/mL was one of the major differences between ATLAS-2M and the other 2 Phase III studies. Snapshot failures in FLAIR and ATLAS at Week 48 carried either Subtype A1 or AG virus, while subjects with HIV-1 RNA ≥50 c/mL in the CVFs in ATLAS-2M carried Subtypes A, A1, B, or C virus at Baseline.

- The results presented in this report are based on data using univariate analysis. The impact of mutations at codon E138 and of the L74I polymorphism on virologic outcome will be further explored with pooled data from all Phase III CAB + RPV LA studies by including other factors (e.g. PK, L74I presence at baseline, gender, regimen, BMI) in the analysis model.

4.2.1.7. Reclassification of Subtype in FLAIR, ATLAS, and ATLAS-2M

Originally, HIV subtyping was based on definitions from either Q2 Solutions (Morrisville, NC US) or Monogram Biosciences (South San Francisco, CA US), the companies that conducted virology testing for FLAIR (201584), ATLAS (201585), and ATLAS-2M (207966). The subtype algorithms used by Monogram Biosciences and Q2 Solutions do not include Subtype A6. Given the strong correlation between L74I and subtype A6 (Lapovok, 2017), further analysis was performed to delineate the primary driver for CVF risk (GSK Document Number 2020N452718_01). This involved applying updated subtyping classifications (research grade, current Los Alamos National Library panel from the HIV Sequence database) to those evaluated by Monogram Biosciences in the individual studies to refine A/A1 subtyping to A6.

Classification of HIV-1 subtype in FLAIR (201584), ATLAS (201585), and ATLAS-2M (207966) study participants was performed using integrase reference sequences obtained from the Los Alamos National Laboratory HIV sequence database. The reference panel included 80 full length genomes from noncirculating recombinant forms representing 14 HIV-1 subtypes, including A1 (n=8), A2 (n=1), A3 (n=1), A4 (n=1), A6 (n=4), B (n=15), C (n=15), D (n=10), F1 (n=8), F2 (n=2), G (n=9), H (n=2), J (n=2), and K (n=2). Subtype was assigned based on Smith-Waterman similarity score for pairwise comparison between sample sequence and each reference sequence (Smith, 1981). Subtype analysis differed from that used by Monogram Biosciences by the addition of integrase sequences to the algorithm and use of an updated Los Alamos National Laboratories reference panel with the inclusion of subtypes A3, A4, and A6 and removal of circulating recombinant forms and subtypes O and N.

17 of the subjects across all 3 Phase III/IIIb studies who did not maintain virologic suppression through Week 48 met CVF criteria. Four of these 17 subjects were excluded from the analysis due to being rollovers from Study 201585 (i.e., having prior exposure to CAB + RPV; n=3) or due to the CVF occurring prior to injections. Table 57 lists each of the subjects who met CVF criteria across the studies in the pooled analysis. Seven subjects were reclassified from their original A, A1, AG subtype to either an A6 or A1 subtyping.

Table 57 Subtypes for Subjects with CVF (Multi-Variable Analysis Population)

Study ID	Unique Subject ID	Reclassification HIV-1 Subtype A6	Reclassification HIV-1 Subtype A1	L74I[a]	Sex	Regimen	Original HIV 1 Subtype Classification
201584	[redacted]	Y	N	Y	M	Q4W	A, A1, AG combined
	[redacted]	Y	N	Y	F	Q4W	A, A1, AG combined
	[redacted]	Y	N	Y	F	Q4W	A, A1, AG combined
201585	[redacted]	Y	N	Y	F	Q4W	A, A1, AG combined

Study ID	Unique Subject ID	Reclassification HIV-1 Subtype A6	Reclassification HIV-1 Subtype A1	L74I[a]	Sex	Regimen	Original HIV 1 Subtype Classification
	[redacted]	Y	N	Y	M	Q4W	A, A1, AG combined
	[redacted]	N	N	N	F	Q4W	A, A1, AG combined
207966	[redacted]	N	N	N	M	Q8W	B (reference level)
	[redacted]	N	Y	Y	F	Q8W	A, A1, AG combined
	[redacted]	N	N	N	M	Q4W	B (reference level)
	[redacted]	N	N	Y	F	Q8W	C
	[redacted]	N	N	N	M	Q8W	B (reference level)
	[redacted]	N	N	N	M	Q4W	B (reference level)
	[redacted]	Y	N	Y	F	Q8W	Other

Source: GSK Document Number 2020N452718_01 Table 2.
a L74I (non-M mixture) INSTI Polymorphism at Baseline.

4.2.2. Phase IIb Studies

4.2.2.1. 200056 (LATTE2)

4.2.2.1.1. Study Design

200056 (LATTE2) is an ongoing open-label, randomized, dose ranging, Phase IIb trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression. Following the 28-day Screening Period, eligible subjects were enrolled into the study and began a 20 - week Induction Period utilizing an oral regimen of CAB 30 mg once daily plus ABC/3TC 600/300 mg once daily. At Week (-4) the treatment regimen was modified to add RPV 25 mg once daily for the remainder of the Induction Period. At Day 1 of the Maintenance Period, eligible subjects were randomized 2:2:1 to receive an IM regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks for 96 weeks, an IM regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks for 96 weeks, or continued on the oral Induction Period regimen of CAB 30 mg + ABC/3TC once daily for 96 weeks (or 100 weeks if continuing on to the Extension Period). All subjects who successfully complete 96 weeks of CAB LA + RPV LA or oral treatment in the Maintenance Period will continue to have access to both CAB LA and RPV LA in the Extension Period. Subjects on the oral regimen not choosing to switch to the long acting regimen will complete their study participation at Week 96. The Extension period will last until study treatment is either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated.

4.2.2.1.2. Protocol Defined Virologic Failure

Virologic failure must be confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between two and four weeks after the initial suspected virologic failure sample. Subjects should receive full dose of IP across all plasma sampling times used for determining virologic failure. For this definition, Baseline viral load is defined as the Day 1 of Induction Period plasma HIV-1 RNA measurement. For the purposes of

clinical management in this study, protocol defined virologic failure (PDVF) is defined as any of the following:

Virologic Non-Response

Less than a 1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4 of Induction Period, which is subsequently confirmed, unless plasma HIV-1 RNA is <400 c/mL.

Virologic Rebound

Rebound in HIV-1 plasma RNA levels to ≥200 c/mL, which is subsequently confirmed, after prior suppression to <200 c/mL.

Two consecutive plasma HIV-1 RNA determinations that are >0.5 $\log_{10}$ c/mL increase in plasma HIV-1 RNA from the nadir value on study, where the lowest HIV-1 RNA value is ≥200 c/mL.

Subjects who met the definition of PDVF were discontinued from the study.

4.2.2.1.3. Viral genotyping and phenotyping

There were 2 subjects with PDVF, defined as confirmed viral load >200 c/mL, through 96 weeks of maintenance treatment (no additional PDVFs between the Week 48 and Week 96 analysis time points).

Subject [redacted] (Q8W IM arm), male, had 81,487 c/mL HIV-1 RNA at Baseline. This subject had 427 c/mL HIV-1 RNA at Week 4 and 5316 c/mL at Week 8. Baseline, Week 4, and Week 8 RT and PRO genotypes and phenotypes were all wild type and unchanged. Baseline and Week 4 IN genotypes are unchanged. Week 8 IN genotype has the addition of R269R/G which is not an INI resistance mutation (CAB FC = 1.0). Baseline, Week 4, and Week 8 IN phenotypes were all susceptible to all integrase inhibitors. The virus was Subtype B.

Subject [redacted] (Q8W IM arm), male, had a viral load of 444,489 c/mL HIV-1 RNA at Baseline. This subject had 463 c/mL HIV-1 RNA at Week 48 and 205 c/mL at the confirmatory visit seven days later. At the time of PDVF this subject had treatment emergent NNRTI resistance K103N, E138G, and K238T with phenotypic resistance to RPV (3.34 FC). The fold change to etravirine (1.91 FC) was below the lower cutoff. The Week 48 Integrase genotype had the treatment emergent integrase resistance mutation Q148R with accompanying resistance to CAB (5.06 FC). The Week 48 sample was not resistant to dolutegravir (1.38 FC). The virus was Subtype AG.

No subjects had PDVF after Week 48, through Week 160 of the study.

Conclusions

- Protocol Defined Virologic Failure with resistance to CAB was uncommon in the LATTE-2 study (0.4%, 1/230) and consisted of the Q148R mutation in the IN coding region.

- PDVF with resistance to RPV was equally uncommon (0.4%, 1/230) and consisted of the E138G mutation in the RT coding region.

4.2.2.2. LAI116482 (LATTE)

Study Design Study LAI116482 is a Phase IIb, randomized, multicentre, parallel group, partially-blinded, two part study evaluating oral CAB in combination with oral RPV. The study is being conducted in 244 HIV-1 infected ART-naive adults. In the Induction Phase, subjects were randomized 1:1:1:1 to 10, 30, or 60 mg of CAB dose regimens or a contemporary control regimen containing EFV, each in combination with fixed-dose dual NRTI therapy (either ABC/3TC or TDF/FTC as chosen by the Investigator). All subjects randomized to a CAB containing arm, who successfully completed 24 weeks on study and had demonstrated virologic suppression (defined as having a plasma HIV-1 RNA <50 c/mL by Week 24, with no signs of virologic rebound) became eligible for the Maintenance Phase of this trial. Subjects randomized to the EFV arm continued their assigned EFV-based ART through Week 96. At the Week 24 visit, subjects who qualified for the Maintenance Phase of this study would:

- continued to receive their originally randomized, blinded dose of oral CAB;
- discontinued the dual NRTI background;
- initiated dosing with oral RPV at a dose of 25 mg once daily.

4.2.2.2.1. Protocol Defined Virologic Failure

Virologic failure must have been confirmed by a repeat and consecutive plasma HIV-1 RNA measurement between two and four weeks after the initial suspected virologic failure sample. Baseline viral load is defined as the Day 1 plasma HIV-1 RNA measurement. For the purposes of clinical management in this study, virologic failure is defined as any of the following:

Virologic Non-response

- Less than a 1.0 $\log_{10}$ c/mL decrease in plasma HIV-1 RNA by Week 4, which is subsequently confirmed, unless plasma HIV-1 RNA is <400 c/mL.
- Two consecutive plasma HIV-1 RNA levels ≥200 c/mL at least 2 weeks but not more than 4 weeks apart on or after Week 16 without evidence of prior suppression to <200 c/mL.

Virologic Rebound

- Rebound in HIV-1 plasma RNA levels to ≥200 c/mL, which is subsequently confirmed, after prior suppression to <200 c/mL.
- Two consecutive plasma HIV-1 RNA determinations that are >0.5 $\log_{10}$ c/mL increase in plasma HIV-1 RNA from the nadir value on study, where the lowest HIV-1 RNA value is ≥200 c/mL.

Subjects who met the definition of virologic failure were discontinued from the study.

Cases of confirmed protocol defined virologic failure triggered virologic resistance testing. The virologic failure definition was intended for guidance and Investigators were instructed to use their discretion as to the most appropriate clinical management of their subjects, if more stringent local guidelines applied.

4.2.2.2.2. Induction Phase

Viral Genotyping and Phenotyping Study Population

Overall, there was a low rate of PDVF during the Induction Phase, with 3 of 181 (<2%) of the subjects meeting PDVF in the CAB treatment arms and 4 of 62 subjects (6%) with PDVF in the EFV treatment arm.

These subjects are described below:

Subject [redacted] (10 mg CAB + TDF/FTC) met the definition of PDVF (virologic rebound) at Week 8 (Data Source: LAI116482 Week 48 CSR Table 7.16). This subject had 17768 (4.25 $\log_{10}$) c/mL HIV-1 RNA at Day 1, suppressed to <50 c/mL HIV-1 RNA at Week 4, then rebounded to 627 (2.8 $\log_{10}$) c/mL HIV-1 RNA at Week 8. The confirmatory HIV-1 RNA at Week 12 was 1331 (3.12 $\log_{10}$) c/mL (Data Source: LAI116482 Week 48 CSR ICH Listing 7.1). The virus was Subtype B.

Subject [redacted] (30 mg CAB + TDF/FTC) met the definition of PDVF (virologic non-response) at Week 4(Data Source: LAI116482 Week 48 CSR Table 7.16). This subject had 21722 (4.34 $\log_{10}$) c/mL HIV-1 RNA at Day 1, 15930 (4.2 $\log_{10}$) c/mL HIV-1 RNA at Week 4 and confirmed with 19194 (4.28 $\log_{10}$) c/mL HIV-1 RNA at Week 8 (Data Source: LAI116482 Week 48 CSR ICH Listing 7.1). The virus was Subtype B.

Subject [redacted] (60 mg CAB + TDF/FTC) met the definition of PDVF (virologic rebound) at Week 8 (Data Source: LAI116482 Week 48 CSR Table 7.16). This subject had 20884 (4.32 $\log_{10}$) c/mL HIV-1 RNA at Day 1, suppressed to 57 (1.76 $\log_{10}$) c/mL HIV-1 RNA at Week 4, then rebounded to 28269 (4.45 $\log_{10}$) c/mL HIV-1 RNA at Week 8. The confirmatory HIV-1 RNA at Week 12 was 961 (2.98 $\log_{10}$) c/mL (Data Source: LAI116482 Week 48 CSR ICH Listing 7.1). The virus was Subtype B.

Subject [redacted] (EFV + ABC/3TC) met the definition of PDVF (virologic non-response) at Week 16 (Data Source: LAI116482 Week 48 CSR Table 7.16). This subject had 29030 (4.46 $\log_{10}$) c/mL HIV-1 RNA at Day 1 and had 417 (2.62 $\log_{10}$) c/mL HIV-1 RNA at Week 16 which was confirmed at Week 20 with 291 (2.46 $\log_{10}$) c/mL HIV-1 RNA. At the follow-up visit (approximately one month after confirmation), the HIV-1 RNA had decreased to 149 (2.17 $\log_{10}$) c/mL (Data Source: LAI116482 Week 48 CSR ICH Listing 7.1). The virus was Subtype B.

Subject [redacted] (EFV + TDF/FTC) met the definition of PDVF (virologic rebound) at Week 4 (Data Source: LAI116482 Week 48 CSR Table 7.16). This subject had 20495 (4.31 $\log_{10}$) c/mL HIV-1 RNA at Day 1, decreased to 181 (2.26 $\log_{10}$) HIV-1 RNA at Week 2 and rebounded to 257 (2.41 $\log_{10}$) c/mL HIV-1 RNA at Week 4. The

confirmatory HIV-1 RNA was 214 (2.33 log_{10}) c/mL at Week 8 (Data Source: LAI116482 Week 48 CSR ICH Listing 7.1). The virus was Subtype B.

Subject [redacted] (EFV + TDF/FTC) met the definition of PDVF (virologic rebound) at Week 8 (Data Source: LAI116482 Week 48 CSR Table 7.16). This subject had 19174 (4.28 log_{10}) c/mL HIV-1 RNA at Day 1, decreased to <50 c/mL HIV-1 RNA at Week 4 and rebounded to 7027 (3.85 log_{10}) c/mL HIV-1 RNA at Week 8. The confirmatory HIV-1 RNA was 5644 (3.75 log_{10}) c/mL at Week 12 (Data Source: LAI116482 Week 48 CSR ICH Listing 7.1). The virus was Subtype B.

Subject [redacted] (EFV +ABC/3TC) receiving EFV was listed a PDVF in LAI116482 Week 96 CSR Table 7.16. This subject had 12122 (4.08 log_{10}) c/mL at Day 1 and the viral load count for this subject increased slightly to14144 (4.15 log_{10}) c/mL at Week 4. However, this subject was withdrawing from the study due to non-compliance / investigator discretion and the withdrawal sample (Week 4) was not considered a valid confirmatory sample by the study virologist.

Viral Genotyping and Phenotyping Results

There were no treatment emergent resistance mutations, nor phenotypic resistance, in any of the subjects with PDVF during the Induction Phase.

Reverse Transcriptase (RT), protease (PRO), and Integrase (IN) genotypes and phenotypes were available at Day 1 for all six subjects. Reverse Transcriptase and PRO genotypes and phenotypes were available at time of PDVF for all six subjects. Integrase genotype was not available at the time of PDVF for Subject [redacted] (EFV + ABC/3TC) and Subject [redacted] (EFV + TDF/FTC). None of the six subjects had treatment emergent resistance mutations in RT or PRO and none of the four subjects with IN genotype at the time of PDVF had any treatment emergent integrase substitutions. All subjects were susceptible to both CAB and raltegravir (RAL) at Day 1. The four subjects for whom phenotypes were available at PDVF were also susceptible to both CAB and RAL (Table 58)

Table 58 Integrase Phenotype at Day 1 and the time of PDVF (On-treatment Phenotypic Resistance Population)

		Day 1		PDVF	
Subject	**Treatment Arm**	**CAB FC**	**RAL FC**	**CAB FC**	**RAL FC**
Subject [redacted]	10 mg CAB	0.79	1.14	0.70	1.21
Subject [redacted]	30 mg CAB	0.81	0.90	0.91	1.00
Subject [redacted]	60 mg CAB	0.73	0.60	0.75	0.65
Subject [redacted]	EFV	1.05	0.77	NA	NA
Subject [redacted]	EFV	0.67	0.80	NA	NA
Subject [redacted]	EFV	1.02	0.96	1.04	0.83

Data Source: 2013N180642_00 Other Listing 12.4.

4.2.2.2.3. Maintenance Phase through Week 96

Viral Genotyping and Phenotyping Study Population

Five subjects met PDVF criteria during maintenance through Week 96: two subjects on CAB 10 mg (Weeks 48 [both RPV and INI RAMS] and 72 [RPV RAMs only]), one subject on 30 mg (Week 36, no RAMs), and two subjects receiving EFV (Weeks 36 and 60, no RAMs). The five subjects are described below:

Subject [redacted] (10 mg CAB + RPV) met the definition of PDVF (virologic rebound) at Week 48 (Data Source: LAI116482 Week 96 Table 7.16). This subject had 13929 (4.14 $\log_{10}$) c/mL HIV-1 RNA at Day 1, suppressed to <50 c/mL HIV-1 RNA at Week 2, then rebounded to 18886 (4.28 $\log_{10}$) c/mL HIV-1 RNA at Week 48. The confirmatory HIV-1 RNA was 8709 (3.94 $\log_{10}$) c/mL (Data Source: LAI116482 Week 96 CSR ICH Listing 7.1). Subject [redacted] had a treatment emergent NNRTI resistance mutation E138Q. Day 1 had the following IN substitutions: D3D/N, E11D, K14R, S17T, M22L, V37I, S39C, V113I, T124A, T125A, I203M, I220L, V234I, D253D/E, R284G. Week 48 IN retained the IN substitutions observed at Day 1 and had additional IN substitutions H51H/R, M178M/L, D232D/N, I251I/V in addition to the treatment emergent resistance mutation Q148R (Data Source: LAI116482 Week 96 CSR Other Listing 12.3). Subject [redacted] had 2.04 FC to ETR and 1.83 FC to RPV at Week 48, neither of which is above the cutoff. The RT/PRO RC decreased from 81 at Day 1 to 44 at Week 48. This subject had 3.08 FC to CAB and 30 FC to RAL at Week 48 (Data Source: LAI116482 Week 96 Other Listing 12.4). The IN RC decreased from 34 at Day 1 to 8.1 at Week 48 (Data Source: LAI116482 Week 96 CSR Other Listing 12.5). The virus was Subtype B.

Subject [redacted] (30 mg CAB + RPV) met the definition of PDVF (virologic rebound) at Week 36 (Data Source: LAI116482 Week 96 Table 7.16). This subject had 7065 (3.85 $\log_{10}$) c/mL HIV-1 RNA at Day 1, suppressed to <50 c/mL HIV-1 RNA at Week 2, then rebounded to 210 (2.32 $\log_{10}$) c/mL HIV-1 RNA at Week 36. The confirmatory HIV-1 RNA at Week 40 was 228 (2.36 $\log_{10}$) c/mL (Data Source: LAI116482 Week 96 CSR ICH Listing 7.1). This subject had no RPV RAMs. IN genotype could not be generated for Subject 601. The virus was Subtype B.

Subject [redacted] (EFV + TDF/FTC) met the definition of PDVF (virologic rebound) at Week 36 (Data Source: LAI116482 Week 96 Table 7.16). This subject had 83284 (4.92 $\log_{10}$) c/mL HIV-1 RNA at Day 1, suppressed to <50 c/mL HIV-1 RNA at Week 12. This subject had >50 c/mL but less than 200 c/mL HIV-1 RNA at Weeks 26, 28 and 32, then rebounded to 203 (2.31 $\log_{10}$) c/mL HIV-1 RNA at Week 36. The confirmatory HIV-1 RNA at Week 40 was 231 (2.36 $\log_{10}$) c/mL (Data Source: LAI116482 Week 96 CSR ICH Listing 7.1). This subject had no treatment emergent resistance mutations. The virus was Subtype B.

Subject [redacted] (EFV + ABC/3TC) met the definition of PDVF (virologic rebound) at Week 60 (Data Source: LAI116482 Week 96 CSR Table 7.16). This subject had 766 (2.88 $\log_{10}$) c/mL HIV-1 RNA at Day 1, suppressed to <50 c/mL HIV-1 RNA at Week 4 then rebounded to 15,903 (4.20 $\log_{10}$) c/mL HIV-1 RNA at Week 60. The confirmatory

HIV-1 RNA was 286 (2.46 log_{10}) c/. This subject had no treatment emergent resistance mutations. The virus was Subtype B.

Subject [redacted] (10 mg CAB + RPV) met the definition of PDVF (virologic rebound) at Week 60 (Data Source: LAI116482 Week 96 CSR Table 7.16). This subject had 31,982 (4.50 log_{10}) c/mL HIV-1 RNA at Day 1,suppressed to <50 c/mL HIV-1 RNA at Week 4) then rebounded to 457 (2.66 log_{10}) c/mL HIV-1 RNA at Week 72. The confirmatory HIV-1 RNA was 609 (2.78 log_{10}) c/mL . Subject [redacted] had treatment emergent NNRTI resistance mutations K101K/E and E138E/A at PDVF (Data Source: LAI116482 Week 96 CSR Table 12.3). Subject [redacted] had 4.6 FC to RPV at Week 72 (1.16 FC to RPV at Day 1. This subject had no treatment emergent IN resistance mutations. (Data Source: LAI116482 Week 96 CS Other Listing 12.4). The virus was Subtype B.

4.2.2.2.4. Additional Virology Results

Subject [redacted] (10 mg CAB + RPV) had 9326 c/mL (3.97 log_{10}) HIV-1 RNA at Day 1, suppressed to <50 c/mL HIV-1 RNA at Week 2, then rebounded to 277 (2.44 log_{10}) c/mL HIV-1 RNA at Week 40. The confirmatory value HIV-1 RNA was <50 c/mL, but rebounded again to 241 (2.38 log_{10}) c/mL HIV-1 RNA at Week 48 (Data Source: LAI116482 Week 96 ICH Listing 7.1). This subject was lost to follow-up prior to confirmation of virologic failure; genotype and phenotype were attempted on Week 48 samples. Week 48 IN Geno and IN Pheno could not be generated. Week 48 had treatment emergent RPV resistance mutations K101K/E and E138E/K and accompanying RPV phenotypic resistance (2.18 FC). The etravirine FC of 2.68 was not above the cuttoff (Data Source: LAI116482 Week 48 CSR Other Listing 12.4). The IN RT/PRO RC decreased from 58 at Day 1 to 30 at Week 48 (Data Source: LAI116482 Week 96 CSR Other Listing 12.5). The virus was Subtype B

Six subjects were inadvertently enrolled in this study in spite of having the primary RPV resistance mutation E138A at screening and were excluded from the Week 96 per protocol analysis (LAI116482 Week 96 CSR Other Listing 12.2). This inclusion error was detected after their enrollment and the subjects were allowed to remain on study. Subject [redacted] (Subtype B virus) and Subject [redacted] (Subtype not determined) were randomized to 10 mg CAB. Each of these subjects had <50 c/mL HIV-1 RNA at Week 2 and remained at <50 c/mL HIV-1 RNA through Week 96**.** Subject [redacted] (Subtype not determined) and Subject [redacted] (Subtype B virus) received 60 mg CAB. Subject [redacted] had <50 c/mL HIV-1 RNA at Week 2 and remained at <50 c/mL HIV-1 RNA through Week 96. Subject [redacted] had <50 c/mL HIV-1 RNA at Week 8 and remained at <50 c/mL HIV-1 RNA through Week 96. Subject [redacted] (Subtype B virus) and Subject [redacted] (Subtype B virus) received EFV + ABC/3TC. Subject [redacted] (Subtype not determined) had <50 c/mL HIV-1 at Week 12 and remained at <50 c/mL HIV-1 RNA through Week 96. Subject [redacted] had <50 c/mL HIV-1 RNA at Week 8 and remained at <50 c/mL HIV-1 RNA through Week 96 (Data Source: LAI116482 Week 96 CSR ICH Listing 7.1).

4.2.2.2.5. PDVFs between Week 96 and Week 144

Three subjects met PDVF criteria during the Open Label Phase between Week 96 and Week 144 (Data Source: 2016N280049_00Table 7.16): two subjects who were

originally randomized to CAB 10 mg (Weeks 108 and 132) and one subject to 30 mg (Week 132). The three subjects are described below:

Subject [redacted] had 385 c/mL HIV-1 RNA at Week 108 and confirmed with 772 c/mL HIV-1 RNA. Week 108 RT genotype was unchanged as compared to Day 1 RT genotype. Week 108 IN genotype has treatment emergent resistance mutation V151V/I. While CAB FC remained unchanged, RAL FC increased from 1.28 and Day 1 to 1.74 at Week 108. The virus was Subtype B.

Subject [redacted] had 908 c/mL HIV-1 RNA at Week 132 and confirmed with 211 c/mL HIV-1 RNA. Week 132 RT genotype, IN genotype, and IN phenotype are unchanged as compared to Day 1 RT genotype, IN genotype, and IN phenotype. Both Day 1 and Week 132 had IN E157Q. The virus was Subtype B.

Subject [redacted] had 836 c/mL HIV-1 RNA at Week 132 and confirmed with 1727 c/mL HIV-1 RNA. Week 132 has treatment emergent RPV mutations K101E and M230M/L with high level resistance to all NNRTIs (12 FC to RPV). Week 132 IN genotype and IN phenotype could not be generated. The virus was Subtype B.

(Data Source: 2016N280049_00 Listing 7.2, Listing 12.1, Listing 12.2, Listing 12.3, Listing 12.5)

4.2.2.2.6. Discussion

There was a very low rate of PDVF in the Induction Phase with just one subject in each of the CAB treatment arms (<2%) and three subjects in the EFV treatment arm (5%) meeting the criteria for PDVF. None of the six subjects with PDVF had treatment emergent resistance mutations in RT or PRO. There was also no treatment emergent phenotypic resistance to NRTI, NNRTI, or PRO in any of the six subjects with PDVF. INI genotype and phenotype was determined at Day 1 and PDVF for all three subjects on CAB, but was unavailable at PDVF for two of the subjects on EFV. None of the three subjects on CAB had treatment emergent IN substitutions or treatment emergent phenotypic INI resistance. The one subject with IN genotype and phenotype at PVDF on EFV also had no treatment emergent IN substitutions or treatment emergent phenotypic INI resistance.

There were five subjects with PDVF in the maintenance phase through Week 96; two on CAB 10 mg + RPV, one on CAB 30 mg + RPV and two on EFV + TDF/FTC. One subject on 10 mg CAB + RPV had treatment emergent RPV resistance mutations K101K/E and E138E/A with accompanying 4.6 FC to RPV. The other subject with PDVF on 10 mg CAB + RPV was on an extreme calorie restricted diet that may have reduced CAB and RPV levels by lower than half of the expected. As a result, treatment emergent RPV resistant mutation E138Q and IN resistance mutation Q148R were observed, resulting in slightly elevated FC against both CAB and RPV. IN Q148R causes high level resistance to RAL and EVG, but no change in DTG IC50. The slight increase in CAB IC50 observed with this sample is consistent with that observed using site directed mutants. Interestingly, the IN RC at PDVF was extremely low, just 8.1%. It is unlikely that this mutation would remain once the selective pressure of CAB is removed.

Six subjects were inadvertently enrolled in this study in spite of having the primary RPV resistance mutation E138A at screening (discovered during Week 48 analysis). Two subjects were randomized to 10 mg CAB, two subjects were randomized to 60 mg CAB, and two subjects were randomized to EFV (both receiving ABC/3TC). All six subjects reached <50 c/mL HIV-1 RNA by Week 2 (10 mg CAB), 8 (60 mg CAB) or 12 (EFV) and remained at <50 c/mL HIV-1 RNA through Week 96. E138A is listed as a polymorphism in the Stanford Database, present in as many as 5% of antiretroviral naïve subjects. The RPV prescribing information states that E138A may reduce the activity of RPV.

Three subjects had PDVF after Week 96. None selected for IN resistance mutations, and only one selected for NNRTI resistance mutations with accompanying RPV resistance.

4.2.2.2.7. Conclusions

- Overall, there was a low rate of PDVF during the Induction Phase, with 3 of 181 (<2%) of subjects meeting PDVF in the CAB treatment arms and 4 of 62 subjects (6%) meeting PDVF in the EFV treatment arm.

- There were no treatment emergent resistance mutations, nor phenotypic resistance, in any of the subjects with PDVF during the Induction Phase.

- There were five subjects with PDVF during the Maintenance Phase through Week 96 including two on 10 mg CAB + RPV, one on 30 mg CAB + RPV, and two on EFV + TDF/FTC.

- One subject on 10 mg CAB + RPV had treatment emergent NNRTI resistance mutations K101K/E and E138E/A with accompanying 4.6 FC to RPV at Week 72. Treatment emergent NNRTI (E138Q) and IN (Q148R) resistance mutations were observed in one subject with PDVF at Week 48 on 10 mg CAB + RPV. This subject had CAB and RPV exposures <50% of the expected concentrations.

- Three additional subjects had PDVF between Weeks 96 and 144. Only one had increased RPV FC. None of the three had increased CAB FC.

4.2.2.2.8. PDVFs post Week 144

There were two subjects in LATTE (LAI116482) with PDVF since Week 144, Subject [redacted] and Subject [redacted] (2018N393939_00). The virology data for these two subjects were obtained from Monogram reports.

Subject [redacted], originally randomized to oral 10 mg CAB + RPV had 21,892 c/mL HIV-1 RNA at Day 1. The HIV-1 RNA was <50 c/mL from Week 2 through Week 108 (with a single blip of 58 c/mL HIV-1 RNA at Week 60. This subject had Suspected Virologic Failure at Weeks 132 (294 c/mL HIV-1 RNA), 144 (270 c/mL HIV-1 RNA), and 168 (201 c/mL HIV-1 RNA) without confirmation. The HIV-1 RNA was 243 c/mL at Week 180 which was confirmed at Week 192 with 1748 c/mL HIV-1 RNA.

Genotype and phenotype were determined at Weeks 132, 144, 180 (PDVF), 192 (Table 59).This subject, who is from the US, has Subtype B virus, selected for RPV (K101E) and CAB (E138K, Q148R) resistance mutations by Week 132. At Week 180, Integrase mutation G140A was selected, which was maintained at Week 192 (Table 59).

Table 59 Phenotypic and Genotypic Analysis of Samples from Subject [redacted]

Visit	HIV-1 RNA (c/mL)	NRTI	NNRTI	Integrase
Day 1	21,892	WT	WT 1.58 FC to RPV	WT 1.17 FC to CAB
Week 132	294	WT	K101E 17 FC to RPV	E138K, Q148R 6.56 FC to CAB
Week 144	270	WT	K101E 19 FC to RPV	E138K, Q148R 7.58 FC to CAB
Week 180 PDVF	243	WT	K101E 21 FC to RPV	E138K, G140A, Q148R 116 FC to CAB RC = 28%
Week 192	1748	WT	K101E 21 FC to RPV	E138K, G140A, Q148R 103 FC to CAB RC = 21%

Data Source: GSK Document No. 2019N404586_00, Listings 12.2, 12.4, and 12.5.

Subject [redacted], originally randomized to oral 60 mg CAB + RPV had 18,787 c/mL RNA at Day 1. HIV-1 RNA was <50 c/mL from Week 2 through Week 204. This subject had suspected virologic failure at Week 216 that wasn't confirmed. This subject had a second suspected virologic failure at Week 264 (656 c/mL HIV-1 RNA) that was confirmed at Week 276 (304 c/mL HIV-1 RNA). Day 1 PhenosenseGT has no NRTI, NNRTI, PI or INI resistance mutations. Week 264 had NNRTI Resistance mutations K101K/E and E138E/K with 1.77 FC to RPV. Week 264 has G140S and Q148R in the Integrase gene with 9.84 FC to CAB (>MAX to Raltegravir). Subject had Subtype B virus.

Module 2.7.3

Summary of Clinical Efficacy

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir sulfate
ADR	Adverse drug reaction
AE	Adverse event
ANCOVA	Analysis of Covariance
ART	Antiretroviral treatment
ARV	Antiretroviral
ATV	Atazanavir
BMI	Body mass index
CAB	Cabotegravir
CAR	Continued/current antiretroviral regimen
CD4+	Cluster of differentiation antigen 4
CD8+	Cluster of differentiation antigen 8
CDC	Centers for Disease Control (US)
CI	Confidence interval
CMH	Cochran-Mantel Haenszel
c/mL	Copies per milliliter
CRF	Case Report Form
CSR	Clinical study report
CVF	Confirmed Virologic Failure
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir
ECG	Echocardiogram
eCRF	Electronic Case Report Form
EFV	Efavirenz
EVG	Elvitegravir
Emax	Maximum effect
FC	Fold change
FDC	Fixed-dose combination
FTC	Emtricitabine
GHO	Global Health Outcomes
GSK	GlaxoSmithKline
HAT-QoL	HIV/AIDS-Targeted Quality of Life Instrument
HIV-1	Human Immunodeficiency Virus Type 1
HIVTSQc	HIV Treatment Satisfaction Questionnaire (change)
HIVTSQs	HIV Treatment Satisfaction Questionnaire (status)
INSTI	Integrase strand transfer inhibitor
ISE	Integrated summary of efficacy
ISS	Integrated summary of safety
IQR	Interquartile range
ITT-E	Intent-to-treat Exposed
ITT-ME	Intent-to-treat Exposed-Maintenance Exposed
ITTE-LA	Intent-to-treat Exposed-Long-acting Injectable
IM	Intramuscular
Janssen	Janssen Sciences Ireland UC

LA	Long-acting Injectable, Extended Release Suspension for Injection, or Prolonged Release Suspension for Injection
LOCF	Last observation carried forward
MCID	Minimal Clinical Important Difference
MVA	Multivariable analysis
ND	Not determined
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
OLI	Oral lead-in
OR	Odds ratio
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamic
PI	Protease inhibitor
PIN	Perception of Injection
PK	Pharmacokinetic
PP	Per-protocol
PRO	Patient Reported Outcomes
PDVF	Protocol Defined Virologic Failure
Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
r	Ritonavir
RAL	Raltegravir
RAM	Resistance-associated mutation
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
RPV	Rilpivirine
SCSR	Synoptic clinical study report
SD	Standard deviation
SDAP	Summary Document Analysis Plan
SOC	Standard of Care
SRDP	Study Results Dissemination Plan
SVF	Suspected virologic failure
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxil fumarate
UK	United Kingdom
US	United States
ViiV Healthcare	ViiV Healthcare Company
ZDV	Zidovudine

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1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

The purpose of this summary is to provide evidence to support the efficacy of CAB, as part of a new monthly or every 2 months 2-drug dosing regimen with RPV, for the treatment of HIV-1 infection in adults. This document summarizes Week 48 efficacy findings from 2 randomized, controlled Phase III studies and 1 randomized, controlled Phase IIIb study of CAB + RPV for the treatment of HIV-1 infection in ART-naïve and ART-experienced adults with no known or suspected resistance to either CAB or RPV.

1.1. Current Therapies and Unmet Clinical Needs

See Clinical Overview m2.5 for a description of current available therapies for the treatment of HIV-1 infection in adults, and a summary of unmet clinical needs in this patient population.

1.2. Overview of the Clinical Development Program

ViiV Healthcare in partnership with Janssen are developing the CAB + RPV regimen for the treatment of HIV-1 infection. ViiV Healthcare is the Sponsor of the CAB + RPV clinical studies, in which both oral and LA injectable CAB + RPV have been evaluated. The oral formulations were evaluated for both lead-in treatment to confirm tolerability prior to LA injections and for oral therapy to cover missed injection visits. This summary document focuses on the CAB data to support the efficacy of CAB for the treatment of HIV-1 infection, as part of a 2-drug regimen with RPV.

1.2.1. Pivotal Phase III Efficacy Studies

Study 201585 is a Phase III trial in HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ART regimen designed to demonstrate non-inferior antiviral activity of switching to CAB + RPV Q4W compared with remaining on CAR.

Study 201584 is a Phase III trial in HIV-1-infected ART-naïve adult subjects designed to demonstrate non-inferior antiviral activity of switching to CAB + RPV Q4W after an Induction Phase of ABC/DTG/3TC compared with remaining on CAR (ABC/DTG/3TC).

Pooled results from Study 201584 and Study 201585 Week 48 are presented in this module. Study 201584 and Study 201585 evaluate the Q4W (monthly) CAB + RPV dosing regimen compared with oral standard of care treatment.

Additional details of the study design for the Phase III studies are provided in Section 1.4. A brief summary of these studies also is provided in the Appendix (Section 7).

1.2.2. Phase IIIb Efficacy Study

Study 207966 is a Phase IIIb trial in HIV-1-infected ART-experienced adult subjects designed to demonstrate the non-inferior antiviral activity of CAB + RPV Q8W compared with CAB + RPV Q4W. Enrolled subjects were virologically suppressed after their participation in Study 201585 or were otherwise suppressed for at least 6 months while receiving oral standard of care therapy.

Week 48 data from Study 207966 are not pooled with the Week 48 data from Studies 201584 and 201585.

1.2.3. Phase II Studies

Study LAI116482 is a Phase IIb dose-ranging trial in HIV-1-infected ART-naïve adult subjects evaluating oral CAB in combination with oral RPV compared with EFV + 2 NRTIs.

Study 200056 is a Phase IIb dose-ranging trial in HIV-1-infected ART-naïve adult subjects evaluating CAB LA in combination with RPV LA following a period of Induction, compared with remaining on oral CAB in combination with 2 NRTIs, to maintain virologic suppression.

Additional details of the study design for these 2 studies are provided in Section 1.4. A brief summary of these studies is provided in the Appendix (Section 7).

1.3. Rationale for Dose Selection

The monthly dosing regimen is the same as that administered in Phase III Studies 201584 and 201585. The CAB + RPV Q4W dose for the Phase III studies was selected on the basis of 2 Phase IIb trials (LAI116482 for oral CAB and RPV, and Study 200056 for CAB LA and RPV LA) (see Section 4.1).

The every 2 months dosing regimen is the same dosing regimen used in Phase IIIb Study 207966. The Q8W CAB + RPV dose for Phase IIIb was selected on the basis of Week 96 results from Phase IIb Study 200056 (see Section 4.1.2.3).

1.3.1. CAB Oral

An OLI of CAB + RPV was included in Studies 201584, 201585, and 207966 to evaluate the potential in each subject for ADRs which would preclude IM dosing. The combination of oral CAB (10, 30, or 60 mg once daily) and oral RPV (25 mg once daily) was administered to HIV-infected subjects in Study LAI116482 (Phase IIb). All oral doses of CAB maintained durable suppression of HIV infection with a 2-drug (CAB + RPV) continuation regimen, and CAB was well tolerated across all doses studied. CAB 30 mg once daily was selected as OLI for Studies 200056, 201584, 201585, and 207966, based on PK, safety, and efficacy results of Study LAI116482. See m2.7.1 for additional details on oral dose selection.

1.3.2. CAB LA

Based on the efficacy and tolerability of CAB + RPV at Week 48 in Phase 2b Study 200056, Q4W LA dosing was selected for further investigation in Phase III Studies 201584 and 201585. The efficacy of the CAB + RPV Q4W regimen was established in the Phase III studies, where once monthly CAB + RPV was non-inferior to CAR in maintaining virologic suppression in HIV-1-infected subjects, with few cases of plasma HIV-1 RNA ≥50 c/mL (via Snapshot) observed in either arm at Week 48. When transitioning from oral SOC, initial injections of CAB + RPV were administered following a one-month lead-in of oral CAB + RPV once daily in all Phase III studies.

Based on the efficacy and tolerability of CAB + RPV at Week 96 in Study 200056, Q8W LA dosing was selected for further investigation in Phase IIIb Study 207966. In Study 200056, 94% of subjects on the CAB + RPV Q8W dosing arm and 87% of subjects on the Q4W dosing arm maintained virologic suppression (HIV-1 RNA <50 c/mL per Snapshot at Week 96), with both regimens exhibiting acceptable tolerability [GSK Doc. No. 2017N337118_00].

Following Phase II, the initiation dose strategy was optimized for the Phase III and IIIb studies to align dosing for both compounds and minimize the number of injections needed to achieve therapeutic plasma concentrations. For both Q4W and Q8W dosing, the CAB LA initiation dose was decreased from 800 mg to 600 mg. For Q4W dosing, the RPV LA initiation dose was increased from 600 mg to 900 mg. For Q8W dosing, RPV LA 900 mg dose was administered 4 weeks after the initial dose, in combination with CAB LA 600 mg. These changes did not alter steady state exposures.

The maintenance dose evaluated for Q4W dosing was CAB LA 400 mg + RPV LA 600 mg while that of Q8W dosing was CAB LA 600 mg + RPV LA 900 mg. Only Q4W dosing was evaluated in Phase III Studies 201584 and 201585, while both Q4W and Q8W dosing are being investigated in Phase IIIb Study 207966.

1.4. Design of Efficacy Studies and Subject Population

Both Phase III, ongoing, pivotal efficacy trials, Studies 201584 and 201585, are randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority trials (Table 1). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

The Phase IIIb Study 207966 is an ongoing, randomized, multicenter, parallel-group, open-label, non-inferiority trial (Table 1). The majority of subjects in Study 207966 were planned to be enrolled from the ongoing Phase III Study 201585 (see Section 1.4). Results from the Week 48 primary analysis of Study 207966 are submitted in this application.

Table 1 Summary of Key Clinical Studies Evaluating Efficacy

Study	Study Design	Population	Treatment details
201584 (FLAIR) Status: Ongoing; Week 96 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on ABC/DTG/3TC	HIV-1-infected ART-naïve adult subjects	**Induction Phase (20 weeks):** Oral ABC/DTG/3TC FDC (NRTI substitution allowed) **Maintenance Phase (100 weeks):** CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs) **Extension Phase and beyond:** Details are provided in the CSR.
201585 (ATLAS) Status: Ongoing; Week 48 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen	HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (52 Weeks):** CAB + RPV group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the first IM dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) Control group: 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI. **Extension Phase and beyond:** Details are provided in the CSR.
207966 (ATLAS-2M) Status: Ongoing; Week 48 CSR completed	Open-label, randomized, Phase IIIb trial to demonstrate non-inferiority of LA CAB + LA RPV Q8W compared with LA CAB + LA RPV Q4W	HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (100 Weeks):** CAB + RPV Q4W group: CAB LA 600 mg + RPV LA 900 mg initiation dose*, CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) CAB + RPV Q8W group: CAB LA 600 mg + RPV LA 900 mg initiation dose*, CAB LA 600 mg + RPV LA 900 mg second initiation dose* administered 4 weeks after the initial dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks (±7 days) *Note: Subjects were either transitioned from Study 201585 (CAB + RPV Q4W or SOC) or from their current SOC. Those transitioning from SOC received oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks followed by appropriate initiation doses. Those transitioning from CAB + RPV Q4W received OLI and

Study	Study Design	Population	Treatment details
			initiation doses during their participation in Study 201585 and started maintenance doses on Day 1 of Study 207966 according to their randomization assignment. **Extension Phase and beyond:** Details are provided in the CSR
200056 (LATTE-2) Status: Ongoing; Week 96 CSR completed, Week 160 CSR completed	Open-label, randomized, dose ranging, Phase IIb trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression	HIV-1-infected ART-naïve adult subjects	**Induction Phase (20 weeks):** Oral CAB 30 mg + ABC/3TC once daily. With oral RPV 25 mg once daily for last 4 weeks **Maintenance Phase (96 weeks):** CAB + RPV Q4W group: CAB LA 800 mg + RPV LA 600 mg initiation dose, CAB LA 400 mg + RPV LA 600 mg every 4 weeks CAB + RPV Q8W group: CAB LA 800 mg + RPV LA 900 mg initiation dose, CAB LA 600 mg second dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks Control group: Oral CAB 30 mg + ABC/3TC once daily **Extension Phase and beyond**: Details are provided in the CSR.
LAI116482 (LATTE) Status: Completed; Week 96 CSR completed; Week 144 SCSR completed	Randomized, partially blind dose ranging, Phase IIb trial evaluating oral CAB in combination with oral RPV	HIV-1-infected ART-naïve adult subjects	**Induction Phase (24 weeks):** CAB group: Oral CAB 10, 30, or 60 mg + ABC/3TC or TDF/FTC once daily Control group: EFV + ABC/3TC or TDF/FTC **Maintenance Phase (72 weeks):** CAB + RPV group: Oral CAB 10, 30, or 60 mg + oral RPV 25 mg once daily Control group: EFV + ABC/3TC or TDF/FTC **Open-Label Phase (post 96 weeks)**: CAB 30 mg + RPV 25 mg

1.5. Efficacy Endpoints

1.5.1. Pivotal Efficacy Studies 201584 and 201585

The primary efficacy endpoint for the 2 pivotal studies is the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (i.e., virologic failure) at Week 48 using the Snapshot algorithm for the ITT-E Population.

The relevant secondary efficacy endpoints for the first 48 weeks of the studies included:

- The proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Algorithm);

- The proportion of subjects with CVF at Week 48;
- Absolute values and changes from Baseline in CD4+ cell counts over time including Week 48;
- Subgroup Analysis: Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (e.g., by age, sex at birth, BMI);
- Subgroup Analysis: Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (e.g., by age, sex at birth, BMI).

In addition, relevant GHO secondary endpoints included the following:

- Change from Baseline in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Week 24 and Week 44.
- For Study 201584, change in treatment satisfaction over time (using the HIVTSQc) at Week 48 (or Withdrawal).
- Change from Baseline in treatment acceptance at Weeks 8, 24, and 48 using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire.

1.5.2. Phase IIIb Study 207966

The primary efficacy endpoint in Phase IIIb Study 207966 is the proportion of subjects with plasma HIV-RNA ≥50 c/mL as per Snapshot Algorithm at Week 48 (ITT-E population).

Additional relevant efficacy endpoints included:

- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot Algorithm (ITT-E population);
- The proportion of subjects with protocol-defined CVF through Week 48;
- Absolute values and changes from Baseline in viral load and CD4+ cell counts over time including Week 48;
- Subgroup analyses: Proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 (e.g., by age, gender (Sex at birth), BMI, race, Baseline CD4+, type of oral treatment [NNRTI, PI, or INSTI], duration of prior CAB LA and RPV LA exposure (0 weeks, 1-24 weeks, >24 weeks) and with protocol-defined CVF over time including Week 48;
- Subgroup analyses: Change from Baseline in CD4+ cell counts by subgroups at Week 48.

In addition, relevant GHO secondary endpoints included:

- Change from Baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIVTSQs at Week 24 and 48, (or Withdrawal);
- Change in treatment satisfaction over time (using the HIVTSQc) at Week 48 (or Withdrawal);

- Preference for CAB LA + RPV LA Q8W or CAB LA + RPV LA Q4W compared with oral ARV and preference for CAB LA + RPV LA Q8W compared with CAB LA + RPV LA Q4W assessed using a preference questionnaire at Week 48 (or Withdrawal).

1.6. Statistical Considerations

1.6.1. Pivotal Efficacy Studies: 201584 and 201585

Details of the statistical analysis methods for the individual studies are found in the individual study RAPs and a brief description is provided in this Section. Statistical methods for the pooled analysis are found in the SDAP and are also described in this Section.

1.6.1.1. Sample Size

Studies 201584 and 201585 were designed to show that the antiviral effect of CAB + RPV regimen is non-inferior to CAR at Week 48 of continuation treatment based on a 6% non-inferiority margin in each individual study and a 4% non-inferiority margin for the pooled analysis of data from each study.

For the pooled analysis, non-inferiority of Pooled CAB + RPV compared with CAR in the proportion of subjects in the ITT-E population with plasma HIV-1 RNA ≥50 c/mL at Week 48 (per the Snapshot Algorithm) can be concluded if the upper bound of a 2-sided 95% confidence interval for the difference in proportions between the 2 treatment arms ([Pooled CAB + RPV] – CAR) is less than 4%.

If f_{la} is the Snapshot failure rate for the Pooled CAB + RPV group and f_c is the Snapshot failure rate for the Pooled CAR group, then the hypotheses can be written as follows:

$$H0: f_{la} - f_c \geq 4\% \qquad H1: f_{la} - f_c < 4\%$$

Each study was designed to randomize approximately 285 subjects per group into the Maintenance Phase at Day 1 (i.e., Baseline) for a combined sample size from both studies of 570 pooled subjects per group. Assuming the true proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL was 3% for the Pooled CAB + RPV group and 2% for the Pooled CAR group, a non-inferiority margin of 4%, and a 2.5% 1-sided significance level, the combined sample size provided 90% power to show non-inferiority for the proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48 in the pooled analysis.

1.6.1.2. Rationale for Non-Inferiority Margin

These non-inferiority margins were chosen in consideration of the FDA 2015 guidance document [FDA, 2015], which was the most current regulatory guidance from either the EMA or FDA and included specific recommendations regarding switch studies. It suggested that margins in the neighborhood of 4% were clinically tolerable, with typical observed rates of virological failure ranging from 1 to 3%.

As Studies 201584 and 201585 were not sufficiently powered individually to rule out 4% virologic failure (HIV-1 RNA ≥50 c/mL per Snapshot algorithm) in excess, the 6% margin chosen in each study can be viewed as defining criteria for assessing the consistency of the study-specific results prior to integration of the studies in the pooled analysis. Assuming an observed control failure rate of 2%, then non-inferiority would be shown in an individual study using a 6% margin if the observed CAB + RPV failure rate was less than 5% (that is, if the observed treatment difference was less than 3 percentage points). Accordingly, if the individual studies were successful in ruling out a 6% margin, the observed results were expected to be similar and reasonable to integrate for the purposes of the primary efficacy assessment based on the pooled analysis. In addition, a virologic failure rate in this range may be clinically tolerable given the CAB + RPV regimen may offer important advantages over standard 3-drug oral regimens such as improved adherence and treatment satisfaction in virologically-suppressed subjects. In addition, the 2-drug regimen of CAB + RPV has the advantage of being NRTI sparing. Therefore, 6% was a reasonable non-inferiority margin for the individual studies, with a more stringent 4% margin applied for the pooled analysis.

1.6.1.3. Analysis Populations

The ITT-E population will consist of all randomly assigned subjects who receive at least 1 dose of study drug. Subjects will be assessed according to their randomized treatment, regardless of the treatment they received. The population used in the primary efficacy analysis will be the ITT-E population.

The PP Population will consist of all subjects in the ITT-E Population with the exception of major protocol violators. The PP Population will be used for sensitivity analysis of the primary endpoint.

The ITT-E population and PP Population for the pooled analyses are the combined ITT-E populations and PP populations of the 2 individual studies. There is no definition change in any of these populations.

The CVF Population consists of subjects who met CVF defined as 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

1.6.1.4. Statistical Analysis Methods

Subjects in Study 201585 were stably suppressed for at least 6 months prior to study entry while subjects in Study 201584 were stably suppressed prior to randomization. Therefore, in both studies, the primary analysis occurred in a switch population and given this similarity in the study populations during the Maintenance phase, along with the similarity of the study designs (Table 1), the efficacy data have been pooled. The primary pooled analyses were based on the ITT-E population using the Snapshot dataset.

For Study 201584, Induction Baseline (Week -20) refers to assessments occurring at or before Week -20 prior to subjects receiving CAR (ABC/DTG/3TC). For both Study 201584 and Study 201585, Baseline refers to assessments occurring at or before randomization, or Day 1.

For the primary comparison, adjusted estimates of the difference in the proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48 between the 2 pooled treatment groups were presented along with 2-sided 95% CIs based on a stratified analysis using CMH weights.

The primary analysis was stratified according to the followed 10 strata, formed by the combination of randomization stratification factors within each study;

- 4 strata from Study 201584 obtained from the joint classification by Induction Baseline (Week -20) HIV-1 RNA (<100,000 c/mL vs. ≥100,000 c/mL) and sex at birth (Male vs. Female).

- 6 strata from Study 201585 obtained from the joint classification by Baseline Third Agent Class (PI, INSTI, or NNRTI) and sex at birth (Male vs. Female).

A sensitivity analysis was also conducted which stratified by 4 strata obtained from the joint classification by Study (201584, 201585) and sex at birth (Male, Female).

The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 groups.

The weighted least squares chi-squared statistic [Fleiss, 1981] was used to test for treatment difference homogeneity across 4 analysis strata obtained from the joint classification by study and sex at birth. Following Lui and Kelly [Lipsitz, 1998], 0.5 was added to each cell in any strata for which the stratum-specific rate estimates of either f_{la} or f_c were 0 or 1, and tests were 1-sided. Tests of homogeneity were assessed at the 1-sided 10% level of significance. Full details of the individual and pooled analyses are contained in the RAP documents for the individual studies and SDAP document for the pooled analysis plan.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

The proportion of virologic failures (HIV-1 RNA ≥50 c/mL per Snapshot algorithm) for each treatment group and the difference between the 2 groups at Week 48 were also summarized by subgroups (including age, sex at birth, and race). The 95% CIs for the differences were calculated using an unconditional exact method with 2 inverted 1-sided tests, separately.

1.6.1.4.1. Statistical Testing Framework for PROs

Across the individual study and pooled analyses, pre-specified tests of hypotheses were performed for the PRO endpoints described in Table 2. A post hoc Bonferroni procedure was used to control type I error at the 5% significance level within each study and within the pooled analysis. The Bonferroni adjusted significance level is such that alpha=0.0029 (0.05/17) for the 17 PROs tested in Study 201585, alpha=0.0027 (0.05/18) for the 18 PROs tested in Study 201584 and alpha=0.0071 (0.05/7) for the 7 PROs tested using the

pooled dataset. The p-values can therefore be judged against the alpha levels in this statistical testing framework.

Table 2 Number of Statistical Test Performed for PRO Endpoints

CAB + RPV compared to CAR	201584	201585	Pooled
HIVTSQs: Change from baseline in Total Score at Week 24 and Week 44	2	2	2
HIVTSQc: Week 48 Total Score	1	0	N/A[a]
PIN (CAB + RPV ONLY): Within arm change from Week 5 to Week 41 and from Week 5 to Week 48 in Acceptance Score	2	2	2
ACCEPT: Change from baseline at Week 8, Week 24 and Week 48 in Acceptance/General Dimension Score	3	3	3
SF-12: Change from baseline at Week 24 and Week 48 in Mental Component Score and Physical Component score	4	4	ND
HAT-QoL: Change from baseline at Week 24 and Week 48 in Life Satisfaction Total Score, HIV Medication Total Score, and Disclosure Worries Total Score	6	6	ND
Total	18	17	7

Note: PIN results are provided within the ISS

a. Only Study 201584 has comparative results, however this table is included in the ISE statistical outputs

1.6.2. Phase IIIb Efficacy Study 207966

Details of the statistical analysis methods for Study 207966 are found in the study RAP and a brief description is provided in this Section. The Week 48 analysis is the primary analysis. A final End-of-Study analysis will be conducted when all subjects have completed the study.

1.6.2.1. Sample Size

Study 207966 planned to randomize approximately 510 subjects per arm. Assuming the true proportion of subjects with HIV-1 RNA ≥50 c/mL is 3% for the Q8W arm and 2% for the Q4W arm, a non-inferiority margin of 4%, and a 2.5% 1-sided significance level, this sample size would provide at least 85% power to show non-inferiority at Week 48 (using unpooled Z test statistic). With this sample size, 90% power would be achieved assuming a 1% treatment difference and true proportions with HIV-1 RNA ≥50 c/mL of 2.63% for the Q8W arm and 1.63% for the Q4W arm.

With 510 subjects per arm and assuming an observed proportion HIV-RNA ≥50 c/mL is 2% for Q4W, the largest observed treatment difference to achieve non-inferiority with respect to a 4% margin is 1.92 percentage points. This equates approximately to observing an excess of 10 subjects on the Q8W arm (10 subjects on Q4W vs. 20 subjects on Q8W).

1.6.2.2. Rationale for Non-Inferiority Margin

A non-inferiority margin of 4% was chosen for the primary analysis in Study 207966 because a Snapshot proportion with HIV-1 RNA ≥50 c/mL at Week 48 in this range is considered clinically tolerable, given the Q8W regimen may offer important advantages over the Q4W regimen such as reduced injection frequency, better adherence and treatment satisfaction. This margin is also in concordance with the current FDA Guidance for Industry [FDA, 2015], which is the most current regulatory guidance from either the EMA or FDA and includes specific recommendations regarding switch studies.

A key secondary analysis evaluated the proportion of subjects with HIV-1 RNA <50 c/mL (according to the Snapshot Algorithm) at Week 48 for the ITT-E population. Subjects with a last available HIV-1 RNA measurement <50 c/mL while the subject was on treatment within the analysis visit window of interest are classified as responders; subjects without evaluable HIV-1 RNA data for the visit of interest or who changed treatment not permitted per protocol before the analysis window are considered non-responders. Full details on the Snapshot Algorithm for computation of the proportion with HIV-1 RNA <50 c/mL is provided in the RAP. The adjusted difference between the randomized arms for the proportions (Q8W – Q4W) and its confidence interval was calculated according to a stratified analysis with CMH weights, as described for the primary endpoint. A non-inferiority margin of -10% was used for this secondary comparison, where if the lower limit of the 95% CI of the difference between the rates (Q8W – Q4W) is greater than -10%, non-inferiority is demonstrated.

1.6.2.3. Analysis Populations

The **ITT-E Population** will consist of all randomly assigned subjects who receive at least 1 dose of study drug. Subjects will be assessed according to their randomized treatment, regardless of the treatment they received. The population used in the primary efficacy analysis was the ITT-E population.

The **PP Population** consists of all subjects in the ITT-E Population with the exception of major protocol violators. The PP Population was used for sensitivity analysis of the primary endpoint.

The **CVF Population** consists of subjects who met CVF defined as 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

1.6.2.4. Statistical Analysis Methods

To evaluate the objectives of the protocol, at least 3 analyses were planned after all subjects completed their visits at Week 24, Week 48, and Week 96. Week 48 is the primary analysis. A final End of Study analysis will be conducted when all subjects have completed the study. Full details of the Week 24, Week 48, Week 96, and End of Study analyses are provided in the RAP. Prior to Week 48 analysis being completed, the Week 24 results were restricted to only those study team members and GSK/ViiV Healthcare senior management who needed to be involved in the analysis and interpretation of the results for reporting to regulatory authorities. Details on protection

against operational bias for the Week 48 analysis are documented in the Blinded Team Operating Principles for Study 207966. There was no planned hypothesis testing on the treatment difference at Week 24 and no changes to study conduct were made based on the Week 24 results.

1.6.2.4.1. Efficacy Analysis

For the primary efficacy analysis, virologic outcome for each subject in the ITT-E Population was calculated according to the Snapshot Algorithm. The primary analysis at Week 48 took place after the last subject had their Week 48 viral load assessed, including a retest if required. As defined by Snapshot, HIV-1 RNA ≥50 c/mL is determined by the last available HIV-1 RNA measurement while the subject was on treatment within the analysis visit window of interest. In addition, subjects without evaluable HIV-1 RNA data for the visit of interest and who discontinued from the Maintenance Phase for reasons not related to adverse events with HIV-1 RNA result at the time of discontinuation ≥50 c/mL or who changed study treatment not permitted per protocol before the analysis window were classified as having HIV-1 RNA ≥50 c/mL.

For the primary efficacy analysis, the adjusted difference between the randomized arms for the proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48 (per Snapshot) and its confidence interval was calculated according to a stratified analysis with CMH weights. This analysis adjusts for the randomization strata (rederived for analysis to correct for stratification errors) according to prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks). The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in proportion between the two arms.

The weighted least squares chi-squared statistic [Fleiss, 1981] was used to assess evidence of treatment difference heterogeneity across strata. Following Lui and Kelly [Lui, 2000], 0.50 was added to each cell in any strata for which the stratum-specific rate estimates of either f_{Q8W} or f_{Q4W} were 0 or 1. Any heterogeneity found to be statistically significant was explored. Stratum-specific analyses were also provided. Investigation of heterogeneity was confined to the primary endpoint. Tests of homogeneity were assessed at the one-sided 10% level of significance. Full details are provided in the RAP.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

On-treatment data collected from extra visits within a window were included in the derivation of the Snapshot response/failure but summary tables using observed case datasets only used the data captured closest to the target visit date. Detailed explanations of the derivation of visit windows are included in the RAP.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

Brief descriptions and key results for the individual Phase III studies, the Phase IIIb study, and the Phase II studies are summarized in Appendix Table 1, and Appendix Table 2.

2.1. Study 201584

The data from Study 201584 indicate that monthly CAB + RPV is effective in maintaining the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to CAR at Week 48.

Of the subjects that completed the Induction Phase, a total of 566 subjects were randomized (1:1) and treated with CAB+ RPV Q4W (n=283) or continued CAR (n=283) (Table 3). Similar proportions of subjects in each treatment group withdrew from the study (CAB + RPV Q4W: 9%; CAR: 8%). The most frequent primary reason for withdrawal was adverse events (CAB + RPV Q4W: 3%; CAR: 1%).

Overall, in the ITT-E population, 2.1% of subjects in the CAB + RPV Q4W group and 2.5% of subjects in the CAR group met the 'virologic failure' primary efficacy endpoint of plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm) (Table 7). Based on a 6% non-inferiority margin, the efficacy analysis demonstrated that CAB + RPV Q4W is non-inferior to CAR at Week 48 because the upper bound of the 95% CI for the adjusted treatment difference [-0.4 (-2.8, 2.1)] is less than 6%. The results for the PP Population were consistent with those from the ITT-E (primary) population. Treatment differences across stratification factors (Baseline HIV-1 RNA and sex at birth) and across additional subgroup analyses (age, race, Baseline CD4+ count, and Baseline CDC stage of disease) are consistent with the finding of non-inferiority observed in the overall population analysis of the primary endpoint (HIV-1 RNA ≥50 c/mL at Week 48).

Once-monthly CAB + RPV continued to be non-inferior to CAR in maintaining virologic suppression at Week 96 in this study, with few subjects having plasma HIV-1 RNA ≥50 c/mL (ITT-E and PP) (see Section 5.1 for summary of efficacy results at Week 96).

2.2. Study 201585

The data from Study 201585 indicate that monthly CAB + RPV is effective in maintaining the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to CAR at Week 48.

A total of 618 subjects were randomized (1:1) to CAB + RPV Q4W (n=310) or to continue CAR (n=308) (Table 3, Section 3.1). Two subjects randomized to the Q4W group did not receive study treatment. Similar proportions of subjects in each treatment group withdrew from the study (CAB+ RPV Q4W: 8%; CAR: 6%). The most frequent primary reason for withdrawal was adverse events (CAB+ RPV Q4W: 4%; CAR: 2%).

Overall, in the ITT-E population, 1.6% of subjects in the CAB + RPV Q4W group and 1.0% of subjects in the CAR group met the 'virologic failure' primary efficacy endpoint

of plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm) (Table 7). Based on a 6% non-inferiority margin, the efficacy analysis demonstrated that CAB + RPV Q4W is non-inferior to CAR at Week 48 because the upper bound of the 95% CI for the adjusted treatment difference 0.7 (-1.2, 2.5)] is less than 6%. The results for the PP Population were consistent with those from the ITT-E (primary) population. Treatment differences across stratification factors (Baseline third agent treatment class and sex at birth) and across additional subgroup analyses (age, race, country, Baseline viral load, Baseline CD4+ count, and Baseline CDC stage of disease) are consistent with the finding of non-inferiority observed in the overall population analysis of the primary endpoint (HIV-1 RNA ≥50 c/mL at Week 48).

2.3. Study 207966

The data from Study 207966 indicate that every 2 months dosing with CAB + RPV is effective in the suppression of plasma HIV-1 RNA (<50 c/mL) and non-inferior to monthly CAB+ RPV at Week 48.

A total of 1049 subjects were randomized (1:1) and treated with CAB + RPV Q8W (n=524) or CAB + RPV Q4W (n=525) (Table 3). Four subjects were randomized but not treated. Among the 1045 subjects who were treated, the duration of exposure was ≥52 weeks for 443/522 (85%) of subjects in the Q8W group and 480/523 (92%) of subjects in the Q4W group. Similar proportions of subjects in each treatment group withdrew from the study (CAB + RPV Q8W: 7%; CAB + RPV Q4W: 8%). Overall, the most common reason for withdrawal was Withdrawal by Subject [27 subjects: Q8W 6 subjects (1%); Q4W 21 subjects (4%)].

Overall, in the ITT-E population, 1.7% of subjects in the CAB + RPV Q8W group and 1.0% of subjects in the CAB + RPV Q4W group met the primary efficacy endpoint of plasma HIV-1 RNA ≥50 c/mL at Week 48 (Table 7). Based on a 4% non-inferiority margin, CAB + RPV Q8W is non-inferior to CAB + RPV Q4W at Week 48 because the upper bound of the 95% CI for the adjusted treatment difference (0.8 [-0.6, 2.2]) is less than 4%. The results for the PP Population were consistent with those from the ITT-E (primary) population.

Treatment differences across the stratification factor (prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks) and across additional subgroup analyses (including age, race, Baseline viral load, Baseline CD4+, Baseline CDC stage of disease, participating countries, and type of oral treatment at Baseline [NNRTI, PI, or INSTI]) are consistent with the finding of non-inferiority observed in the overall population analysis of the primary endpoint (HIV-1 RNA ≥50 c/mL at Week 48) (Table 21). The proportion of Snapshot virologic failures (HIV-1 RNA ≥50 c/mL) was numerically higher in the Q8W arm (5/137, 3.6%) compared with the Q4W arm (0/143, 0%) in female subjects, as well as in subjects with a BMI ≥30 kg/m^2 (Q8W 6/113, 5.3%; Q4W 2/98, 2%); however, ad-hoc heterogeneity tests were not significant. A multivariable logistic regression analysis of subjects in Study 207966 demonstrated that the strongest association of Snapshot HIV-1 RNA ≥50 c/mL was BMI. Not all factors, including the presence of pre-existing resistance mutations and PK levels at the time of failure, were considered in this model. Additionally, Multivariable and Baseline factors analyses were conducted using

data from Studies 201584, 201585, and 207966, and these findings are summarized in Section 4.2.3.

2.4. Study 200056

In Study 200056, at Week 160, 83% of subjects receiving CAB + RPV monthly IM dosing (Q4W) and 90% of subjects receiving CAB + RPV bimonthly dosing (Q8W) maintained virologic suppression (HIV-1 RNA <50 c/mL by the Snapshot algorithm) [GSK Doc. No. 2018N380094_00]. The difference in virologic success was primarily due to non-virologic reasons. Of the 44 subjects in the oral treatment group who opted to switch to CAB + RPV (Q4W or Q8W) at Week 100 (beginning of the Extension phase), 100% (Q4W) and 97% (Q8W) maintained virologic suppression (HIV-1 RNA <50 c/mL) at Week 160. In the Maintenance and Extension periods of this study there have been 3 PDVFs, 2 in the Q8W arm and 1 in the oral CAB arm. No PDVFs were observed in the Q4W arm throughout the study and no additional PDVFs have been observed since Week 48.

2.5. Study LAI116482

In Study LAI116482, at Week 96, 79% (CAB 10 mg group), 85% (CAB 30 mg group), 93% (CAB 60 mg group) and 83% (EFV 600 mg group) of subjects maintained virologic suppression (HIV-1 RNA <50 c/mL) [GSK Doc. No. 2014N216014_00]. After the last subject completed the Week 96 visit the study was unblinded and all subjects, including those in the EFV group, were transitioned to the Sponsor selected regimen of CAB 30 mg + RPV 25 mg. The transition took place between Weeks 108 and 120. There were 9 PDVFs on the CAB arms with 3 occurring between Week 96 and Week 144.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Study Populations

Unless otherwise specified, study population results are presented for randomized subjects in the ITT-E Population.

In both Study 201584 and Study 201585, HIV-1-infected subjects with any evidence of primary resistance based on the presence of any known major INSTI or NNRTI resistance-associated mutation, except for K103N, were excluded.

In Study 201584, Study 201585 and in the pooled analysis, the number of subjects was similar between the treatment groups for each of the study populations analyzed (ITT-E, PP) (Data Source: ISE/ISS Table 1.01). Of the subjects that completed the Induction Phase of Study 201584, 566 subjects were randomized (1:1) and treated with CAB + RPV (n=283) or continued CAR (n=283). In Study 201585, 618 subjects were randomized (1:1) to the CAB+ RPV treatment group (n=310) or continued CAR (n=308). Two subjects in Study 201585 were randomized to the Q4W treatment group but did not receive study treatment.

In Study 207966, the number of subjects was similar between the treatment groups for each of the study populations analyzed (Data Source: GSK Doc. No. 2019N406358_01 Table 1.12). A total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W: 524 subjects; Q4W: 525 subjects) (Data Source: GSK Doc. No. 2019N406358_01 Table 1.12). Four subjects were randomized but did not receive study treatment (2 subjects in each of the Q8W and Q4W groups). A total of 253/1045 (24%) subjects (Q8W, 126 subjects; Q4W, 127 subjects) from the Q4W group of Study 201585 were randomized and treated in Study 207966.

3.2. Subject Disposition

In Study 201584, Study 201585, and the pooled analysis, the number of subjects randomized and treated was similar across the Q4W and CAR treatment groups (Data Source: ISS/ISE Table 1.01). Similar proportions of subjects in each treatment group withdrew from the study, including less than 1% that were lost to follow-up (Table 3).

In Study 207966, the number of subjects randomized and treated was similar across the Q8W and Q4W treatment groups (Data Source: GSK Doc. No. 2019N406358_01 Table 1.12). The proportion of subjects withdrawn during the Maintenance Phase was low and comparable between the 2 treatment groups, and similar to the withdrawal rate observed in the individual and pooled analysis of Studies 201584 and 201585.

Table 3 Summary of Subject Disposition for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E) – Maintenance Phase

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W N = 283	CAR N = 283	CAB + RPV Q4W N = 308	CAR N = 308	CAB + RPV Q4W N = 591	CAR N = 591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Completion Status, n (%)								
Ongoing at time of analysis	258 (91)	261 (92)	1 (<1)	0	259 (44)	261 (44)	486 (93)	481 (92)
Completed	0	0	281 (91)	290 (94)	281 (48)	290 (49)	0	0
Withdrawn	25 (9)	22 (8)	26 (8)	18 (6)	51 (9)	40 (7)	36 (7)	42 (8)
Primary reason[a]/subreason[b] for withdrawal, n (%)								
Adverse Event	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)	12 (2)	13 (2)
Lack of efficacy	5 (2)	3 (1)	3 (<1)	4 (1)	8 (1)	7 (1)	9 (2)	3 (<1)
Protocol defined virologic failure (CVF)	5 (2)[c]	3 (1)	3 (<1)	4 (1)	8 (1)	7 (1)	8 (2)	2 (<1)
Insufficient viral load response	0	0	0	0	0	0	1 (<1)	1 (<1)
Protocol deviation	0	1 (<1)	5 (2)	3 (<1)	5 (<1)	4 (<1)	1 (<1)	1 (<1)
Non-compliance with study treatment	0	0	1 (<1)	0	1 (<1)	0	1 (<1)	0
Non-compliance with protocol procedures	0	0	2 (<1)	2 (<1)	2 (<1)	2 (<1)	1 (<1)	0
Pregnancy	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)[d]	3 (<1)[d]
Prohibited medication use	0	1 (<1)	0	0	0	1 (<1)	0	1 (<1)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W N = 283	CAR N = 283	CAB + RPV Q4W N = 308	CAR N = 308	CAB + RPV Q4W N = 591	CAR N = 591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Subject reached protocol-defined stopping criteria	0	0	1 (<1)	0	1 (<1)	0	0	0
Subject met GSK defined Liver Chemistry Stopping Criteria	0	0	1 (<1)	0	1 (<1)	0	0	0
Lost to follow-up	2 (<1)	2 (<1)	1 (<1)	1 (<1)	3 (<1)	3 (<1)	2 (<1)	0
Physician Decision	2 (<1)	5 (2)	2 (<1)	0	4 (<1)	5 (<1)	5 (<1)	1 (<1)
Pregnancy	0	1 (<1)	2 (<1)	0	2 (<1)	1 (<1)	0	0
Other	2 (<1)[e]	4 (1)[f]	0	0	2 (<1)	4 (1)	5 (<1)[g]	1 (<1)[h]
Withdrawal by Subject	7 (2)	7 (2)	1 (<1)	5 (2)	8 (1)	12 (2)	6 (1)	21 (4)
Frequency of visits	1 (<1)	4 (1)	0	3 (<1)	1 (<1)	7 (1)	3 (<1)	6 (1)
Burden of travel or lack of access to travel	1 (<1)	0	0	0	1 (<1)	0	0	1 (<1)
Subject relocated	1 (<1)	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)	0	5 (<1)
Work schedule[i]	0	0	0	2 (<1)	0	2 (<1)	0	1 (<1)
Intolerability of injections	2 (<1)	0	0	0	2 (<1)	0	1 (<1)	4 (<1)
Subject was incarcerated	1 (<1)	0	0	0	1 (<1)	0	0	1 (<1)
Other, specify	1 (<1)[j]	1 (<1)[k]	0	0	1 (<1)	1 (<1)	3 (<1)[l]	10 (1)[m]

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W N = 283	CAR N = 283	CAB + RPV Q4W N = 308	CAR N = 308	CAB + RPV Q4W N = 591	CAR N = 591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Outcome of Adverse Events Which Lead to Withdrawal, n (%)								
Fatal	0	0	0	1 (<1)[n]	0	1 (<1)	0[o]	0
Non-fatal	9 (3)	4 (1)	13 (4)	4 (1)	22 (4)	8 (1)	12 (2)	13 (2)

Data Source: ISE/ISS Table 1.03, GSK Doc. No. 2019N406358_01 Table 1.4.

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC

a. Subjects may have only 1 primary reason for withdrawal
b. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than one subreason underneath a single primary reason. Subjects are not required to indicate subreasons.
c. This includes 1 subject who did not have confirmation of protocol defined virologic failure-- the subreason for discontinuation was updated post database lock from "PDVF" to "Investigator discretion" with a comment of "suspicion of virologic failure".
d. Protocol-specified withdrawal criteria met.
e. 1 Subject needed at least 6 months anti-coagulation for thrombosis; 1 Subject was unreliable with appointments and frequently rescheduled (Investigator feared prolonged dosing interval with subsequent virologic failure).
f. 2 Subjects for noncompliance with study treatment and protocol procedures; 1 Subject due to the ViiV Healthcare Safety and Labelling Committee decision (subject had acute hepatitis E infection followed by continued cocaine use); 1 Subject did not show up or was late for visits.
g. 1 subject developed resistance to RPV, 1 subject had pulmonary tuberculosis, 1 subject WD per investigator discretion and medical monitor decision due to beta HCG being positive (no confirmation of IU pregnancy), 1 subject was taking ZDV, 3TC, EFV, ABC, ATV, ritonavir before study start and was randomized in error but later WD during oral lead in phase, 1 subject required long-term anticoagulant therapy.
h. WD due to overall status of the subject including subject's significant cardiovascular history.
i. Includes subreasons: "Withdrew consent due to very busy work schedule" (n=1), and "Unable to comply with protocol's visits due to working schedule" (n=1) and withdrew "due to business" (n=1).
j. Pregnancy thoughts in near future
k. Subject decision to stop ABC/DTG/3TC
l. 1 subject planning to become pregnant, 1 subject wanted to switch to a non-integrase inhibitor regimen due to potential weight gain side effect, 1 subject due to burden of procedures.
m. 1 subject with anxiety related to suicidality assessment, 1 subject WD due to new safety updates a concern for patient wanting to have a baby in the future, 3 subjects for "burden of procedures", 1 subject for frequency of injections, 1 subject for depressive syndrome and pain at injection site, 1 subject for family problems, 1 subject WD due to problems with work/study schedule and ISR, 1 subject for planned move to other country.
n. Methamphetamine overdose
o. One death was reported 98 days after the subject's last dose of study drug. The cause of death was sepsis during the long-term follow up phase, as a result of complications of acute pancreatitis during the Maintenance Phase.

3.3. Demographic and Baseline Characteristics

3.3.1. Demographic Characteristics

Demographic characteristics generally were similar across treatment groups in the pooled analysis and individual Studies 201584 and 201585 (Table 4). Of note, 27% and 28% of subjects were women in the pooled analysis in the CAB + RPV and CAR groups, respectively. Further, 17% and 21% of subjects were 50 years of age or older in the pooled analysis in the CAB + RPV and CAR groups, respectively.

In Study 207966, demographic characteristics generally were similar between the 2 treatment groups (Table 4). Although the majority of subjects were male, the study enrolled 27% females (per Sex at Birth). Almost half (46%) of all subjects were aged 35 to <50 years of age, with a median (range) of 42 (19 to 83) years. Further, 27% of subjects were 50 years of age or older in both the Q4W and Q8W groups. The predominant race was White- White/Caucasian/European heritage (72%).

Table 4 Summary of Demographic Characteristics for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Demographic Characteristic	CAB + RPV Q4W N=283	CAR N=283	CAB + RPV Q4W N = 308	CAR N = 308	CAB + RPV Q4W N = 591	CAR N = 591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Age (yrs)								
Mean	35.9	36.0	41.6	43.2	38.9	39.8	42.7	42.3
Standard Deviation	10.17	9.82	9.99	11.43	10.46	11.28	11.16	10.58
Median	34.0	34.0	40.0	43.0	38.0	38.0	42.0	42.0
Min	19	18	21	18	19	18	20	19
Max	68	68	74	82	74	82	83	75
Age, Groups (yrs)								
<35	143 (51)	145 (51)	80 (26)	80 (26)	223 (38)	225 (38)	137 (26)	145 (28)
35 to <50	107 (38)	109 (39)	162 (53)	132 (43)	269 (46)	241 (41)	242 (46)	239 (46)
≥50	33 (12)	29 (10)	66 (21)	96 (31)	99 (17)	125 (21)	143 (27)	139 (27)
Sex at Birth, n (%)								
Female	63 (22)	64 (23)	99 (32)	104 (34)	162 (27)	168 (28)	137 (26)	143 (27)
Male	220 (78)	219 (77)	209 (68)	204 (66)	429 (73)	423 (72)	385 (74)	380 (73)
Height (cm) at Baseline[a]								
Mean	173.6	173.5	172.2	172.5	172.9	173.0	173.0	173.3
Standard Deviation	9.61	8.89	9.41	10.46	9.52	9.74	9.46	9.88
Median	174.0	174.0	173.0	173.0	174.0	173.0	174.0	174.0
Min.	142	151	139	142	139	142	144	134
Max.	203	200	198	196	203	200	200	198
Weight (kg)[a]								
Mean	75.72	75.11	77.69	79.50	76.75	77.40	79.75	80.40
Standard Deviation	14.569	15.668	15.901	17.877	15.297	16.984	16.046	17.406
Median	74.0	74.0	76.00	77.55	75.00	75.20	77.50	78.00
Min	46.0	36.0	41.2	48.2	41.2	36.0	49.0	41.8
Max	125.6	148.0	139.4	162.8	139.4	162.8	142.8	170.1

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Demographic Characteristic	CAB + RPV Q4W N=283	CAR N=283	CAB + RPV Q4W N = 308	CAR N = 308	CAB + RPV Q4W N = 591	CAR N = 591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Body Mass Index (kg/m^2) at Baseline[a]								
Mean	25.109	24.934	26.203	26.742	25.679	25.876	26.677	26.782
Standard Deviation	4.4190	4.8797	5.1022	5.7692	4.8144	5.4330	5.2023	5.7877
Median	24.100	24.000	25.500	25.500	24.900	24.800	25.724	25.923
Min	17.3	12.6	15.30	17.80	15.30	12.60	17.75	16.57
Max	44.9	47.4	50.90	57.70	50.90	57.70	48.27	77.52
Ethnicity, n (%)								
Hispanic / Latino	28 (10)	40 (14)	35 (11)	34 (11)	63 (11)	74 (13)	71 (14)	65 (12)
Not Hispanic / Latino	255 (90)	243 (86)	273 (89)	274 (89)	528 (89)	517 (87)	451 (86)	458 (88)
Race, n (%)								
American Indian or Alaskan Native	3 (1)	6 (2)	8 (3)	8 (3)	11 (2)	14 (2)	17 (3)	11 (2)
Asian-Central/South Asian Heritage	2 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)	1 (<1)	1 (<1)
Asian-East Asian Heritage	1 (<1)	2 (<1)	13 (4)	8 (3)	14 (2)	10 (2)	20 (4)	12 (2)
Asian-Japanese Heritage	8 (3)	12 (4)	0	0	8 (1)	12 (2)	0	2 (<1%)
Asian-South East Asian Heritage	1 (<1)	0	8 (3)	5 (2)	9 (2)	5 (<1)	8 (2)	7 (1)
Black or African American	47 (17)	56 (20)	62 (20)	77 (25)	109 (18)	133 (23)	101 (19)	90 (17)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
White-Arabic/North African Heritage	5 (2)	3 (1)	2 (<1)	2 (<1)	7 (1)	5 (<1)	2 (<1)	4 (<1)
White-White/Caucasian/ European Heritage	211 (75)	198 (70)	212 (69)	205 (67)	423 (72)	403 (68)	368 (70)	388 (74)
Mixed White							0	1 (<1)
Multiple	4 (1)	3 (1)	2 (<1)	2 (<1)	6 (1)	5 (<1)	2 (<1)	6 (1)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Demographic Characteristic	CAB + RPV Q4W N=283	CAR N=283	CAB + RPV Q4W N = 308	CAR N = 308	CAB + RPV Q4W N = 591	CAR N = 591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Race Subgroups, n (%)								
African American/African Heritage	47 (17)	56 (20)	62 (20)	77 (25)	109 (18)	133 (23)	101 (19)	90 (17)
Asian	12 (4)	15 (5)	22 (7)	13 (4)	34 (6)	28 (5)	29 (6)	22 (4)
White	216 (76)	201 (71)	214 (69)	207 (67)	430 (73)	408 (69)	370 (71)	393 (75)
Other	8 (3)	9 (3)	10 (3)	11 (4)	18 (3)	20 (3)	22 (4)	17 (3)

Data Source: ISE/ISS Table 1.07, GSK Doc. No. 2019N406358_01 Table 1.14, Table 1.16
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
201584 Baseline values = Induction Baseline (Week -20)

3.3.2. Baseline Characteristics

3.3.2.1. Studies 201584 and 201585

Baseline disease characteristics were similar across treatment groups overall and in the individual Phase III studies (Table 5). Subjects in Study 201585 were stably suppressed prior to study entry and both arms had been receiving ART for a median of 52 months prior to randomization.

3.3.2.2. Study 207966

Baseline disease characteristics were similar across the Q4W and Q8W treatment groups. Subjects in this study were stably suppressed prior to study entry.

Hepatitis Status at Baseline

At Baseline, 2 (<1%) subjects in the Q8W group and 1 (<1%) subjects in the Q4W group tested positive for hepatitis B virus only and 5 (<1%) subjects in the Q8W group and 6 (1%) subjects in the Q4W group tested positive for hepatitis C virus only. No subject tested positive for both hepatitis B and C virus (Data Source: GSK Doc. No. 2019N406358_01 Table 1.18). All 3 hepatitis B virus positive subjects were hepatitis B core antibody positive and surface antibody negative. Based upon hepatitis B viral DNA testing, none of these subjects were thought to have occult active hepatitis B infection and were therefore permitted to participate in the study.

Prior Exposure to CAB + RPV

A summary of prior exposure to CAB + RPV during participation in Phase IIIb Study 207966 is presented in Exposure Section 3.3.3.2.

Table 5 Summary of Baseline Characteristics for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W N=283	CAR N=283	CAB + RPV Q4W N=308	CAR N=308	CAB + RPV Q4W N=591	CAR N=591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Induction Baseline (Week -20) HIV-1 RNA c/mL, n (%)								
<1000	9 (3)	5 (2)	NA	NA	NA	NA	NA	NA
1000 to <10,000	64 (23)	71 (25)	NA	NA	NA	NA	NA	NA
10,000 to <50,000	95 (34)	113 (40)	NA	NA	NA	NA	NA	NA
50,000 to <100,000	59 (21)	38 (13)	NA	NA	NA	NA	NA	NA
100,000 to <200,000	30 (11)	33 (12)	NA	NA	NA	NA	NA	NA
≥200,000	26 (9)	23 (8)	NA	NA	NA	NA	NA	NA
Time from First HIV-1 RNA <50 c/mL until Maintenance Phase Start								
Median (Weeks) (IQR)	16.10 (12.40, 16.10)	16.10 (15.30, 16.30)	NA	NA	NA	NA	NA	NA
Time Since First ART Until Maintenance Phase Start								
Time	20 weeks[a]	20 weeks[a]	52 months[b] (IQR 33, 87)	52 months[b] (IQR 33, 84)	N/A	N/A	NA	NA
Baseline CD4+ (cells/mm^3)								
Median (IQR)	624 (473, 839)	625 (472, 799)	654 (497, 816)	653 (488, 844)	645 (487, 824)	641 (480, 821)	642 (499, 827)	688 (523, 878)
Baseline CD4+ (cells/mm^3), n (%)								
<350	19 (7)	27 (10)	23 (7)	27 (9)	42 (7)	54 (9)	35 (7)	27 (5)
≥350 to <500	64 (23)	60 (21)	56 (18)	57 (19)	120 (20)	117 (20)	96 (18)	89 (17)
≥500	200 (71)	196 (69)	229 (74)	224 (73)	429 (73)	420 (71)	391 (75)	407 (78)
Derived Baseline CDC Classification, n (%)								
HIV infection Stage 1	200 (71)	196 (69)	229 (74)	224 (73)	429 (73)	420 (71)	391 (75)	407 (78)
HIV infection Stage 2	78 (28)	82 (29)	78 (25)	83 (27)	156 (26)	165 (28)	129 (25)	113 (22)
HIV infection Stage 3	5 (2)	5 (2)	1 (<1)	1 (<1)	6 (1)	6 (1)	2 (<1)	3 (<1)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W N=283	CAR N=283	CAB + RPV Q4W N=308	CAR N=308	CAB + RPV Q4W N=591	CAR N=591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Induction Baseline (Week -20) Most Prevalent HIV-1 Subtype								
A	46 (16)	36 (13)	NA	NA	NA	NA	NA	NA
B	174 (61)	174 (61)	NA	NA	NA	NA	NA	NA
C	18 (6)	20 (7)	NA	NA	NA	NA	NA	NA
Alternate Background NRTI at End of Induction Phase, n (%)								
3TC and ABC	1 (<1)	1 (<1)	NA	NA	NA	NA	NA	NA
FTC/TAF	3 (1)	3 (1)	NA	NA	NA	NA	NA	NA
FTC/TDF	9 (3)	10 (4)	NA	NA	NA	NA	NA	NA
3TC and TDF	2 (<1)	1 (<1)	NA	NA	NA	NA	NA	NA
Baseline Third Agent Class, n (%)								
NNRTI	NA	NA	155 (50)	155 (50)	NA	NA	368 (70)	382 (73)
INSTI	NA	NA	102 (33)	99 (32)	NA	NA	334 (64)	341 (65)
PI	NA	NA	51 (17)	54 (18)	NA	NA	115 (22)	111 (21)
Hepatitis B, n (%)								
Non-reactive	282 (>99) [c,d]	283 (100) [c]	308 (100)	308 (100)	NA	NA	NA	NA
Negative	NA	NA	NA	NA	NA	NA	520 (>99)	521 (>99)
Positive	NA	NA	NA	NA	NA	NA	2 (<1) [e]	1 (<1) [e]

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W N=283	CAR N=283	CAB + RPV Q4W N=308	CAR N=308	CAB + RPV Q4W N=591	CAR N=591	CAB + RPV Q8W N=522	CAB + RPV Q4W N=523
Hepatitis C, n (%)								
Non-reactive	264 (93)	274 (97)	285 (93)	277 (90)	NA	NA	NA	NA
Reactive	19 (7)	9 (3)	23 (7)	31 (10)	NA	NA	NA	NA
Negative	NA	NA	NA	NA	NA	NA	517 (>99)	516 (99)
Positive	NA	NA	NA	NA	NA	NA	5 (<1)	6 (1)

Data Source: GSK Doc. No. 2017N345267_00 Table 1.25, Table 1.29, Table 1.37, Table 1.42, Table 1.43; GSK Doc. No. 2018N370336_00, Table 1.19, Table 1.31, Table 1.32; ISE/ISS Table 1.08, Table 1.09, GSK Doc. No. 2019N406358_01 Table 1.18, Table 1.19, Table 1.21, Table 1.28

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

a. Represents the 20-week Induction period for Study 201584
b. Median results are presented
c. Status at Induction Baseline (Week -20) for Study 201584
d. 1 subject was not excluded from the study because HBV result was non-reactive based on local labs.
e. In Study 207966, n=3 subjects classified as hepatitis B positive at entry were allowed to participate in the study based on clinical determination. These 3 subjects were found to be Hepatitis B s Ab negative, Hepatitis B c Ab positive and Hepatitis B s Ab <5. Per protocol they were required to undergo testing for Hep B DNA. All 3 subjects had Hep B DNA below the level of quantification but with HBV DNA reported as detected. All three subjects had testing for HBV DNA undertaken at a different time point where the HBV DNA was <LLQ and not detected. Based upon these results, these subjects were not considered to have active Hep B infection and were allowed to participate in the study.

3.3.3. Extent of Exposure

3.3.3.1. Studies 201584 and 201585

In Study 201584 and Study 201585, the overall extent of exposure to study drug during the Maintenance Phase was similar across the treatment groups through 52 weeks (Data Source: GSK Doc. No. 2017N345267_00 Table 3.1, GSK Doc. No. 2018N370336_00 Table 3.1, ISE/ISS Table 3.01). In the pooled analysis, the mean duration of exposure to oral CAB + RPV was 5.6 weeks (Data Source: ISE/ISS Table 3.01). For injectable CAB + RPV, in the pooled analysis, the mean number of injection visits was 12.5 with an exposure of approximately 50 weeks (Data Source: ISE/ISS Table 3.02). This includes 36% of subjects from Study 201584 that were on-treatment for more than 64 weeks at the time of the analysis data cut-off (as expected since the Maintenance Phase continues up to Week 100 for Study 201854) (Data Source: ISE/ISS Table 3.03).

3.3.3.2. Study 207966

Study 207966 included subjects from the ongoing Study 201585 (Q4W or CAR) and additional subjects receiving ART SOC. Subjects randomized from current ART SOC or transitioning from the CAR arm of Study 201585 had no prior exposure to CAB + RPV (oral or injectable). Subjects transitioning from the IM CAB + RPV Q4W arm in Study 201585 and subjects who transitioned from CAR to the Q4W arm within the Extension Phase of Study 201585 and then transitioned to Study 207966 had prior exposure to CAB+ RPV. Prior exposure to CAB + RPV was a stratification factor and therefore was similar between the 2 treatment groups (Table 6).

Table 6 Prior Exposure to CAB + RPV (ITT-E Population) - Study 207966

Prior Exposure to CAB + RPV (Weeks)	Q8W (N=522) n (%)	Q4W (N=523) n (%)
0 Weeks	327 (63)	327 (63)
1-24 Weeks	69 (13)	68 (13)
>24 – 48 Weeks	0	1 (<1)
>48 Weeks	126 (24)	127 (24)

Data Source: GSK Doc. No. 2019N406358_01 Table 1.22
Note: Prior exposure to CAB + RPV was calculated based on the prior CAB and/or RPV taken in Study 201585, as recorded in eCRF.

During the OLI phase, the duration of exposure was similar between the Q8W and Q4W treatment groups (median 39 days in each group, range Q8W: 19 – 85 days; Q4W: 19 -77 days). Some subjects required additional time on OLI to ensure assessment of individual safety and tolerability prior to receiving the LA regimen. During the Maintenance Phase of the study, the duration of exposure to CAB + RPV LA was ≥52 weeks for 85% of subjects in the Q8W group and 92% of subjects in the Q4W group (Data Source: GSK Doc. No. 2019N406358_01 Table 3.1).

3.4. Comparison of Efficacy Results Across Studies

Subjects in Study 201585 were stably suppressed for at least 6 months prior to study entry (median 52 months) and randomization while subjects in Study 201584 were stably suppressed for a median of 16.10 weeks prior to randomization (Table 5). Therefore, in both studies, the primary analysis occurred in a 'switch' population and given this similarity in the study populations during the Maintenance phase along with the similarity of the study designs (Table 1), the efficacy data have been pooled. Furthermore, results pertaining to the primary endpoint were consistent between Studies 201584 and 201585 [homogeneity tests described in Section 1.6.1], allowing both study data sets to be pooled and subgroup analyses to be based upon the pooled data set. The primary pooled analyses were based on the ITT-E population using the Snapshot datasets.

3.4.1. Primary Efficacy Result: Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot Analysis)

Results from Study 201584 and 201585 demonstrated once-monthly CAB + RPV was non-inferior to CAR in maintaining virologic suppression in HIV-1-infected subjects, with few cases of plasma HIV-1 RNA ≥50 c/ml per the Snapshot Algorithm in either arm (Table 7). Within each of the individual Studies 201584 and 201585, non-inferiority was achieved with the upper bound of the 95% CI for the adjusted treatment difference below 6%. For the pooled analysis, the primary efficacy endpoint was achieved with the upper bound of the 95% CI for the adjusted treatment difference below 4%. Of note, this more stringent 4% non-inferiority margin was achieved in each of the Phase III pivotal studies. The results for the PP Population were consistent with those from the ITT-E (primary) population (Table 8).

In Study 207966, the primary efficacy analysis demonstrated that CAB + RPV Q8W was non-inferior to CAB + RPV Q4W in maintaining virologic suppression in HIV-1-infected subjects at Week 48, with few subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot Algorithm in either group for the ITT-E population (Table 7). The adjusted treatment difference between the Q8W and Q4W group was 0.8 (95% CI -0.6, 2.2) which met the non-inferiority criterion, i.e., upper bound of the 95% CI below 4%, for the primary endpoint for the ITT-E population (plasma HIV-1 RNA ≥50 c/mL per Snapshot). Results for the PP population were similar to the ITT-E population (Table 8).

In the ITT-E population (pooled data from Studies 201584 and 201585), the proportion of subjects with HIV-1 RNA ≥50 c/mL among subjects receiving Q4W treatment in the CAB + RPV group (11/591, 1.9%) was similar to the proportion of subjects with HIV-1 RNA ≥50 c/mL receiving CAB + RPV in the Q8W group (9/522, 1.7%) and Q4W group (5/523, 1%) in Study 207966.

Table 7 Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E Population)

Treatment[a]	Number of Virologic Failures/Total Assessed (%)	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV Q4W	6/283 (2.1)	-0.4 (-2.8, 2.1)	-0.4 (-2.8, 2.1)
CAR	7/283 (2.5)		
201585			
CAB + RPV Q4W	5/308 (1.6)	0.7 (-1.1, 2.4)	0.7 (-1.2, 2.5)
CAR	3/308 (1.0)		
Pooled Studies 201584 and 201585			
CAB + RPV Q4W	11/591 (1.9)	0.2 (-1.3, 1.7)	0.2 (-1.4, 1.7)
CAR	10/591 (1.7)		
Study 207966			
CAB + RPV Q8W	9/522 (1.7)	0.8 (-0.6, 2.2)	0.8 (-0.6, 2.2)
CAB + RPV Q4W	5/523 (1.0)		

Data Source: ISE/ISS Table 2.01, GSK Doc. No. 2019N406358_01 Table 2.1

a. In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

b. For Pooled Data: Difference: Proportion on CAB + RPV (Q4W IM) – Proportion on Control (unadjusted). For Study 207966: Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W

c. Based on CMH stratified analysis adjusting to Baseline viral load and Gender for Study 201584; adjusting to 3rd ART class and Gender for Study 201585; and adjusting to 10 strata for pooled analysis. For Study 207966: based on CMH stratified analysis adjusting for Baseline stratification factor of prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

Table 8 Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (PP Population)

Treatment[a]	Number of Virologic Failures/Total Assessed (%)	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV Q4W	6/278 (2.2)	-0.3 (-2.8, 2.2)	-0.3 (-2.8, 2.2)
CAR	7/282 (2.5)		
201585			
CAB + RPV Q4W	4/294 (1.4)	0.3 (-1.4, 2.1)	0.3 (-1.4, 2.1)
CAR	3/292 (1.0)		
Pooled Studies 201584 and 201585			
CAB + RPV Q4W	10/572 (1.7)	0.0 (-1.5, 1.5)	0.0 (-1.5, 1.5)
CAR	10/574 (1.7)		
207966			
CAB + RPV Q8W	7/516 (1.4)	0.4 (-0.9, 1.7)	0.4 (-0.9, 1.7)
CAB + RPV Q4W	5/514 (1.0)		

Data Source: ISE/ISS Table 2.03, GSK Doc. No. 2019N406358_01 Table 2.2

a. In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

b. Difference: Proportion on CAB + RPV (Q4W IM) – Proportion on CAR (unadjusted). For Study 207966, Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W.

c. Based on CMH stratified analysis adjusting to Baseline viral load and Gender for Study 201584; adjusting to 3rd ART class and Gender for Study 201585; and adjusting to 10 strata for pooled analysis. For Study 207966, based on CMH stratified analysis adjusting prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

3.4.1.1. Plasma HIV-1 RNA ≥50 c/mL by Randomization Strata

3.4.1.1.1. Study 201584 and Study 201585

To assess the generalizability of the primary efficacy endpoint results (proportion of subjects with HIV-1 RNA ≥50 c/mL), consistency of the treatment effect was explored in pre-specified tests of homogeneity across randomization stratification factors. These were 1-way tests across each individual factor within each study, and across 4 analysis strata from the joint classification by study and sex at birth in the pooled dataset. A post hoc test of treatment homogeneity across the 10 randomization factors combined from each study (4 randomization strata from the 2-by-2 classification of Induction Baseline HIV-1 RNA category by sex at birth for Study 201584 and 6 randomization strata from the 3-by-2 classification of Baseline third agent class and sex at birth for Study 201585) was also performed.

A consistent showing of non-significant tests of homogeneity across randomization strata (p-value ≥0.10), were observed, supporting the overall primary endpoint conclusion of non-inferiority.

Induction Baseline (Week -20) HIV-1 RNA and Sex at Birth (Study 201584)

For Study 201584, the treatment effect (CAB + RPV Q4W vs. CAR) for the primary endpoint was consistent across the randomization stratification factors of Induction Baseline (Week -20) HIV-1 RNA and sex at birth (p-value ≥0.10 for prespecified test of homogeneity of treatment effect across the analysis strata) (Table 9).

Table 9 Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 in Study 201584 (Maintenance Phase)- Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number of Virologic Failures/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Induction Baseline (Week -20) HIV-1 RNA	HIV-1 RNA <100,000 c/mL	CAB + RPV Q4W	227	4/227 (1.8)	-0.4 (-3.6, 2.5)
		CAR	227	5/227 (2.2)	
	HIV-1 RNA ≥100,000 c/mL	CAB + RPV Q4W	56	2/ 56 (3.6)	0.0 (-9.2, 9.2)
		CAR	56	2/ 56 (3.6)	
	p-value for Test of Homogeneity[b]				0.907
Sex at Birth	Female	CAB + RPV Q4W	63	3/63 (4.8)	3.2 (-4.3, 12.0)
		CAR	64	1/64 (1.6)	
	Male	CAB + RPV Q4W	220	3 220 (1.4)	-1.4 (-4.7, 1.6)
		CAR	219	6/219 (2.7)	
	p-value for Test of Homogeneity[b]				0.179

Data Source: GSK Doc. No. 2017N345267_00 Table 2.4.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM. CAR = ABC/DTG/3TC.

a. Difference: Proportion on CAB + RPV - Proportion on CAR. 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.

b. 1-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 will be used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Baseline Third Agent and Sex at Birth (Study 201585)

For Study 201585, the treatment effect (CAB + RPV Q4W vs. CAR) for the primary endpoint was consistent across the randomization stratification factors of Baseline third agent class (NNRTI, INSTI or PI) and sex at birth (p-value ≥0.10 for prespecified test of homogeneity of treatment effect across the analysis strata) (Table 10).

Table 10 Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 in Study 201585 (Maintenance Phase) - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number of Virologic Failures/Total Assessed (%)	Difference in Proportion (95% CI)[a]
Baseline Third Agent Class	PI	CAB + RPV Q4W	51	1/51 (2.0)	2.0 (-1.8, 5.8)
		CAR	54	0/54	
	INSTI	CAB + RPV Q4W	102	0/102	-2.0 (-4.8, 0.8)
		CAR	99	2/99 (2.0)	
	NNRTI	CAB + RPV Q4W	155	4/155 (2.6)	1.9 (-0.9, 4.7)
		CAR	155	1/155 (0.6)	
	p-value for Test of Homogeneity[b]				0.177
Sex at Birth	Female	CAB + RPV Q4W	99	2/99 (2.0)	2.0 (-0.8, 4.8)
		CAR	104	0/104	
	Male	CAB + RPV Q4W	209	3/209 (1.4)	0.0 (-2.3, 2.3)
		CAR	204	3/204 (1.5)	
	p-value for Test of Homogeneity[b]				0.321

Data Source: GSK Doc. No. 2018N370336_00 Table 2.5
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.
a. Difference: Proportion on CAB + RPV - Proportion on CAR.
b. 1-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Study and Sex at Birth

In the pooled analysis, the treatment effect (CAB + RPV Q4W vs. CAR) for the primary endpoint was consistent across the cross-classification by study and sex at birth (p-value ≥0.10 for prespecified tests of treatment-by-strata interaction) (Table 11) and across the 10 randomization factors combined from each study (p-value ≥0.10 from post hoc test (Data Source: ISE/ISS Table 2.01).

Table 11 Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 in the Pooled Analysis by Study and Sex at Birth - Snapshot Analysis (ITT-E Population)

Study	Sex at Birth	Treatment	N	Number of Virologic Failures/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Study 201584	Female	CAB + RPV Q4W	63	3/63 (4.8)	3.2 (-4.3, 12.0)
		CAR	64	1/64 (1.6)	
	Male	CAB + RPV Q4W	220	3/220 (1.4)	-1.4 (-4.7, 1.6)
		CAR	219	6/219 (2.7)	
Study 201585	Female	CAB + RPV Q4W	99	2/99 (2.0)	2.0 (-1.7, 7.1)
		CAR	104	0/104	
	Male	CAB + RPV Q4W	209	3/209 (1.4)	0.0 (-3.0, 2.9)
		CAR	204	3/204 (1.5)	
	p-value for Test of Homogeneity[b]				0.327

Data Source: ISE/ISS Table 2.06.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
a. Difference = Proportion on CAB + RPV – Proportion on CAR (unadjusted). 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.
b. 1-sided p-value from weighted least squares chi-squared statistic.

3.4.1.1.2. Study 207966

Prior exposure to CAB + RPV

Prior exposure to CAB + RPV was a stratification factor in Phase IIIb Study 207966. The number of subjects randomized into Study 207966 study without prior exposure to CAB + RPV was 654/1045 (63%), while 137/1045 (13%) had 1-24 weeks of prior exposure to CAB + RPV, and 254/1045 (24%) had >24 weeks of prior exposure to CAB + RPV (Table 6). Within each randomization strata (prior exposure to CAB + RPV), the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot Algorithm) was similar between treatment groups (Table 12). The treatment effect (Q8W vs Q4W) for the primary endpoint was consistent across randomization stratification factors of prior exposure to CAB + RPV, 0 weeks, 1-24 weeks, and >24 weeks, supporting the overall primary endpoint conclusion.

Table 12 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 by Randomization Strata Study 207966 - Snapshot Analysis (Maintenance Phase) (ITT-E Population)

Analysis Strata	Weeks	Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Prior Exposure to CAB + RPV	0	CAB + RPV Q8W	327	5/327 (1.5)	0.0 (-2.2, 2.2)
		CAB + RPV Q4W	327	5/327 (1.5)	
	1-24	CAB + RPV Q8W	69	3/69 (4.3)	4.3 (-1.3, 12.3)
		CAB + RPV Q4W	68	0/68	
	>24	CAB + RPV Q8W	126	1/126 (0.8)	0.8 (-2.2, 4.4)
		CAB + RPV Q4W	128	0/128	
P-value for Test of Homogeneity[b] among 3 levels of prior exposure					0.346

Data Source: GSK Doc. No. 2019N406358_01 Table 2.4

a. Unadjusted Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W. 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.
b. One-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 will be used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.
c. Note: Randomization strata are rederived using the prior exposure to CAB + RPV in Study 201585, collected from eCRF.

3.4.2. Secondary Efficacy Results

3.4.2.1. Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis)

In Study 201584, Study 201585, and the pooled analysis, monthly CAB + RPV was non-inferior to CAR with plasma HIV-1 RNA <50 c/mL at Week 48 (Table 13). The lower bound of 95% CI for the adjusted treatment difference between CAB + RPV and CAR was greater than the pre-defined non-inferiority margin of -10%. Snapshot analysis using viral load cutoffs of HIV-1 RNA <200 c/mL demonstrated the same general trend (Data Source: ISE/ISS Table 2.12). These results are consistent with the conclusion drawn from the primary efficacy analysis that monthly CAB + RPV is non-inferior to CAR in maintaining virologic suppression in HIV-1-infected subjects.

In Phase IIIb Study 207966, the majority of subjects in both treatment groups remained suppressed (plasma HIV-1 RNA <50 c/mL) at Week 48 (Q8W: 94%; Q4W: 93, Table 13). The adjusted treatment difference between Q8W and Q4W was 0.8% (95% CI, -2.1%, 3.7%), which met the non-inferiority criterion for this secondary endpoint for the ITT-E population. Results for the PP Population were consistent with those for the ITT-E Population (Data Source: GSK Doc. No. 2019N406358_01 Table 2.9).

In the ITT-E population (pooled data for Studies 201584 and 201585), the proportion of subjects with HIV-1 RNA <50 c/mL among subjects receiving Q4W treatment in the CAB + RPV group (550/591, 93%) was similar to the proportion of subjects with HIV-1 RNA <50 c/mL receiving CAB + RPV in the Q8W group (492/522, 94%) and Q4W group (489/523, 93%) in Study 207966 (Table 13).

Across the 3 studies, CAB + RPV, dosed monthly in Studies 201584 and 201585 and dosed monthly or every 2 months in Study 207966, maintained virologic suppression in 94% (1531 of 1636) of subjects through Week 48 (Table 13).

Table 13 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E)

Treatment	Number Responded[a]/ Total Assessed (%)	Difference in Proportion, % (95% CI)[b]	Adjusted Difference in Proportion, % (95% CI)[c]
201584			
CAB + RPV Q4W	265/283 (94)	0.4 (-3.7, 4.4)	0.4 (-3.7, 4.5)
CAR	264/283 (93)		
201585			
CAB + RPV Q4W	285/308 (93)	-2.9 (-6.7, 0.8)	-3.0 (-6.7, 0.7)
CAR	294/308 (96)		
Pooled Studies 201584 and 201585			
CAB + RPV Q4W	550/591 (93)	-1.4 (-4.1, 1.4)	-1.4 (-4.1, 1.4)
CAR	558/591 (94)		
p-value for Test of Homogeneity[d]			0.765
Study 207966			
CAB + RPV Q8W	492/522 (94)	0.8 (-2.2, 3.7)	0.8 (-2.1, 3.7)
CAB + RPV Q4W	489/523 (93)		

Data Source: ISE/ISS Table 2.08, GSK Doc. No. 2019N406358_01 Table 2.8.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
a. Number Responded = Number of subjects with HIV-1 RNA <50 c/mL
b. Difference: Proportion on CAB + RPV – proportion on CAR. (unadjusted). For Study 207966, Difference: proportion on Q8W – Proportion on Q4W.
c. Based on CMH stratified analyses adjusting to Baseline viral load and sex at birth for Study 201584; adjusting to 3rd ART class and sex at birth for Study 201585; and adjusting to 10 strata for pooled analysis. For Study 207966, Based on CMH stratified analysis adjusting for prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).
d. One-sided p-value from weighted least squares statistic, across 10 randomization strata for pooled analysis.

3.4.2.1.1. Plasma HIV-1 RNA <50 c/mL by Randomization Strata

Studies 201584 and 201585

To assess the generalizability of the secondary efficacy endpoint results (proportion with HIV-1 RNA <50 c/mL), consistency of the treatment effect was explored in pre-specified tests of homogeneity across randomization stratification factors (1-way tests across each individual factor within study) as described in Section 1.6.1.4.

A consistent showing of non-significant tests of homogeneity across randomization strata (p-value ≥0.10), were observed, supporting the overall conclusion of non-inferiority.

Induction Baseline (Week -20) HIV RNA Viral Load and Sex and Birth (Study 201584)

For Study 201584, the treatment effect (CAB + RPV Q4W vs. CAR) for the secondary endpoint of HIV-1 RNA <50 c/mL was consistent across the randomization stratification factors of Induction Baseline (Week -20) HIV-1 RNA and sex at birth (p-value ≥0.10 for prespecified tests of treatment-by-strata interaction) (Table 14).

Table 14 Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 in Study 201584 (Maintenance Phase) - Snapshot Analysis (ITT-E)

Analysis Strata		Treatment	N	Number Responded[a]/Total Assessed (%)	Difference in Proportion (95% CI)[b]
Induction Baseline (Week -20) HIV-1 RNA	HIV-1 RNA <100,000 c/mL	CAB + RPV Q4W	227	215/227 (95)	1.8 (-2.8, 6.5)
		CAR	227	211/227 (93)	
	HIV-1 RNA ≥100,000 c/mL	CAB + RPV Q4W	56	50/ 56 (89)	-5.4 (-17.5, 5.6)
		CAR	56	53/ 56 (95)	
	p-value for Test of Homogeneity [c]				0.206
Sex at Birth	Female	CAB + RPV Q4W	63	58 / 63 (92)	-3.2 (-13.5, 6.4)
		CAR	64	61 / 64 (95)	
	Male	CAB + RPV Q4W	220	207 / 220 (94)	1.4 (-3.4, 6.4)
		CAR	219	203 / 219 (93)	
	p-value for Test of Homogeneity [c]				0.348

Data Source: GSK Doc. No. 2017N345267_00 Table 2.9.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

a. Number Responded = Number of subjects with HIV-1 RNA <50 c/mL
b. Difference: Proportion on CAB + RPV - Proportion on CAR (unadjusted). 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.
c. 1-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 will be used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Baseline Third Agent and Sex at Birth (Study 201585)

For Study 201585, the treatment effect (CAB + RPV Q4W vs. CAR) for the secondary endpoint of HIV-1 RNA <50 c/mL was consistent across the randomization stratification factors of Baseline third agent class (NNRTI, INSTI or PI) and sex at birth (p-value ≥0.10 for prespecified tests of treatment-by-strata interaction) (Table 15).

Table 15 Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 in Study 201585 (Maintenance Phase)- Snapshot Analysis (ITT-E)

Analysis Strata		Treatment	N	Number Responded[a]/Total Assessed (%)	Difference in Proportion (95% CI)[b]
Baseline Third Agent Class	PI	CAB + RPV Q4W	51	47/ 51 (92)	-2.3 (-11.9, 7.3)
		CAR	54	51/ 54 (94)	
	INSTI	CAB + RPV Q4W	102	96/102 (94)	-1.8 (-7.8, 4.1)
		CAR	99	95/ 99 (96)	
	NNRTI	CAB + RPV Q4W	155	142/155 (92)	-3.9 (-9.3, 1.6)
		CAR	155	148/155 (95)	
	p-value for Test of Homogeneity[c]				0.881
Sex at Birth	Female	CAB + RPV Q4W	99	92/ 99 (93)	-1.3 (-8.1, 5.4)
		CAR	104	98/104 (94)	
	Male	CAB + RPV Q4W	209	193/209 (92)	-3.7 (-8.2, 0.7)
		CAR	204	196/204 (96)	
	p-value for Test of Homogeneity[c]				0.558

Data Source: GSK Doc. No. 2018N370336_00 Table 2.10
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.
a. Number Responded = Number of subjects with HIV-1 RNA <50 c/mL
b. Difference: Proportion on CAB + RPV - Proportion on CAR.
c. 1-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Study 207966

Prior Exposure to CAB

Results for the proportion of subjects with plasma HIV-1 RNA <50 c/mL by randomization strata (prior exposure to CAB + RPV) up to Week 48 were similar to the overall results (Table 16).

Table 16 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Randomization Strata Study 207966 - Snapshot Analysis (Maintenance Phase) (ITT-E Population)

Analysis Strata	Weeks	Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a,b]
Prior Exposure to CAB + RPV	0	CAB + RPV Q8W	327	306/327 (94)	1.8 (-2.3, 6.0)
		CAB + RPV Q4W	327	300/327 (92)	
	1-24	CAB + RPV Q8W	69	66/69 (96)	0.1 (-8.3, 8.6)
		CAB + RPV Q4W	68	65/68 (96)	
	>24	CAB + RPV Q8W	126	120/126 (95)	-1.6 (-7.4, 3.7)
		CAB + RPV Q4W	128	124/128 (97)	
P-value for Test of Homogeneity[c]					0.550

Data Source: GSK Doc. No. 2019N406358_01 Table 2.10

a. Unadjusted Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W.
b. 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.
c. One-sided p-value from weighted least squares chi-squared statistic. A p-value <0.10 will be used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

3.4.2.1.2. Plasma HIV-1 RNA <50 c/mL by Visit (Study 207966) (Maintenance Phase)

At the planned Week 48 analysis, CAB + RPV had a similar high rate of virologic success (HIV-1 RNA <50 c/mL) for both the Q8W and Q4W treatment groups (Table 17). Results for the proportion of subjects with plasma HIV-1 RNA <50 c/mL by visit up to Week 48 were similar to the overall results.

Table 17 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit up to Week 48 for Study 207966 (Maintenance Phase)-Observed Case (ITT-E Population)

Visit	Plasma HIV-1 RNA <50 c/mL	
	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Baseline	519 (>99)	513 (98)
Week 4	N/A	519 (>99)
Week 8	510 (98)	509 (97)
Week 16	507 (97)	510 (98)
Week 24	497 (95)	499 (95)
Week 32	492 (94)	495 (95)
Week 40	492 (94)	487 (93)
Week 48	492 (94)	489 (93)

Data Source: GSK Doc. No. 2019N406358_01 Table 2.15

3.4.2.2. Study Outcomes at Week 48: Snapshot Algorithm Outcomes

Snapshot outcomes at Week 48 for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 are shown in Table 18. Snapshot outcomes at Week 48 for subjects receiving CAB + RPV Q4W regimen (pooled data from Studies 201584 and 201585) are consistent with results observed in the CAB + RPV Q8W and Q4W treatment groups in Study 207966.

Table 18 Snapshot outcomes at Week 48 for Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E)

Outcome	Study 201584		Study 201585		Studies 201584 and 201585 Pooled		Study 207966	
	CAB + RPV Q4W N=283 n (%)	CAR N=283 n (%)	CAB + RPV Q4W N=308 n (%)	CAR N=308 n (%)	CAB + RPV Q4W N=591 n (%)	CAR N=591 n (%)	CAB + RPV Q8W N=522 n (%)	CAB + RPV Q4W N=523 n(%)
HIV-1 RNA <50 c/mL	265 (93.6)	264 (93.3)	285 (92.5)	294 (95.5)	550 (93.1)	558 (94.4)	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL	6 (2.1)	7 (2.5)	5 (1.6)	3 (1.0)	11 (1.9)	10 (1.7)	9 (1.7)	5 (1.0)
Data in window not below threshold	2 (0.7)	2 (0.7)	1 (0.3)	1 (0.3)	3 (0.5)	3 (0.5)	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	4 (1.4)	3 (1.1)	3 (1.0)	2 (0.6)	7 (1.2)	5 (0.8)	6 (1.1)	2 (0.4)
Discontinued for other reason while not below threshold	0	2 (0.7)	1 (0.3)	0	1 (0.2)	2 (0.3)	0	1 (0.2)
Change in background therapy	0	0	0	0	0	0	0	0
No Virologic Data	12 (4.2)	12 (4.2)	18 (5.8)	11 (3.6)	30 (5.1)	23 (3.9)	21 (4.0)	29 (5.5)
Discontinued study due to AE or death	8 (2.8)	2 (0.7)	11 (3.6)	5 (1.6)	19 (3.2)	7 (1.2)	9 (1.7)	13 (2.5)
Discontinued study for other reasons	4 (1.4)	10 (3.5)	7 (2.3)	6 (1.9)	11 (1.9)	16 (2.7)	12 (2.3)	16 (3.1)
On study but missing data in window	0	0	0	0	0	0	0	0

Data Source: ISE/ISS Table 2.05, GSK Doc. No. 2019N406358_01 Table 2.3

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

3.4.2.3. Proportion of Subjects with Confirmed Virologic Failure

In Study 201584, Study 201585 and Study 207966, CVF was defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL. In the individual studies and in the pooled analyses of Study 201584 and Study 201585, few subjects met CVF criteria through Week 48 (Table 19). For the pooled analysis, CVF rates for both the CAB + RPV arm and the CAR group was 7/591 (1.2%).

In the pooled analysis of Study 201584 and Study 201585, Kaplan-Meier estimates of the proportion of subjects without efficacy related discontinuation (CVF or discontinuation due to lack of efficacy) by Week 48 were 98.6% for CAB + RPV and 98.8% for CAR, the difference and 95% CI were -0.2% (-1.5%, 1.1%) indicating no statistical difference between arms (Data Source: ISE/ISS Table 2.11).

Rates of CVF in Study 201584, Study 201585, and the pooled analysis were <1.5% in the CAB + RPV Q4W group and in the CAR group through Week 48. When CVF did occur in the CAB + RPV Q4W group, it was associated with RT and/or IN mutations that decreased drug susceptibility to CAB (6/7 with INSTI RAM with FC to CAB range 5.22-9.36 in Study 201584 and 0.82-2.7 in Study 201585) and/or RPV (6/7 with RPV RAM with FC to RPV range 0.97-7.09 in Study 201584 and 2.4-6.5 in Study 201585) (Data Source: GSK Doc. No. 2017N345267_00 Table 7.10; GSK Doc. No. 2018N370336_00 Table 8.7). In some cases, PBMC results revealed pre-existing archived mutations. All subjects with CVF were offered an alternative fully active oral ART regimen and consenting subjects were entered into LTFU. The details of viral resistance are presented in m2.7.2.4.

In Study 207966, the CVF rate among subjects receiving CAB + RPV in the Q8W group (8/522, 1.5.%) was higher than in the Q4W group (2/523, 0.4%). CVF with INSTI RAMs present at time of failure was observed in 7/9 subjects (1/10 did not amplify the IN region), with decreased sensitivity to CAB in 4/8 subjects (Data Source: GSK Doc. No. 2019N406358_01 Table 7.1, Table 7.4; and Data Source Known to Sponsor). RPV RAMs were observed in 7/10 subjects at time of failure and NNRTI RAMs were observed in 8/10 subjects at time of failure, with decreased sensitivity to RPV in 9/10 subjects (Data Source: GSK Doc. No. 2019N406358_01 Table 7.2, Table 7.4 and Data Source Known to Sponsor). Pre-existing, archived NNRTI RAMs and RPV RAMs detected through testing of PBMC DNA were present in 6/10 and 5/10 subjects, respectively, and pre-existing INSTI mutations were present in 1/10 subjects (Data Source: GSK Doc. No. 2019N406358_01 Table 7.8). Mutations at the Q148 position in the integrase coding region are primarily responsible for resistance to CAB. In Study 207966, in addition to mutations at the Q148 position (n=4), N155H also was present in 5 subjects meeting CVF criteria with 2 of these subjects presenting with both N155N/H + Q148Q/R (Data Source: GSK Doc. No. 2019N406358_01 Table 7.1 and Data Source Known to Sponsor). See m2.7.2.4 for complete information on pre-existing mutations and viral load.

Across the 3 studies (Studies 201584, 201585, and 207966), there were 17 subjects (17/1636, 1.04%) who did not maintain virologic suppression through their first 48 weeks of exposure to CAB + RPV (monthly or every 2 months dosing) and met CVF criteria

(Table 19). Covariates and their relationship with an outcome of CVF were investigated in a multivariable analysis in subjects without previous exposure to CAB + RPV (N=1039), as described in Section 4.2.3.

Table 19 Cumulative Summary of Confirmed Virologic Failure by Visit in Study 201584, Study 201585, Studies 201584 and 201585 Pooled Data, and Study 207966 (ITT-E Population)

Time Point	201584		201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W N=522 n (%)	CAB + RPV Q4W N=523 n (%)
Week 4	0	0	0	0	0	0	0	0
Week 8	1 (0.4)	1 (0.4)	1 (0.3)	0	2 (0.3)	1 (0.2)	1 (0.2)	0
Week 12	1 (0.4)	2 (0.7)	2 (0.6)	0	3 (0.5)	2 (0.3)	1 (0.2)	0
Week 16	1 (0.4)	3 (1.1)	2 (0.6)	0	3 (0.5)	3 (0.5)	4 (0.8)	1 (0.2)
Week 20	2 (0.7)	3 (1.1)	2 (0.6)	2 (0.6)	4 (0.7)	5 (0.8)	4 (0.8)	1 (0.2)
Week 24	2 (0.7)	3 (1.1)	3 (1.0)	2 (0.6)	5 (0.8)	5 (0.8)	7 (1.3)	1 (0.2)
Week 28	3 (1.1)	3 (1.1)	3 (1.0)	2 (0.6)	6 (1.0)	5 (0.8)	7 (1.3)	1 (0.2)
Week 32	3 (1.1)	3 (1.1)	3 (1.0)	3 (1.0)	6 (1.0)	6 (1.0)	7 (1.3)	2 (0.4)
Week 36	3 (1.1)	3 (1.1)	3 (1.0)	3 (1.0)	6 (1.0)	6 (1.0)	7 (1.3)	2 (0.4)
Week 40	3 (1.1)	3 (1.1)	3 (1.0)	4 (1.3)	6 (1.0)	7 (1.2)	7 (1.3)	2 (0.4)
Week 44	3 (1.1)	3 (1.1)	3 (1.0)	4 (1.3)	6 (1.0)	7 (1.2)	7 (1.3)	2 (0.4)
Week 48	4 (1.4)	3 (1.1)	3 (1.0)	4 (1.3)	7 (1.2)	7 (1.2)	8 (1.5)	2 (0.4)

Data Source: ISE/ISS Table 2.09, GSK Doc. No. 2019N406358_01 Table 2.23

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Note: The summary is the proportion of CVF up to the analysis visit.

Note: 1 subject with CVF did not have resistance testing performed. This subject had a pause in oral therapy because of a false positive pregnancy, resulting in CVF and study withdrawal prior to initiating LA therapy.

3.4.2.4. Absolute Values and Change from Baseline in plasma HIV-1 RNA at Week 48

In Study 201584, Study 201585, and Study 207966, subjects were to be virologically suppressed prior to randomization. Thus, clinically meaningful changes in absolute values and change from Baseline in plasma HIV-1 RNA at Week 48 were not expected in the overall population. Based on the stable mean log10 c/mL observed for plasma HIV-1 RNA over time, it can be inferred that no clinically relevant differences in absolute values and changes from Baseline in plasma HIV-1 RNA through Week 48 occurred across the treatment arms in these studies (Data Source: GSK Doc. No. 2017N345267 Table 2.19, GSK Doc. No. 2018N370336_00 Table 2.20, GSK Doc. No. 2019N406358_01 Table 2.22, Table 2.28, Table 2.38).

3.4.2.5. Absolute Values and Changes from Baseline CD4+ Cell Counts

Subjects in Study 201584 were stably suppressed prior to Day 1, and subjects in Study 201585 and Study 207966 were stably suppressed prior to study entry. Median (IQR) Baseline CD4+ cell counts are presented in Table 5. Clinically relevant change from Baseline in CD4+ and CD8+ cell counts were not observed in any study.

In Study 201584, the median [range] increases from Baseline through Week 48 in CD4+ cell counts of 46 [-1228 to 683] cells/mm3 (CAB + RPV Q4W) and of 80 [-450 to 985] cells/mm3 (CAR) were observed (Data Source: GSK Doc. No. 2017N345267_00 Table 2.25). The mean absolute CD4+ cell count at Week 48 was 703 cells/mm3 for the CAB + RPV Q4W arm and 731 cells/mm3 for the CAR group (Data Source: GSK Doc. No. 2017N345267_00 Table 2.29).

In Study 201585, the median [range] increases from Baseline through Week 48 in CD4+ cell counts of 4 [-536 to 801] cells/mm3 for CAB + RPV Q4W and of 14 [-1043 to 521] cells/mm3 for CAR were observed (Data Source: GSK Doc. No. 2018N370336_00 Table 2.25). The mean absolute CD4 + cell count at Week 48 was 685 cells/mm3 for the CAB + RPV Q4W arm and 717 cells/mm3 for the CAR group (Data Source: GSK Doc. No. 2018N370336_00 Table 2.26).

In Study 207966, the median Baseline CD4+ cell count was 642 cells/mm3 in the Q8W group and 688 cells/mm3 in the Q4W group (Table 5). Mean and median CD4+ cell counts remained stable from Baseline in both treatment groups over time. Median [range] changes from Baseline through Week 48 in CD4+ cell counts of 5 [-622, 692] cells/mm3 for the CAB + RPV Q8W group and of -8 [-1049 to 1525] cells/mm3 for the Q4W group were observed (Data Source: GSK Doc. No. 2019N406358_01 Table 2.29). The mean [median] absolute CD4 + cell count at Week 48 was 685.9 cells/mm3 [647 cells/mm3] for the Q8W group and 700 cells/mm3 [661 cells/mm3] for the Q4W group (Data Source: GSK Doc. No. 2019N406358_01 Table 2.31).

3.5. Comparison of Results in Subgroups

Subgroup analyses were conducted to evaluate consistency of the primary findings across subgroups. In many subgroups, the number of subjects was small; thus, results should be interpreted with caution.

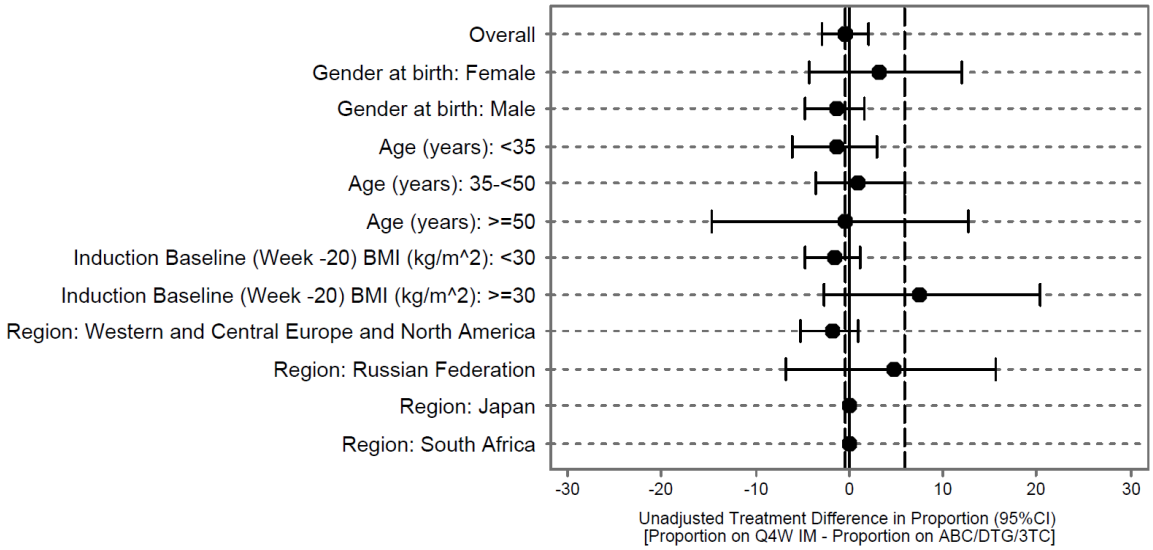
In Study 201584, Study 201585, and the pooled analysis, there were no meaningful differences between treatment groups observed for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL when analyzed by subgroup, and there were no statistically significant differences in treatment effect between the treatment groups in any subgroups.

In Study 207966, treatment differences on the primary endpoint [proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot algorithm)] generally were consistent with the overall comparisons across the following subgroups: demographic factors [age, gender (Sex at Birth), race, BMI], Baseline CDC stage of disease, Baseline HIV-1 RNA, Baseline CD4+ lymphocyte count, prior oral treatment (NNRTI, PI or INSTI), and participating country (Table 10 and Data Source: GSK Doc. No. 2019N406358_01 Table 2.5).

3.5.1. Subgroup Analysis for Study 201584 (HIV-1 RNA ≥50 c/mL at Week 48)

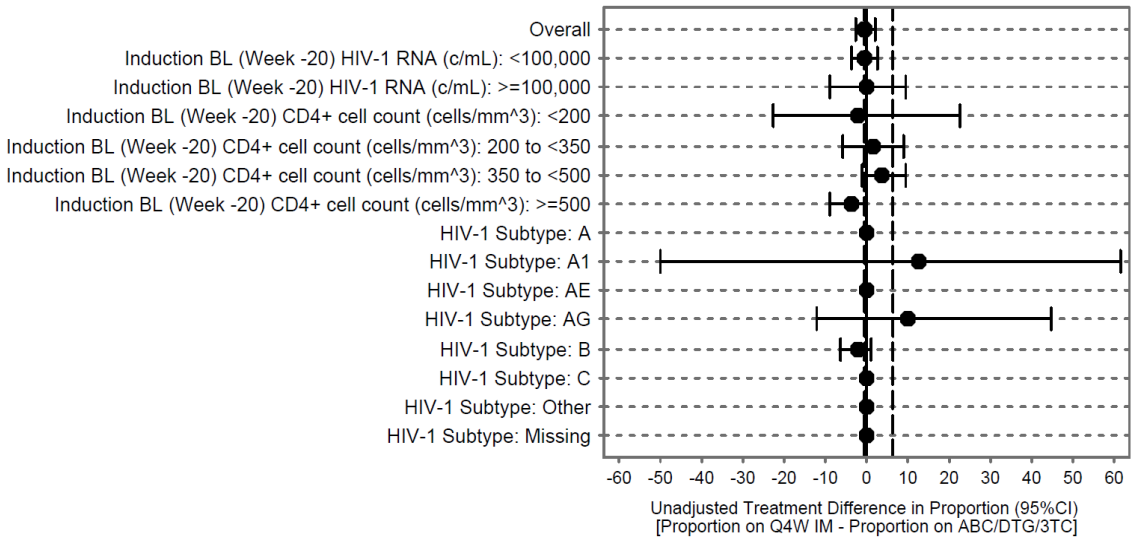
No meaningful differences between treatment groups were observed for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL when analyzed by subgroup. A Forest plot for selected subgroups, displaying the treatment difference estimate for each subgroup along with the associated 95% CI, are provided in Figure 1 and Figure 2.

Figure 1 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Selected Demographic Subgroups for Study 201584 (Maintenance Phase) - Snapshot Analysis



Data Source: GSK Doc. No. 2017N345267_00 Figure 2.11
Note: Q4W IM = CAB + RPV group, ABC/DTG/3TC = CAR
Note: The dashed reference line on the right at 6% represents the non-inferiority margin while the dashed reference line on the left represents the overall difference in proportion CAB + RPV - CAR (unadjusted).
Note: 95% CIs were calculated using the normal approximation for overall and using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic for the subgroups.

Figure 2 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Selected HIV Disease Characteristic Subgroups for Study 201584 (Maintenance Phase) - Snapshot Analysis



Data Source: GSK Doc. No. 2017N345267_00 Figure 2.12
Note: Q4W IM = CAB + RPV group, ABC/DTG/3TC = CAR
Note: The dashed reference line on the right at 6% represents the non-inferiority margin while the dashed reference line on the left represents the overall difference in proportion CAB + RPV - CAR (unadjusted).
Note: 95% CIs were calculated using the normal approximation for overall and using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic for the subgroups.

A proportionally higher rate of HIV-1 RNA ≥50 c/mL was observed in subjects with HIV-1 A1 subtype treated with CAB + RPV Q4W compared with CAR (3/8 [37.5%] vs. 1/4 [25%], respectively) (Data Source: GSK Doc. No. 2017N345267_00 Table 2.5). The 95% confidence intervals were wide given the small sample size, limiting the ability to draw conclusions about this subtype (Figure 2). Further details related to HIV-1 subtype are presented in m2.7.2.4. For further details on all subgroups, see Data Source: GSK Doc. No. 2017N345267_00 Figure 2.2 and Table 2.5.

Study outcomes of subjects with plasma HIV-1 RNA of <50 c/mL at Week 48 by subgroup: age, race, country, Induction Baseline (Week -20) HIV-1 RNA, visit of first suppression (HIV-1 RNA <50 c/mL), Baseline HIV-1 RNA, Induction Baseline (Week -20) CD4+ count, Baseline CD4+ count, Baseline CDC category, HIV-1 subtype, K103N mutation at Induction Baseline (Week -20) and BMI at Induction Baseline (Week -20) are provided in Data Source: GSK Doc. No. 2017N345267_00 Table 2.6.

3.5.2. Subgroup Analysis for Study 201585 (HIV-1 RNA ≥50 c/mL at Week 48)

No meaningful differences between treatment groups were observed for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL when analyzed by subgroup (selected subgroups are shown in Table 20 and Data Source: GSK Doc. No. 2018N370336_00 Table 2.40).

Table 20 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 in Study 201585 by Select Subgroup (Maintenance Phase) - Snapshot Analysis - (ITT-E Population)

Subgroups	Analysis Strata	Treatment	N	Number of Virologic Failures/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Age (years)	<35	CAB + RPV Q4W	80	0/80	-1.3 (-6.9, 3.6)
		CAR	80	1/80 (1.3)	
	35 - <50	CAB + RPV Q4W	162	4/162 (2.5)	1.7 (-2.0, 5.6)
		CAR	132	1/132 (0.8)	
	≥50	CAB + RPV Q4W	66	1/66 (1.5)	0.5 (-4.6, 7.4)
		CAR	96	1/96 (1.0)	
Race	White	CAB + RPV Q4W	214	3/214 (1.4)	0.4 (-2.2, 3.2)
		CAR	207	2/207 (1.0)	
	Non-White	CAB + RPV Q4W	94	2/94 (2.1)	1.1 (-3.6, 6.7)
		CAR	101	1/101 (1.0)	
	Black/African American	CAB + RPV Q4W	62	2/62 (3.2)	1.9 (-4.3, 10.0)
		CAR	77	1/77 (1.3)	
	Non-Black/African American	CAB + RPV Q4W	246	3/246 (1.2)	0.4 (-2.0, 2.8)
		CAR	231	2/231 (0.9)	
Baseline CD4+ cell count (cells/mm^3)	<350	CAB + RPV Q4W	23	0/23	-3.7 (-19.0, 11.4)
		CAR	27	1/27 (3.7)	
	350 to <500	CAB + RPV Q4W	56	2/56 (3.6)	3.6 (-2.9, 12.4)
		CAR	57	0/57	
	≥500	CAB + RPV Q4W	229	3/229 (1.3)	0.4 (-2.1, 3.1)
		CAR	224	2/224 (0.9)	

Data Source: GSK Doc. No. 2018N370336_00 Table 2.40

Note: Results for countries, Baseline viral load, and Baseline CDC category are provided in Data Source: GSK Doc. No. 2018N370336_00 Table 2.40.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.

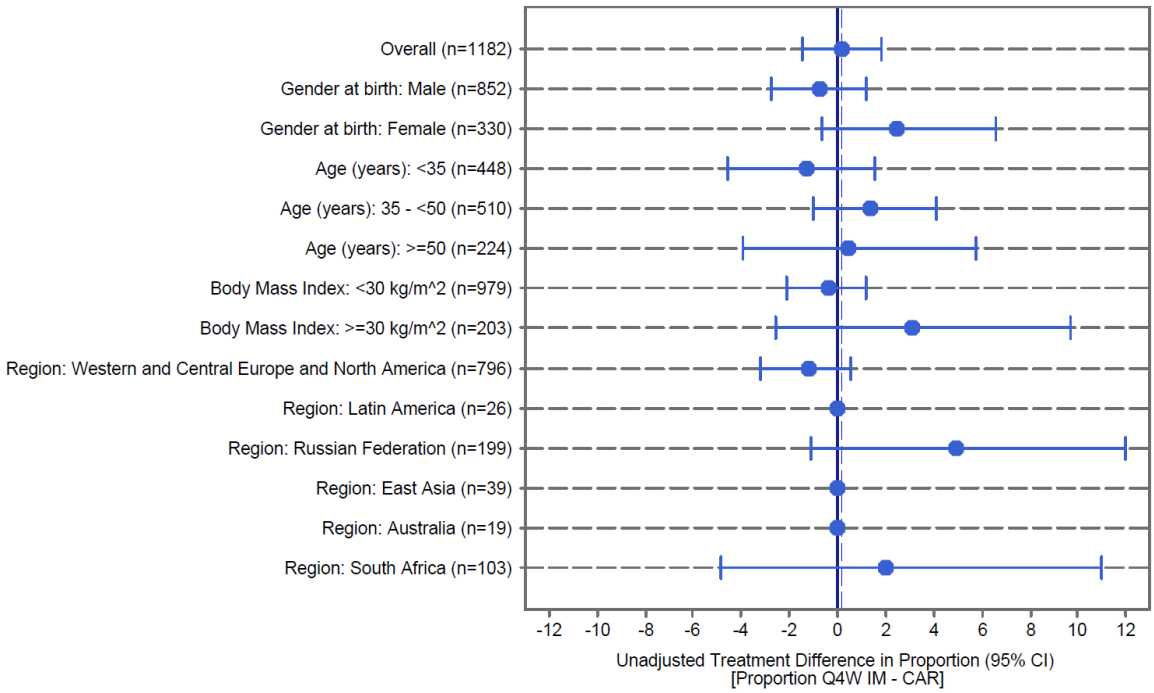
a. Difference: Proportion on CAB + RPV - Proportion on CAR (unadjusted). 95% CIs were calculated using an unconditional exact method with 2 inverted 1-sided tests based on the score statistic.

Study outcomes of subjects with plasma HIV-1 RNA of <50 c/mL at Week 48 by subgroup: age, race, country, sex at birth, Baseline third agent class, Baseline viral load, Baseline CD4+ count, Baseline CDC category are provided in Data Source: GSK Doc. No. 2018N370336_00 Table 2.7.

3.5.3. Pooled Subgroup Analysis (HIV-1 RNA ≥50 c/mL at Week 48 for Study 201584 and Study 201585)

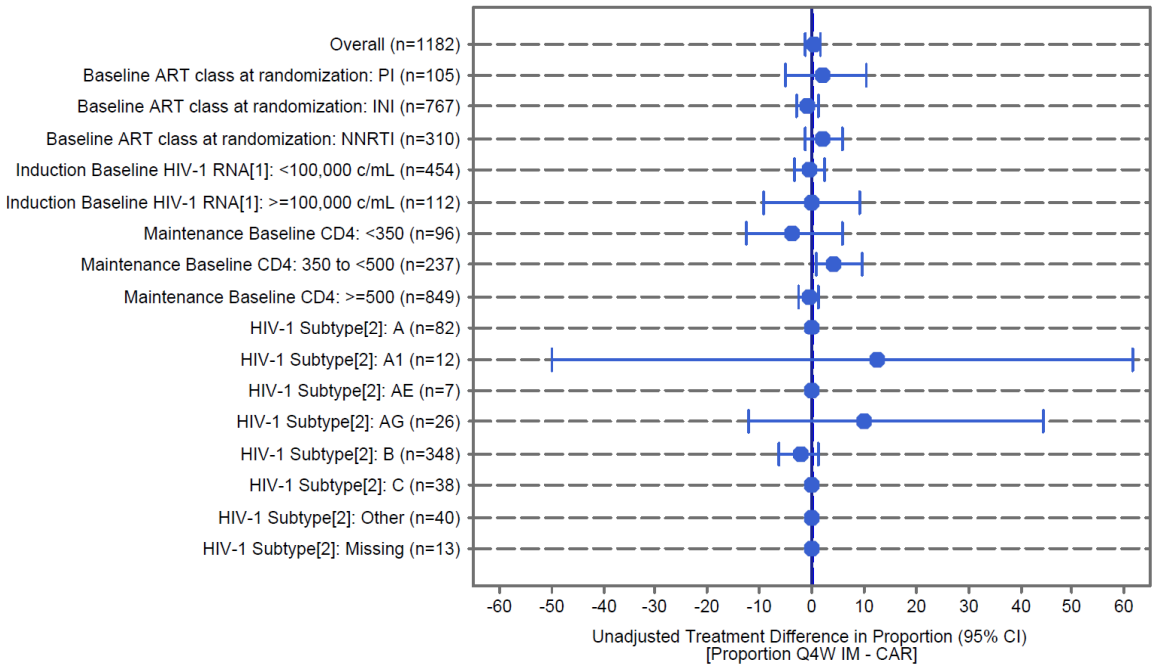
No meaningful differences between treatment groups were observed for proportion of subjects with plasma HIV-1 RNA ≥50 c/mL when analyzed by subgroup. A Forest plot for selected subgroups, displaying the treatment difference estimate for each subgroup along with the associated 95% CI, are provided in Figure 3 and Figure 4.

Figure 3 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Selected Demographic Subgroups (Maintenance Phase) - Snapshot Analysis - Pooled Studies 201584 and 201585



Data Source: ISE/ISS Figure 2.06
Note: Q4W IM = CAB + RPV group, For Study 201584, CAR = ABC/DTG/3TC.
Note: The dashed line represents the overall difference in proportion (CAB + RPV - CAR).
Note: East Asia includes Japan and Republic of Korea; Latin America includes Mexico and Argentina.
Note: Confidence intervals are not produced when both treatment groups have no subjects with HIV-1 RNA ≥50 c/mL within a subgroup.

Figure 4 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Selected HIV Disease Characteristics Subgroups (Maintenance Phase) - Snapshot Analysis - Pooled Studies 201584 and 201585



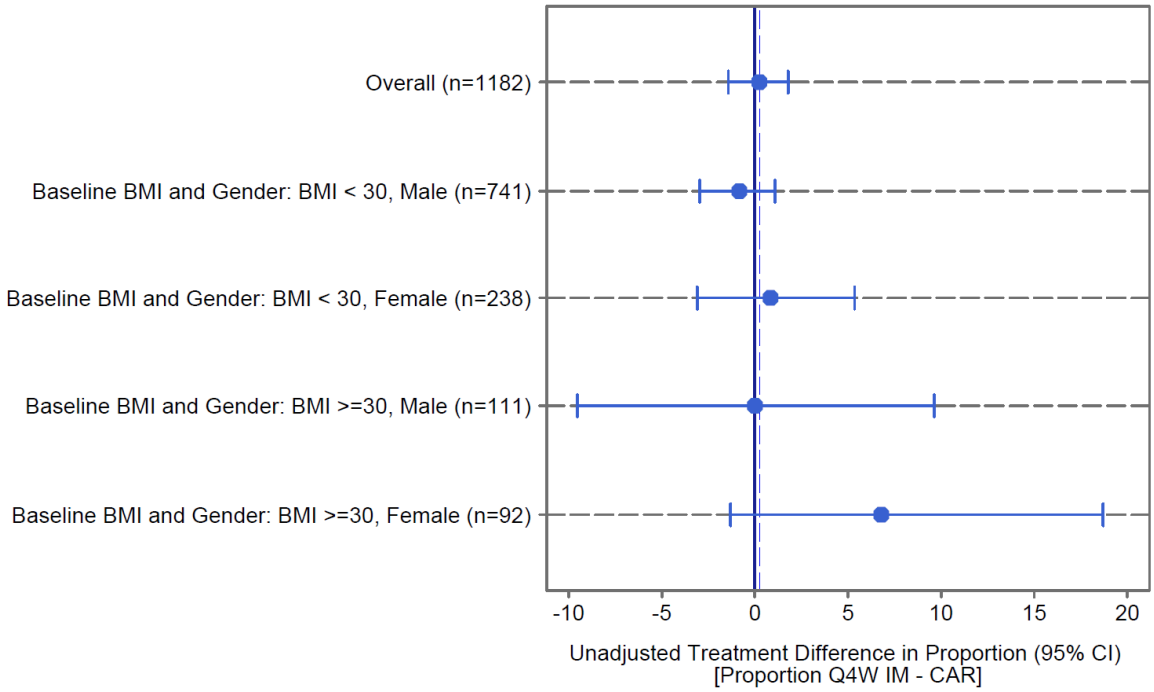
Data Source: ISE/ISS Figure 2.07
Note: Q4W IM = CAB + RPV group, For Study 201584, CAR = ABC/DTG/3TC.
Note: The dashed line represents the overall difference in proportion (CAB + RPV - CAR).
Note: All subgroups are pooled except [1], [2] which are from study 201584 only.
Note: Confidence intervals are not produced when both treatment groups have no subjects with HIV-1 RNA ≥50 c/mL within a subgroup.

For further details on all subgroups, see Data Source: ISE/ISS Table 2.07.

3.5.3.1. Evaluation of BMI by Sex at Birth - Pooled Studies 201584 and 201585

To further explore the observations within the separate subgroups of BMI and sex at birth, an unplanned exploratory analysis was conducted within the cross-classification of BMI by sex at birth (Figure 5). Although most females with BMI ≥30 kg/m^2 successfully maintained viral suppression over 48 weeks, 3 of the overall 11 subjects with HIV-1 RNA ≥50 c/mL in the CAB + RPV arm were observed in this smallest subgroup. Of note, however, the test of evidence against homogeneity of the treatment difference across the four joint subgroups was not statistically significant (p=0.301). Further details on BMI by sex at birth can be found in ISE/ISS Table 2.18, ISE/ISS Table 1.18 and ISE/ISS Table 1.19.

Figure 5 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA ≥50 c/mL at Week 48 by Subgroup - Baseline BMI and Gender (Exploratory) - Snapshot Analysis - Pooled Studies 201584 and 201585



Data Source: ISE/ISS Figure 2.05
Note: Q4W IM = CAB + RPV group, For Study 201584, CAR = ABC/DTG/3TC.
Note: The dashed line represents the overall difference in proportion (CAB + RPV - CAR).

3.5.4. Subgroup Analysis for Phase IIIb Study 207966 (HIV-1 RNA ≥50 c/mL at Week 48)

3.5.4.1. Baseline Characteristics and Key Demographic Subgroups

Treatment differences on the primary endpoint (proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48 [Snapshot algorithm]) generally were consistent with the overall comparisons across the following subgroups: demographic factors (age, gender [Sex at Birth], race, BMI), Baseline CDC stage of disease, Baseline HIV-1 RNA, Baseline CD4+ lymphocyte count, prior oral treatment (NNRTI, PI, or INSTI), and participating country (Table 21 and Data Source: GSK Doc. No. 2019N406358_01 Table 2.5). The proportion of Snapshot virologic failures was numerically higher in the Q8W arm compared with the Q4W arm in female subjects (5/137 [3.6%] and 0/143 [0%]) versus (4/385 [1.0%] and 5/380 [1.3%]) in males. The proportion of subjects with Snapshot virologic failures also was higher in the Q8W arm compared with the Q4W arm among subjects with a BMI ≥30 kg/m^2 (6/113 [5.3%] and 2/98 [2.0%]) versus in subjects with BMI<30 kg/m^2 (3/409 [0.7%] and 3/425 [0.7%]). The differences in proportions are not regarded as clinically relevant.

It is important to note that females were ~27% of the overall study population. For both females and males, virologic success rates (HIV-1 RNA <50 c/mL) were similar between the Q8W and Q4W treatment groups, and consistent with results of the overall key secondary endpoint conclusion (Data Source: GSK Doc. No. 2019N406358_01 Table 2.7, Table 2.8).

In the subgroup of subjects from Study 207966 with BMI ≥30 kg/m^2, the sample size is relatively smaller (20% of the overall study population). The result in this BMI subgroup is consistent with the result from the overall key secondary endpoint conclusion. In both BMI subgroups, virologic success rates (HIV-1 RNA <50 c/mL) were similar between the Q8W and Q4W treatment arms. A multivariable logistic regression analysis exploring factors potentially associated with Snapshot HIV-1 RNA ≥50 c/mL demonstrated that the strongest association was BMI (Data Source: GSK Doc. No. 2019N406358_01 Table 5.2, Table 5.6). As described in Section 4.2.2, this analysis showed that for the total study population, a BMI ≥30 kg was associated with an odds ratio of 5.0 for Snapshot HIV-1 RNA ≥50 c/mL. Note that not all factors, inclusive of pre-existing resistance mutations and PK levels at the time of failure, were considered in this model. The relatively small number of events limits the ability to make robust conclusions regarding subgroup analyses. Additionally, Multivariable and Baseline factors analyses were conducted using data from Studies 201584, 201585, and 207966, and these findings are summarized in Section 4.2.3.

Table 21 Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL by Baseline Characteristics and Key Demographic Subgroups - Snapshot Analysis (Maintenance Phase) (ITT-E Population)

Subgroup		Treatment CAB + RPV	Number of HIV-1 RNA ≥50 c/mL/Total Assessed (%)	Difference in Proportion (95% CI)[a, b]
Age (years)				
	<35	CAB + RPV Q8W	4/137 (2.9)	2.2 (-1.3, 6.7)
		CAB + RPV Q4W	1/145 (0.7)	
	35 -<50	CAB + RPV Q8W	3/242 (1.2)	0.4 (-1.9, 2.9)
		CAB + RPV Q4W	2/239 (0.8)	
	≥50	CAB + RPV Q8W	2/143 (1.4)	0.0 (-3.9, 3.7)
		CAB + RPV Q4W	2/139 (1.4)	
Sex at Birth				
	Male	CAB + RPV Q8W	4/385 (1.0)	-0.3 (-2.1, 1.5)
		CAB + RPV Q4W	5/380 (1.3)	
	Female	CAB + RPV Q8W	5/137 (3.6)	3.6 (0.7, 8.3)
		CAB + RPV Q4W	0/143	
Race				
	White	CAB + RPV Q8W	5/370 (1.4)	0.1 (-1.8, 2.0)
		CAB + RPV Q4W	5/393 (1.3)	
	Black/African-American	CAB + RPV Q8W	4/101 (4.0)	4.0 (-0.4, 10.0)
		CAB + RPV Q4W	0/90	
BMI (kg/m^2)				
	<30	CAB + RPV Q8W	3/409 (0.7)	0.0 (-1.4, 1.5)
		CAB + RPV Q4W	3/425 (0.7)	
	≥30	CAB + RPV Q8W	6/113 (5.3)	3.3 (-2.6, 9.5)
		CAB + RPV Q4W	2/ 98 (2.0)	

Subgroup		Treatment CAB + RPV	Number of HIV-1 RNA ≥50 c/mL/Total Assessed (%)	Difference in Proportion (95% CI)[a, b]
CD4+ (cells/ mm3)				
	<350	CAB + RPV Q8W	1/ 35 (2.9)	-0.8 (-16.6, 11.8)
		CAB + RPV Q4W	1/ 27 (3.7)	
	350 - <500	CAB + RPV Q8W	1/ 96 (1.0)	1.0 (-3.2, 5.8)
		CAB + RPV Q4W	0/89	
	≥500	CAB + RPV Q8W	7/391 (1.8)	0.8 (-1.0, 2.8)
		CAB + RPV Q4W	4/407 (1.0)	
Derived Baseline CDC Category				
	Stage I	CAB + RPV Q8W	7/391 (1.8)	0.8 (-1.0, 2.8)
		CAB + RPV Q4W	4/407 (1.0)	
	Stage II	CAB + RPV Q8W	2/129 (1.6)	1.6 (-1.9, 5.5)
		CAB + RPV Q4W	0/113	
	Stage III	CAB + RPV Q8W	0/2	-33.3 (-90.6, 60.4)
		CAB + RPV Q4W	1/ 3 (33.3)	
Prior Exposure to CAB + RPV (weeks)[c]				
	0	CAB + RPV Q8W	5/327 (1.5)	0.0 (-2.2, 2.2)
		CAB + RPV Q4W	5/327 (1.5)	
	≥1	CAB + RPV Q8W	4/195 (2.1)	2.1 (0.1, 5.2)
		CAB + RPV Q4W	0/196	
Baseline Third Agent Class				
	CAB + RPV	CAB + RPV Q8W	4/195 (2.1)	2.1 (0.1, 5.2)
		CAB + RPV Q4W	0/196	
	NNRTI	CAB + RPV Q8W	1/151 (0.7)	-0.6 (-4.1, 2.5)
		CAB + RPV Q4W	2/156 (1.3)	
	INSTI	CAB + RPV Q8W	3/136 (2.2)	0.8 (-3.2, 5.1)
		CAB + RPV Q4W	2/141 (1.4)	
	PI	CAB + RPV Q8W	1/ 40 (2.5)	-0.8 (-15.0, 10.5)
		CAB + RPV Q4W	1/ 30 (3.3)	

Data Source: GSK Doc. No. 2019N406358_01 Table 2.5.

a. Difference: Proportion on Q8W - Proportion on Q4W.

b. 95% CIs were calculated using an unconditional exact method with two inverted one-sided tests based on the score statistic.

c. For subjects with >24 weeks of prior exposure to CAB + RPV, the adjusted CMH treatment difference (95% CI) between Q8W and Q4W is 2.0 (0.1, 4.0). The p value from the Test of Homogeneity between 1-24 and >24 weeks prior exposure is 0.250 (Data Source: GSK Doc. No. 2019N406358_01 Table 2.6).

A summary of study outcomes (50 c/mL threshold) at Week 48 by subgroup (age, race, Sex at Birth, country, Baseline CD4+ cell count, Baseline HIV-1 RNA, Derived Baseline CDC Category, prior exposure to CAB + RPV, Baseline BMI, and Baseline Third Agent Class) (Maintenance Phase) using the Snapshot analysis is presented in Data Source: GSK Doc. No. 2019N406358_01 Table 2.7).

3.5.4.2. Change from Baseline in CD4+ Cell Counts by Subgroups

No meaningful differences between treatment groups were observed in the change from Baseline in CD4+ cell counts when analyzed by Baseline covariates and demographic subgroups (Data Source: GSK Doc. No. 2019N406358_01 Table 2.30).

3.5.4.3. Cumulative Proportion of Subjects with CVF up to Week 48 by Randomization Strata

No meaningful differences between treatment groups were observed for the proportion of subjects with CVF when analyzed by randomization strata (prior exposure to CAB + RPV, Table 22). During the Maintenance Phase, no subjects with >24 weeks prior exposure to CAB + RPV met CVF criteria.

Table 22 Cumulative Proportion of Subjects meeting CVF up to Week 48 by Randomization Strata (Maintenance Phase) (ITT-E Population)

Prior Exposure to CAB + RPV (Weeks)	Visit	CVF	
		CAB + RPV Q8W n/N (%)	CAB + RPV Q4W n/N (%)
0	Week 16	3/327 (0.9)	1/327 (0.3)
	Week 24	5/327 (1.5)	1/327 (0.3)
	Week 32	5/327 (1.5)	2/327 (0.6)
1-24	Week 8	1/69 (1.4)	0/68
	Week 24	2/69 (2.9)	0/68
	Week 48	3/69 (4.3)	0/68
>24	Week 8	0/126	0/128
	Week 16	0/126	0/128
	Week 24	0/126	0/128
	Week 32	0/126	0/128
	Week 48	0/126	0/128

Data Source: GSK Doc. No. 2019N406358_01 Table 1.22, Table 2.23, Figure 2.7.
Note: Only visits at which at least one new CVF occurred are included.
Note: No subjects with > 24 weeks prior exposure to CAB + RPV met CVF during the Maintenance Phase.

3.6. Other Efficacy Observations

3.6.1. Oral Lead-in

Across Studies 201584 and 201585, 1 subject only met CVF criteria during CAB + RPV OLI (Data Source: GSK Doc. No. 2017N345267_00 Listing 34). This subject interrupted oral therapy due to a false positive pregnancy test. In Study 207966, of the 654 (63%) subjects who received OLI, no subjects met CVF criteria during the OLI (Data Source: GSK Doc. No. 2019N406358_01 Table 1.8, Listing 4). This result, combined with the Week 96 results of Study LAI116482 [GSK Doc. No. 2014N216014_00], provide support that oral once-daily treatment with CAB 30 mg + RPV 25 mg is effective at maintaining virologic suppression prior to initiation of LA dosing.

3.6.2. Oral Therapy Experience

Oral therapy was permitted in the Phase II and Phase III protocols to ensure that dosing flexibility was available during planned absences from a clinical site (e.g., vacation, travel, etc.), while allowing subjects to remain on LA dosing over time. In Study 201584 and Study 201585, a total of 18 subjects (201584: 11 subjects; 201585: 7 subjects)

received oral therapy for durations ranging from 3 days to approximately 2 months. All but 2 subjects were able to resume IM dosing (Table 23) and no cases of CVF were observed during a period of oral therapy or following resumption of IM dosing.

Table 23 Summary of Oral Therapy Experience in Phase III Study 201584 and Study 201585

Study ID	Duration of Oral Therapy (Days)[a]	Resumed LA Treatment	Reason for Oral Therapy
201584	29	Y	International travel
	4	Y	Late delivery of study treatment to site
	5	Y	Late delivery of study treatment to site
	4	Y	Late delivery of study treatment to site
	61	Y	Holiday
	35	Y	Holiday
	20	Y	Holiday
	29	Y	International travel
	57	N	Holiday – Visa issues resulted in subject being Lost to Follow-Up
	55	N	Requirement for oral anti-coagulation – unable to resume LA dosing due to need for chronic anticoagulation
	28	Y	Holiday
201585	4	Y	Temperature excursion that impacted available study drug
	28	Y	Holiday
	28	Y	Holiday
	21	Y	International Travel
	4	Y	Injection delay due to AE
	29	Y	Temperature excursion that impacted available study drug
	22	Y	To correct site scheduling error

Note: All subjects on CAB + RPV in Study 201584 and 201585 receive Q4W treatment (IM dosing was scheduled for every 4 weeks.
Note: This table contains oral therapy information beyond the cut-off date for Week 48 statistical analysis. This additional information is included for informational purposes.
a. Each row represents oral therapy information for an individual subject.

In Study 207966 (Phase IIIb), subjects adhered to the planned treatment schedule for CAB + RPV administration, with few injections administered outside of the allowable ±7 day window. No injections were missed without coverage with a planned oral therapy strategy for either the Q8W or Q4W regimens. The duration of oral therapy ranged from 2 to 64 days (GSK Doc No. 2019N406358_01 Listing 60). There were fewer oral therapy episodes in the Q8W group compared to the Q4W group (Q8W = 4; Q4W =7). 3 of the 4 subjects in the Q8W group received oral therapy due to delayed injection schedule and 1 subject received oral therapy for a planned missed injection (Data Source: GSK Doc. No. 2019N406358_01 Table 3.4). The fewer oral episodes in the Q8W group potentially reflects the extended dosing interval offered by Q8W versus Q4W dosing.

In Study 200056 (Phase IIb), 8 subjects temporarily received oral therapy for a duration ranging from 17 to 56 days. All subjects were able to resume IM dosing (Table 24) and

no cases of CVF were observed during a period of oral therapy or following resumption of IM dosing.

Table 24 Summary of Oral Therapy Experience in Study 200056 (Phase IIb)

Study	Treatment[a]	Study Period	Duration of Oral Therapy (Days)	Resumed LA treatment
200056	Q8W	Maintenance	17	Y
	Q8W[b]	Maintenance	55 (CAB)	Y
			27 (RPV)	Y
	Q8W	Maintenance	56	Y
	Q4W	Maintenance	27	Y
	Q4W	Maintenance	22	Y
		Extension	28	Y
	Q4W	Extension	26	Y
	Q4W	Maintenance	56	Y
	Q8W	Extension	56	Y

a. Each row represents oral therapy information for an individual subject.
b. 1 subject in the Q8W arm received the wrong oral therapy regimen for a portion of this period. The subject was prescribed the oral arm regimen of CAB 30 mg + ABC/3TC 600/300 mg instead of CAB 30 mg + RPV 25 mg for the first 28 days of oral bridge. The mistake was addressed, and the subject was given the correct regimen for the remaining 27 days. There were no issues of safety or efficacy and the subject remains in the study currently.

In addition to the use of oral therapy in Studies 201584, 201585, 207966 and 200056, results from LAI116482 provide evidence for the safety and efficacy of oral CAB 30 mg + oral RPV 25 mg once daily for >2 years, a period greatly exceeding the intended duration of oral therapy use.

3.7. Patient-Reported Outcomes

Health outcome assessments are described in Section 7.9 of the protocols for the Phase III Studies 201584 and 201585, and in Section 7.8 of the Phase IIIb Study 207966 protocol.

A review of key subject demographic and clinical characteristics relevant to health outcomes assessments at Baseline demonstrates that the study populations are different between Study 201584 and Study 201585 in terms of number of years on previous ART (Table 4, Table 5). This difference in study populations, limits the ability to compare experience with regard to oral therapy, LA therapy and the demands of living with daily HIV treatment. Therefore, the evaluation of PROs within Study 201584 and Study 201585 remains important.

3.7.1. HIVTSQs Scores

3.7.1.1. Studies 201584 and 20585

In Study 201584 and Study 201585, the CAB + RPV Q4W group demonstrated greater improvements in total treatment satisfaction compared with the CAR group (Table 25).

This difference was significant at each timepoint for Study 201585. For Study 201585, the change in treatment satisfaction between Baseline and Week 44 achieved the MCID based on the commonly applied, distribution-based approach, of ½ standard deviation [Norman, 2003]. In Study 201584, high mean Baseline values were observed; 59.3 (SD 7.37) and 59.1 (SD 7.55) in the CAB + RPV and CAR arms, respectively (Data Source: GSK Doc. No. 2017N345267_00 Table 6.23). This demonstrates ceiling effects with the HIVTSQs in Study 201584, limiting the possibility of detecting a significant increase in mean difference between treatment groups at Week 44.

There was a significant treatment-by-baseline interaction detected in the pooled analysis at Week 24 ($p<0.01$) and Week 44 ($p<0.01$) (Table 25).

Table 25 Statistical Analysis of HIVTSQs – Change from Baseline in Total Treatment Satisfaction Score by Visit for Study 201584, Study 201585, and Pooled Data – LOCF (Maintenance Phase) (ITT-E)

Treatment	Visit	N	n	Adjusted Mean[a]	95% CI of Adjusted Mean	Adjusted Mean Difference	95% CI of Adjusted Mean Difference	p-value
201584[e]								
Week 24	CAB + RPV Q4W	283	257	1.6	(0.8, 2.5)	2.2	(1.0, 3.4)	<0.001[b]
	CAR	283	253	-0.5	(-1.4, 0.3)			
Week 44	CAB + RPV Q4W	283	257	1.3	(0.5, 2.1)	0.7	(-0.4, 1.9)	0.217[b]
	CAR	283	256	0.5	(-0.3, 1.4)			
201585[f]								
Week 24	CAB + RPV Q4W	308	300	6.43	(5.59, 7.28)	5.39	(4.17, 6.60)	<0.001[c]
	CAR	308	288	1.05	(0.18, 1.91)			
Week 44	CAB + RPV Q4W	308	300	6.12	(5.21, 7.03)	5.68	(4.37, 6.98)	<0.001[c]
	CAR	308	294	0.44	(-0.48, 1.37)			
Pooled Studies 201584 and 201585[g]								
Week 24	CAB + RPV Q4W	591	557	4.2	(3.6, 4.8)	3.9	(3.0, 4.8)	<0.001[d]
	CAR	591	543	0.3	(-0.3, 0.9)			
Week 44	CAB + RPV Q4W	591	557	3.9	(3.2, 4.5)	3.4	(2.5, 4.3)	<0.001[d]
	CAR	591	552	0.5	(-0.1, 1.2)			

Data Source: GSK Doc. No. 2017N345267_00 Table 6.24, GSK Doc. No. 2018N370336_00 Table 7.24, ISE/ISS Table 2.16

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC

Note: Mean HIVTSQs Baseline scores in Study 201584 were 59.3 (SD 7.4) and 59.1 (SD 7.6) for the CAB + RPV and CAR groups, respectively (Data Source: Study 201584 Table 6.21).

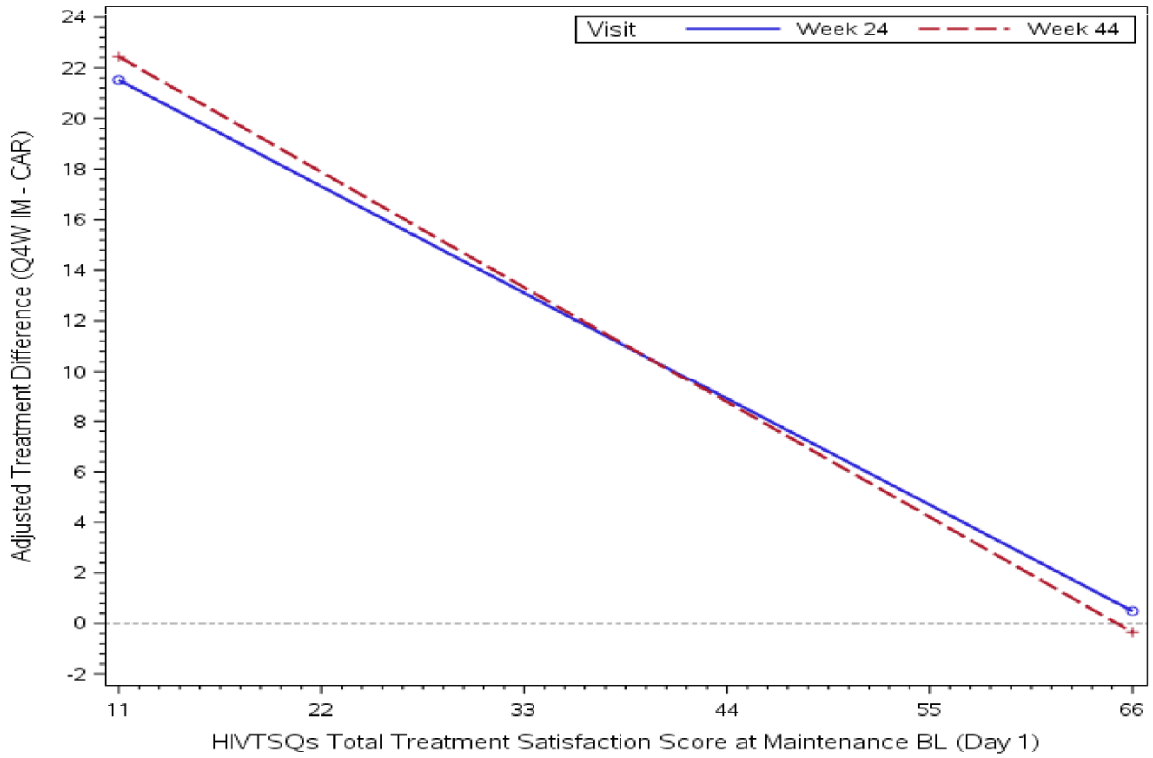
Note: Mean HIVTSQs Baseline scores in Study 201585 were 55.3 (SD 9.1) and 55.4 (SD 8.7) for the CAB + RPV and CAR groups, respectively (Data Source: Study 201585 Table 7.22).

Note: Interaction between treatment group and baseline at each timepoint was investigated but not included in the main analysis model and was considered to be 'significant' if p-value is <0.1.

a. Adjusted mean is the estimated mean change from Baseline score by visit in each treatment calculated from a ANCOVA model including the covariates: Baseline Score, sex at birth, age (<50, ≥50), and race (white, non-white) for pooled analysis; additional covariates included were; for Study 201585 third agent class (INSTI, PI, NNRTI) and for Study 201584 Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL).
b. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0027.
c. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0029.
d. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0071.
e. p-value for interaction between treatment group and Baseline score = 0.039, 0.007 for each visit (Week 24, Week 44), respectively.
f. p-value for interaction between treatment group and Baseline score = <0.01, <0.01 for each visit (Week 24, Week 44), respectively.
g. p-value for interaction between treatment group and Baseline score = <0.01, <0.01 for each visit (Week 24, Week 44), respectively.

The interaction plot shown in Figure 6, shows that the treatment difference at both timepoints is more pronounced in subjects with lower satisfaction scores at baseline. This is consistent with the presence of a ceiling effect at Baseline for this questionnaire. Of note, the results presented in Table 25 were produced from a main analysis model without treatment-by-baseline interaction effects.

Figure 6 Interaction Plot for Treatment-by-Baseline: Statistical Analysis of HIVTSQs – Change from Baseline in Total Treatment Satisfaction Score (LOCF) by Visit – Maintenance Phase – Pooled Studies 201584 and 201585



Data Source: ISE/ISS Figure 2.08
Note: Q4W IM = CAB + RPV group, For Study 201584, CAR = ABC/DTG/3TC.
Note: Adjusted treatment difference for mean change from baseline is estimated from ANCOVA model at each visit including baseline score, sex at birth, age (<50, ≥50 years), race (white, non-white), treatment and interaction between treatment and baseline as covariates.
Note: The Treatment Difference is CAB + RPV – CAR.

3.7.1.2. Study 207966

In Phase IIIb Study 207966, differential results were observed based on prior CAB + RPV exposure; thus, results here are presented separately for the population of subjects with prior exposure to CAB + RPV and without prior exposure to CAB + RPV.

For subjects without prior exposure to CAB + RPV (0 weeks) Baseline HIVTSQs mean total [SD] scores were similar between the two treatment groups at 57.73 [9.21] points for Q8W group and 56.72 [9.34] points for Q4W group (GSK Doc. No. 2019N406358_01

Table 6.18). HIVTSQs total scores significantly improved from Baseline at Weeks 24 and 48 for both treatment groups, after adjusting for Baseline score, sex at birth, age, race (white, non-white), and third agent class (INSTI, PI, NNRTI). A statistically significant difference between Q8W and Q4W CAB + RPV LA groups in adjusted mean change from Baseline in treatment satisfaction was observed at both timepoints, in favor of the Q8W dosing (Table 26).

Table 26 Statistical Analysis of HIVTSQs – Change from Baseline in Total HIVTSQs Score by Visit for Subjects Without Prior Exposure to CAB + RPV – LOCF – Study 207966

Visit	Treatment	N	n	Adjusted Mean[a]	95% CI of Adjusted Mean	Adjusted Diff (Q8W-Q4W)	95% CI of TRT diff	p-value for TRT diff[b]
Week 24	CAB + RPV Q8W	327	319	5.07	(4.36, 5.78)	1.07	(0.07, 2.07)	0.036
	CAB + RPV Q4W	327	323	4.00	(3.29, 4.70)			
Week 48	CAB + RPV Q8W	327	319	4.86	(4.02, 5.69)	1.74	(0.56, 2.91)	0.004
	CAB + RPV Q4W	327	323	3.12	(2.29, 3.95)			

Data Source: GSK Doc. No. 2019N406358_01 Table 6.21.

Note: 12-item HIVTSQs min score: 0 (very dissatisfied); max score: 66 (very satisfied)

a. Adjusted mean is the estimated mean change from baseline score by visit in each treatment calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, ≥50 years) and race (white, non-white).

b. The p-values for interaction between treatment group and baseline score at Week 24 and Week 48 respectively are: 0.065 and 0.004. Interaction term is considered to be 'significant' at the level of <0.10.

HIVTSQs mean total [SD] scores for subjects with prior exposure to CAB + RPV (≥1 week) were high at Baseline (62.22 [5.41] points for Q8W group and 61.98 [6.72] points for Q4W group) and remained stable across Weeks 24 and 48 after adjusting for Baseline Score, sex at birth (female, male), age (<50, ≥50 years), race (white, non-white) and prior exposure to CAB + RPV (1 to 24, >24 weeks), without significant differences between the two treatment groups (GSK Doc. No. 2019N406358_01 Table 6.18, Table 27).

Table 27 Statistical Analysis of HIVTSQs – Change from Baseline in Total HIVTSQs Score by Visit for Subjects with Prior Exposure to CAB + RPV – LOCF – Study 207966

Visit	Treatment	N	n	Adjusted Mean[a]	95% CI of Adjusted Mean	Adjusted Diff (Q8W-Q4W)	95% CI of TRT diff	p-value for TRT diff[b]
Week 24	CAB + RPV Q8W	195	191	0.59	(-0.03, 1.21)	0.07	(-0.81, 0.95)	0.871
	CAB + RPV Q4W	196	193	0.52	(-0.10, 1.14)			
Week 48	CAB + RPV Q8W	195	191	0.44	(-0.27, 1.15)	0.48	(-0.52, 1.48)	0.344
	CAB + RPV Q4W	196	194	-0.05	(-0.75, 0.66)			

Data Source: GSK Doc. No. 2019N406358_01 Table 6.22.
Note: 12-item HIVTSQs min score: 0 (very dissatisfied); max score: 66 (very satisfied).
a. Adjusted mean is the estimated mean change from baseline score by visit in each treatment calculated from an ANCOVA model including the covariates: Baseline Score, sex at birth (female, male), age (<50, ≥50 years), race (white, non-white) and prior exposure to CAB + RPV (1 to 24, >24 weeks).
b. The p-values for interaction between treatment group and baseline score at Week 24 and Week 48 respectively are: 0.688 and 0.255. Interaction term is considered to be 'significant' at the level of <0.10.

For subjects without prior CAB + RPV exposure, key drivers for change from Baseline in HIVSTQs total score were items 6 (flexibility of recent HIV treatment), 5 (convenience associated with HIV treatment) and 10 (satisfaction to continue with present HIV treatment) (Data Source: GSK Doc. No. 2019N406358_01, Table 6.20). Baseline scores for individual items in the HIVSTQs were comparable with similar means and medians in both treatment groups.

3.7.2. HIVTSQc Scores

3.7.2.1. Study 201584

Baseline values for the HIVTSQs were higher in Study 201584 compared with Study 201585 and limit the possibility to show significant increase in mean difference between treatment groups (Data Source: GSK Doc. No. 2017N345267_00 Table 6.21, GSK Doc. No. 2018N370336_00 Table 7.22). To account for this ceiling effect, the HIVTSQc change version was used at Week 48. The HIVTSQc, administered at a single point in time (Week 48), compares subjects' experience with their treatment compared with their treatment at Baseline. Based on this analysis, subjects in the CAB + RPV group reported a statistically significant improvement in treatment satisfaction compared with subjects in the CAR group when compared to the Induction Phase (Table 28).

Table 28 Statistical Analysis of HIVTSQc in Study 201584 – Total Treatment Satisfaction Score Change at Week 48 (Maintenance Phase) (ITT-E)

Treatment	N	n	Adjusted Mean	S.E. of Adjusted Mean	Adjusted Mean Difference	95% CI of Adjusted Mean Difference	p-value
CAB + RPV Q4W	283	263	29.6	0.49	4.1	(2.8, 5.5)	<0.001[a]
CAR	283	266	25.5	0.48			

Data Source: GSK Doc. No. 2017N345267_00 Table 6.27.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.
Note: Estimates are calculated from an ANOVA model adjusting for Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL), sex at birth (female, male), age (<50, ≥50 Years) and race (white, non-white).
a. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0027.

3.7.2.2. Study 207966

In Study 207966, the HIVTSQc was administered at Week 48 in both the Q4W and Q8W treatment groups, to assess how satisfaction with CAB + RPV approximately a year within the study compares to the HIV therapy subjects were receiving prior to entering the study, with the intention to account for potentially high Baseline values (ceiling effects) with HIVTSQs. High total HIVTSQ change scores were reported in both treatment groups for subjects without prior exposure to CAB + RPV at Week 48. The change in satisfaction from prior treatment (SOC) significantly favored the Q8W group compared with Q4W group at Week 48 (Table 29).

Table 29 Statistical Analysis of HIVTSQc – Total HIVTSQc Score at Week 48 for Subjects Without Prior CAB + RPV Exposure – Study 207966

Treatment	N	n	Adjusted Mean	95% CI of Adjusted Mean	Adjusted Diff (Q8W-Q4W)	95% CI (Q8W-Q4W)	p-value (Q8W-Q4W)
CAB + RPV Q8W	327	312	28.9	(27.9, 29.9)	1.9	(0.5, 3.2)	0.008
CAB + RPV Q4W	327	315	27.1	(26.1, 28.0)			

Data Source: GSK Doc. No. 2019N406358_01 Table 6.43.
Note: 12-item HIVTSQc min score: -33 (much less satisfied now); max score: 33 (much more satisfied now).

HIVTSQ change scores for subjects with prior CAB + RPV exposure in both treatment groups also were high at Week 48. A significant difference favoring the Q8W group compared with the Q4W group in change in satisfaction from prior treatment (Q4W CAB + RPV) was observed at Week 48 (Table 30).

Table 30 Statistical Analysis of HIVTSQc – Total HIVTSQc Score at Week 48 for Subjects Enrolling into Study 207966 from Q4W Group in Study 201585

Treatment	N	n	Adjusted Mean[a]	95% CI of Adjusted Mean	Adjusted Diff (Q8W-Q4W)	95% CI of TRT diff	p-value for TRT diff
CAB + RPV Q8W	126	124	29.1	(27.4, 30.8)	4.4	(2.0, 6.9)	<0.001
CAB + RPV Q4W	127	125	24.7	(22.9, 26.4)			

Data Source: GSK Doc. No. 2019N406358_01 Table 6.29.
Note: 12-item HIVTSQc min score: -33 (much less satisfied now); max score: 33 (much more satisfied now).
a. Adjusted mean is the estimated mean change score in each treatment calculated from an ANCOVA model including the covariates: Sex at birth (female, male), age (<50, ≥50 years) and race (white, non-white).

3.7.3. ACCEPT Scores

To measure the concept of medication acceptance, we included the General Acceptance domain from the ACCEPT questionnaire in the Phase III and IIIb studies. This measure asks subjects to weigh the advantages and disadvantages of their treatment and may be a predictor of future adherence.

3.7.3.1. Studies 201584 and 201585

In Study 201585, the CAB + RPV Q4W group demonstrated statistically significant improvements in acceptance of HIV treatment, compared with the CAR group from Baseline to Week 44 (Table 31). This difference was significant at all timepoints for Study 201585. The high Baseline values observed in Study 201584 do not allow for a significant increase in mean difference between treatment groups from Baseline to Week 44, indicating ceiling effects with this measure (Data Source: GSK Doc. No. 2017N345267_00 Table 6.32).

Baseline characteristics relevant to health outcomes assessments of Study 201584 and Study 201585 demonstrate that there are important differences in the study populations. Notably, subjects from Study 201584 were naïve to treatment, while those from Study 201585 had been on ART for a mean of approximately 5.4 years prior to participating in the study (Data Source: GSK Doc. No. 2018N370336_00 Table 1.31). Therefore, subjects from Study 201585 had significantly more experience with HIV treatments and are able to offer a more nuanced assessment of the demands of HIV treatment.

Table 31 Statistical Analysis – Change from Baseline in General Acceptance Domain of the ACCEPT Questionnaire for Study 201584, Study 201585, and Pooled Data – Adjusted LOCF

Treatment	Visit	N	n	Adjusted Mean[a]	95% CI of Adjusted Mean	Adjusted Mean Difference	95% CI of Adjusted Mean Difference	p-value
201584[e]								
Week 8	CAB + RPV Q4W	283	253	3.3	(0.8, 5.8)	2.2	(-1.4, 5.7)	0.232[b]
	CAR	283	256	1.2	(-1.3, 3.6)			
Week 24	CAB + RPV Q4W	283	255	3.7	(1.1, 6.4)	2.7	(-1.0, 6.4)	0.154[b]
	CAR	283	261	1.1	(-1.5, 3.7)			
Week 48	CAB + RPV Q4W	283	255	3.0	(0.4, 5.6)	2.2	(-1.4, 5.8)	0.236[b]
	CAR	283	262	0.8	(-1.7, 3.4)			
201585[f]								
Week 8	CAB + RPV Q4W	308	302	8.9	(6.3, 11.6)	7.9	(4.1, 11.7)	<0.001[c]
	CAR	308	287	1.0	(-1.7, 3.8)			
Week 24	CAB + RPV Q4W	308	303	12.3	(9.9, 14.8)	6.9	(3.3, 10.4)	<0.001[c]
	CAR	308	295	5.5	(3.0, 8.0)			
Week 48	CAB + RPV Q4W	308	302	13.7	(11.2, 16.3)	10.7	(7.1, 14.4)	<0.001[c]
	CAR	308	298	3.0	(0.4, 5.6)			
Pooled Studies 201584 and 201585[g]								
Week 8	CAB + RPV Q4W	591	555	6.3	(4.4, 8.1)	5.0	(2.4, 7.7)	<0.001[d]
	CAR	591	545	1.2	(-0.7, 3.1)			
Week 24	CAB + RPV Q4W	591	558	8.4	(6.6, 10.2)	5.0	(2.4, 7.5)	<0.001[d]
	CAR	591	558	3.4	(1.6, 5.2)			
Week 48	CAB + RPV Q4W	591	557	8.8	(7.0, 10.6)	6.8	(4.2, 9.4)	<0.001[d]
	CAR	591	562	2.0	(0.2, 3.8)			

Data Source: GSK Doc. No. 2017N345267_00 Table 6.33, GSK Doc. No. 2018N370336_00 Table 7.33, ISE/ISS Table 2.14
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC
Note: Interaction between treatment group and baseline at each timepoint was investigated but not included in the main analysis model and was considered to be 'significant' if p-value is <0.1.

a. Adjusted mean is the estimated mean change from Baseline score by visit in each treatment calculated from a ANCOVA model including the covariates: Baseline Score, sex at birth, age (<50, ≥50), and race (white, non-white) for the pooled analysis; for Study 201585 third agent class (INSTI, PI, NNRTI) and for Study 201584 Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL).
b. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0027.
c. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0029.
d. Statistical significance can be claimed if the p-value is less than Bonferroni adjusted alpha of 0.0071.
e. p-value for interaction between treatment group and Baseline score = 0.165, 0.781, 0.519 for each visit (Week 8, Week 24, Week 48), respectively.
f. p-value for interaction between treatment group and Baseline score = 0.05, <0.01, <0.01 for each visit (Week 8, Week 24, Week 48), respectively.
g. p-value for interaction between treatment group and Baseline score = 0.01, <0.01, <0.01 for each visit (Week 8, Week 24, Week 48), respectively.

3.7.3.2. Study 207966

To measure the concept of medication acceptance, we included the General Acceptance domain from the ACCEPT questionnaire in Study 207966.

For subjects without prior exposure to CAB + RPV (0 weeks) in Study 207966, Baseline General Acceptance mean (SD) scores were similar between the 2 treatment groups at 81.5 (25.23) points for the Q8W group and 81.8 (25.98) points for the Q4W group. General Acceptance scores significantly improved from Baseline at Weeks 24 and 48 for both treatment groups, after adjusting for Baseline score, sex at birth, age, race (white, non-white). No significant differences between Q8W and Q4W CAB + RPV groups in adjusted mean change from Baseline in treatment acceptance were observed at any timepoint. (Table 32).

Table 32 Statistical Analysis of Change from Baseline in General Acceptance Score by Visit for Subjects Without Prior Exposure to CAB + RPV – LOCF (ITT-E Population) – Study 207966

Visit	Treatment	N	n	Adjusted Mean CFB	95% CI of Adjusted Mean	Adjusted Diff (Q8W-Q4W)	95% CI (Q8W-Q4W)	p-value (Q8W-Q4W)
Week 24	CAB + RPV Q8W	327	319	5.8	(3.2, 8.5)	1.7	(-2.1, 5.4)	0.379
	CAB + RPV Q4W	327	323	4.2	(1.5, 6.8)			
Week 48	CAB + RPV Q8W	327	319	6.8	(4.3, 9.3)	1.1	(-2.4, 4.6)	0.525
	CAB + RPV Q4W	327	324	5.7	(3.2, 8.1)			

Data Source: GSK Doc. No. 2019N406358_01 Table 6.36.
Note: General Acceptance min score 0 (not at all acceptable); max score 100 (totally acceptable).

General Acceptance mean (SD) scores for subjects with prior exposure to CAB + RPV (≥1 weeks) were high at Baseline (89.3 [20.03] points for the Q8W group and 91.2 [16.74] points for the Q4W group) and remained stable across Weeks 24 and 48 after adjusting for Baseline Score, sex at birth (female, male), age (<50, ≥50 years), race (white, non-white), and prior exposure to CAB + RPV (1 to 24, >24 weeks), without significant differences between the two treatment groups (Table 33).

Table 33 Statistical Analysis of Change from Baseline in General Acceptance Score by Visit for Subjects with Prior Exposure to CAB + RPV – LOCF (ITT-E Population) – Study 207966

Visit	Treatment	N	n	Adjusted Mean	95% CI of Adjusted Mean	Adjusted Diff (Q8W-Q4W)	95% CI (Q8W-Q4W)	p-value (Q8W-Q4W)
Week 24	CAB + RPV Q8W	195	192	-0.4	(-3.0, 2.2)	0.5	(-3.1, 4.2)	0.772
	CAB + RPV Q4W	196	194	-1.0	(-3.5, 1.6)			
Week 48	CAB + RPV Q8W	195	192	-1.0	(-3.9, 2.0)	0.9	(-3.2, 5.1)	0.659
	CAB + RPV Q4W	196	194	-1.9	(-4.8, 1.1)			

Data Source: GSK Doc. No. 2019N406358_01 Table 6.37.
Note: General Acceptance min score 0 (not at all acceptable); max score 100 (totally acceptable).

3.7.4. Treatment Preference

3.7.4.1. Study 201584 and Study 201585

In the ITT-E population, 86% (266/308) of the LA arm subjects in Study 201585 and 91% (257/283) of LA arm subjects in Study 201584 rated the LA treatment as their preferred option over daily oral therapy after 48 weeks of treatment. 2% (7/308) in Study 201585 and 1% (2/283) in Study 201584 preferred daily oral treatment, with the remaining 11% (35/308) and 8% (24/283), respectively, classified as missing data (Data Source: GSK Doc. No. 2018N370336_00 Table 7.39; GSK Doc. No. 2017N345267_00 Table 6.39). A post hoc analysis of subjects with response data at Week 48 showed that almost all responders preferred the LA regimen over CAR: 97% (266/273) in Study 201585 and 99% (257/259) in Study 201584 (Data Source: Known to Sponsor). No participant refused to respond to the preference question.

3.7.4.2. Study 207966

In Study 207966, treatment preference results were stratified by prior exposure to CAB + RPV and treatment group (Table 34). Aggregate results were reported for subjects randomized to the Q4W group.

Table 34 Subject Disposition by Prior Exposure to CAB + RPV (ITT-E Population) – Study 207966

Analysis Strata	Weeks	Treatment	N
Prior Exposure to CAB + RPV	0	Q8W	327
		Q4W	327
	≥1	Q8W	195
		Q4W	196

Data Source: GSK Doc. No. 2019N406358_01 Table 1.22, Table 1.28, Table 6.21, Table 6.22.

At Week 48, of subjects randomized to Q4W treatment group (N=523) with recorded response to the preference question (n=497), 94% (468/497) preferred Q4W dosing of CAB + RPV compared with 3% (16/497) who preferred oral CAB + RPV (Data Source: GSK Doc. No. 2019N406358_01, Table 6.40). Another 3% (13/497) reported no preference. These are subjects with no experience of Q8W dosing of CAB + RPV. Reasons for their preference are shown in Table 35.

Table 35 Reasons for Preference for Subjects in the CAB + RPV Q4W Group – Study 207966 (Maintenance Phase)

Question	Response	Reasons for preference for CAB + RPV Q4W N = 468 n/N (%)	Reasons for preference for CAB + RPV Oral N = 16 n/N (%)
What is the main practical attribute of this HIV therapy supporting your preference?	Mode of administration	143/468 (31)	2/16 (13)
	Frequency of administration	244/468 (52)	2/16 (13)
	Time required for administration	17/468 (4)	3/16 (19)
	Scheduling visits	29/468 (6)	1/16 (6)
	Storing medications	12/468 (3)	0/16
	Impact of side effects	12/468 (3)	7/16 (44)
	Other	11/468 (2)	1/16 (6)
What is the main benefit related to this HIV therapy supporting your preference?	More convenient	374/468 (80)	8/16 (50)
	Less stressful	33/468 (7)	3/16 (19)
	Less stigma	13/468 (3)	0/16
	Easier to take drug exactly as prescribed	33/468 (7)	1/16 (6)
	More efficacious	10/468 (2)	0/16
	Other	5/468 (1)	4/16 (25)

Data Source: GSK Doc. No. 2019N406358_01, Table 6.46.
Note: In Preference questionnaire, Questions 2 and 3 were skipped if a subject responded with 'No preference' in Question 1. Subjects in Q4W ATLAS-2M did not receive injectable regimen of CAB LA + RPV LA every 8 weeks during the study and therefore cannot have this treatment as their preferred treatment. Oral daily HIV Treatment refers to the oral medication of CAB + RPV subjects received during the oral lead-in period.

At Week 48, of subjects randomized to Q8W treatment group without prior exposure to CAB + RPV (N=327) with recorded response to the preference question (n=306), 98%

(300/306) preferred Q8W dosing of CAB + RPV compared with 1% (4/306) who preferred oral CAB + RPV (Data Source: GSK Doc. No. 2019N406358_01, Table 6.39). Less than 1% of these subjects (2/306) reported no preference. These are subjects with no experience of Q4W dosing of CAB + RPV. Reasons for their preference are shown in the Table 36.

Table 36 Reasons for Preference for Subjects in CAB + RPV Q8W Group Without Prior CAB + RPV Exposure – Study 207966 (Maintenance Phase)

Question	Response	Reasons for preference for CAB + RPV Q8W N = 300 n/N (%)	Reasons for preference for CAB + RPV Oral N = 4 n/N (%)
What is the main practical attribute of this HIV therapy supporting your preference?	Mode of administration	66/300 (22)	1/4 (25)
	Frequency of administration	173/300 (58)	0/4
	Time required for administration	14/300 (5)	0/4
	Scheduling visits	23/300 (8)	0/4
	Storing medications	9/300 (3)	0/4
	Impact of side effects	11/300 (4)	1/4 (25)
	Other	4/300 (1)	2/4 (50)
What is the main benefit related to this HIV therapy supporting your preference?	More convenient	233/300 (78)	2/4 (50)
	Less stressful	22/300 (7)	1/4 (25)
	Less stigma	11/300 (4)	0/4
	Easier to take drug exactly as prescribed	20/300 (7)	0/4
	More efficacious	10/300 (3)	0/4
	Other	4/300 (1)	1/4 (25)

Data Source: GSK Doc. No. 2019N406358_01, Table 6.45.
Note: In Preference questionnaire, Questions 2 and 3 were skipped if a subject responded with 'No preference' in Question 1. Only subjects who has received the treatment (e.g., injectable regimen of CAB LA + RPV LA every 4 weeks) during the study can have this treatment as their preferred treatment. Oral daily HIV Treatment refers to the oral medication of CAB + RPV subjects received during the oral lead-in period.

At Week 48, of subjects randomized to Q8W treatment group with prior exposure to CAB + RPV (N=195) with recorded response to the preference question (n=191), 94% (179/191) preferred Q8W dosing of CAB + RPV compared with 3% (6/191) preferring Q4W dosing and 2% (4/191) preferring oral CAB + RPV. 1% (2/191) reported no preference (Data Source: GSK Doc. No. 2019N406358_01, Table 6.39). Reasons for their preference are shown in Table 37.

Table 37 Reasons for Preference for Subjects in the CAB + RPV Q8W Group with Prior CAB + RPV Exposure - Study 207966 (Maintenance Phase)

Question	Response	Reasons for preference for CAB + RPV Q8W N = 179 n/N (%)	Reasons for preference for CAB + RPV Q4W N = 6 n/N (%)	Reasons for preference for CAB + RPV Oral N = 4 n/N (%)
What is the main practical attribute of this HIV therapy supporting your preference?	Mode of administration	27/179 (15)	0/6	3/4 (75)
	Frequency of administration	112/179 (63)	1/6 (17)	0/4
	Time required for administration	7/179 (4)	1/6 (17)	1/4 (25)
	Scheduling visits	25/179 (14)	2/6 (33)	0/4
	Storing medications	1/179 (<1)	1/6 (17)	0/4
	Impact of side effects	5/179 (3)	1/6 (17)	0/4
	Other	2 179 (1)	0/6	0/4
What is the main benefit related to this HIV therapy supporting your preference?	More convenient	140/179 (78)	6/6 (100)	2/4 (50)
	Less stressful	16/179 (9)	0/6	0/4
	Less stigma	4/179 (2)	0/6	0/4
	Easier to take drug exactly as prescribed	13/179 (7)	0/6	2/4 (50)
	More efficacious	4/179 (2)	0/6	0/4
	Other	2/179 (1)	0/6	0/4

Data Source: GSK Doc. No. 2019N406358_01 Table 6.45.
Note: In Preference questionnaire, Questions 2 and 3 were skipped if a subject responded with 'No preference' in Question 1. Only subjects who has received the treatment (e.g., injectable regimen of CAB LA + RPV LA every 4 weeks) during the study can have this treatment as their preferred treatment. Oral daily HIV Treatment refers to the oral medication of CAB + RPV subjects received during the oral lead-in period.

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

This section describes the data relevant to dose selection decisions made with CAB and RPV and concludes with the data and subsequent decisions regarding the selected dose in adults with HIV-1 infection.

Clinical pharmacology data to support dose recommendations in various patient populations and with concomitant medications are detailed in m2.7.2.

4.1. Dose Selection

The CAB + RPV regimen consists of an OLI phase of at least 4 weeks, followed by monthly or every 2 months CAB LA + RPV LA IM injections. An OLI of CAB + RPV was included in Study 201584, Study 201585, and Study 207966 to evaluate the potential in each subject for ADRs which would preclude IM dosing. The monthly CAB + RPV

dosing regimen begins with an initiation dose consisting of single 3 mL IM injections of CAB LA 600 mg + RPV LA 900 mg followed by a continuation dose of single 2 mL IM injections of CAB LA 400 mg + RPV LA 600 mg every month thereafter. The every 2 months CAB + RPV dosing regimen begins with initiation doses consisting of the first 2 IM injections of CAB LA 600 mg + RPV LA 900 mg separated by 1 month, followed by continuation doses of IM CAB LA 600 mg + RPV LA 900 mg every 2 months.

In exceptional circumstances for subjects requiring a brief interruption in IM therapy, short-term oral therapy (CAB 30 mg + RPV 25 mg once daily) is permitted in accordance with proposed labeling. Dose selection was based on efficacy and safety from 2 Phase IIb studies; Study LAI116482 (oral CAB 30 mg) and Study 200056 (CAB LA + RPV LA). Week 96 results from Study 200056 supported the evaluation of the CAB + RPV Q8W regimen in comparison to Q4W dosing in Phase IIIb Study 207966.

The pivotal Phase III Studies 201584 and 201585 demonstrated the non-inferiority of the CAB + RPV Q4W regimen compared with CAR at Week 48 in subjects with prior evidence of virologic suppression. In addition, comparable efficacy was observed across key demographic subgroups. Based on population PK analysis using pooled data from Phase IIb and Phase III studies, no dose adjustment of CAB LA is required based on demographic characteristics (age, gender, race, BMI, weight), Hepatitis co-infection, smoking status, or laboratory parameters.

4.1.1. Dose Selection for CAB Oral

4.1.1.1. Study LAI116482 and Study 200056

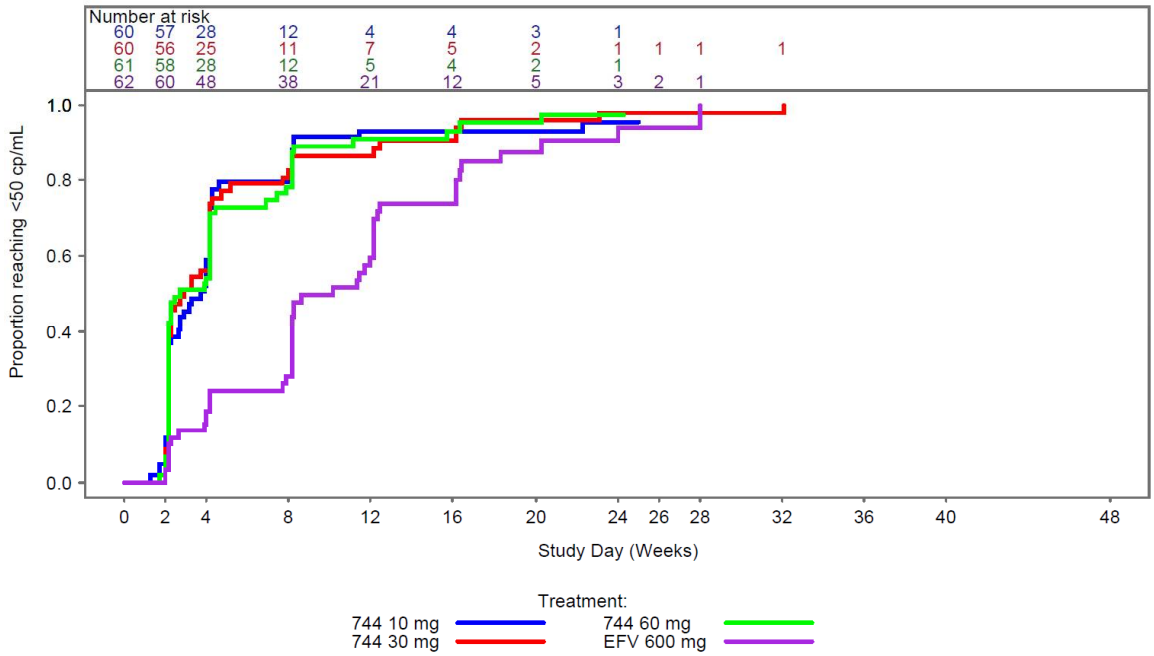
CAB 30 mg once daily (in combination with oral RPV 25 mg once daily) is recommended as short-term OLI to assess tolerability prior to IM CAB LA injections and for short-term oral therapy for planned interruptions of CAB LA IM injection dosing during CAB LA + RPV LA treatment. Oral CAB was evaluated as OLI and oral therapy in Phase III and in Phase IIb Study 200056 and supported by long-term safety and efficacy of oral CAB + oral RPV for maintenance of virologic suppression in Phase IIb Study LAI116482.

Study LAI116482 was conducted to support dose selection of oral CAB required to maintain virologic suppression when given in combination with the marketed oral formulation of RPV [GSK Doc No. 2013N180642_00]. This study first evaluated the dose-response relationship of oral CAB for inducing virologic suppression in combination with 2 NRTIs and secondly, the durability for maintaining virologic suppression following switch to dual treatment with oral CAB + RPV. Efficacy and safety from LAI116482 following oral CAB administration supported extrapolation to LA dosing that targeted comparable systemic exposure (see m2.7.2).

HIV-infected, ART-naïve subjects were randomized to receive oral CAB 10 mg, 30 mg, or 60 mg once daily in combination with 2 NRTIs or an oral comparator for 24 weeks during the Induction Period. In subjects with viral suppression, the 2 NRTIs were replaced with oral RPV at Week 24 and dosing with CAB continued for an additional 72 weeks during the Maintenance Period.

All 3 doses of oral CAB once daily, in combination with 2 NRTIs, achieved mean decreases in plasma HIV-1 RNA of >2.6-log10 c/mL at Week 20/24 [GSK Doc. No. 2014N216014_00]. A differentiated dose-response relationship was not observed [Data Source: GSK Doc. No. 2014N216014_00]. The rate of reduction in plasma HIV-1 RNA viral load, as evidenced by the time to achieve virologic suppression, was similar across oral CAB doses (Figure 7).

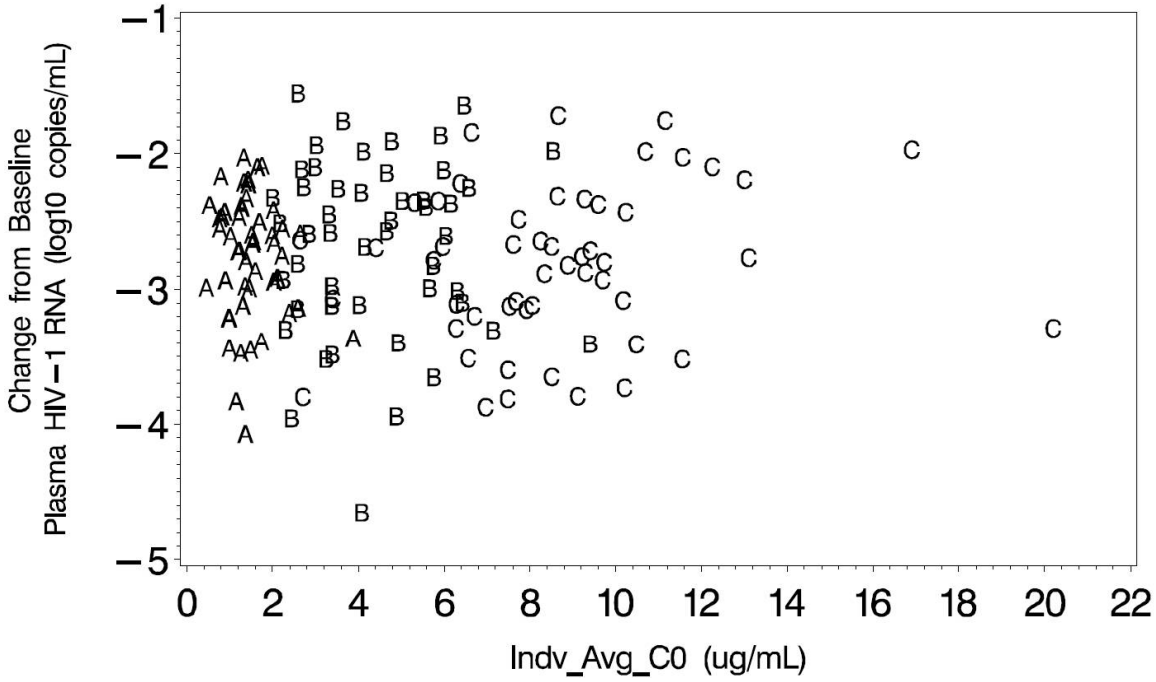
Figure 7 Kaplan-Meier Plot of Time to Virological Suppression (HIV-1 RNA <50 copies/mL) Confirmed



Data Source: GSK Doc.No.2013N180642_00 (LAI116482): Figure 6

No relationship between plasma CAB PK parameters and reduction in plasma HIV-1 RNA was established due to the strong and rapid antiviral response observed for the 3 oral CAB once daily regimens of 10 mg, 30 mg, and 60 mg in combination with 2 NRTIs (Figure 8). No PK/PD relationship for antiviral efficacy could be established given low rate of PDVF (1 subject in each CAB dosing arm) with no evidence of treatment-emergent genotypic or phenotypic INSTI or NNRTI resistance. These Week 24 results enabled the continued evaluation of all 3 oral CAB doses, each combined with RPV 25 mg, during the Maintenance Period [GSK Doc. No. 2013N168724_00].

Figure 8 Individual Week 24 Change from Baseline in Plasma HIV RNA versus Individual Average Cabotegravir C0



Data Source: GSK Doc. No. 2013N168724_00 (LAI116482) Figure 9
Note: Treatment A= CAB 10 mg; Treatment B = CAB 30 mg; Treatment C = CAB 60 mg

When administered with oral RPV 25 mg once daily, all 3 oral CAB doses demonstrated similar efficacy at the Week 48 primary endpoint of the Maintenance Period [GSK Doc. No. 2013N180642_00]. At Week 48, no PK/PD relationship for antiviral efficacy could be established given low rate of PDVF (1 subject in each CAB 10 mg + RPV and CAB 30 mg + RPV dosing arms). 1 PDVF subject (CAB 10 mg + RPV) had evidence of treatment-emergent genotypic and phenotypic INSTI or NNRTI resistance with low CAB and RPV exposures likely resulting from documented extreme-calorie restricted diet [GSK Doc. No. 2013N180642_00].

Dose selection of the middle dose (30 mg) was pre-specified if comparable efficacy, safety, and PK were observed given healthy volunteer PK indicated CAB LA 400 mg IM monthly administration would achieve steady-state exposures between oral CAB 10 mg and 30 mg and would be sufficiently high to assess safety and tolerability during a short OLI prior to IM administration.

In Study 200056, CAB 30 mg once daily (in combination with 2 NRTIs) was used to induce suppression of HIV. Oral RPV 25 mg once daily was added as OLI to the induction regimen 4 weeks prior to randomization in the Maintenance Phase (Table 1). In Study 200056, CAB 30 mg once daily demonstrated a favorable safety profile in combination with oral RPV 25 mg once daily during the OLI. Steady-state mean CAB trough concentrations following oral administration were consistent with those observed in Study LAI116482. Subjects randomized to remain on oral treatment received oral CAB 30 mg + 2 NRTIs for 96 weeks during the Maintenance Phase. Oral CAB 30 mg

once daily was safe and well tolerated when co-administered with oral RPV 25 mg once daily for 4 weeks and with 2 NRTIs up to 96 weeks. [GSK Doc. No. 2017N337118_00].

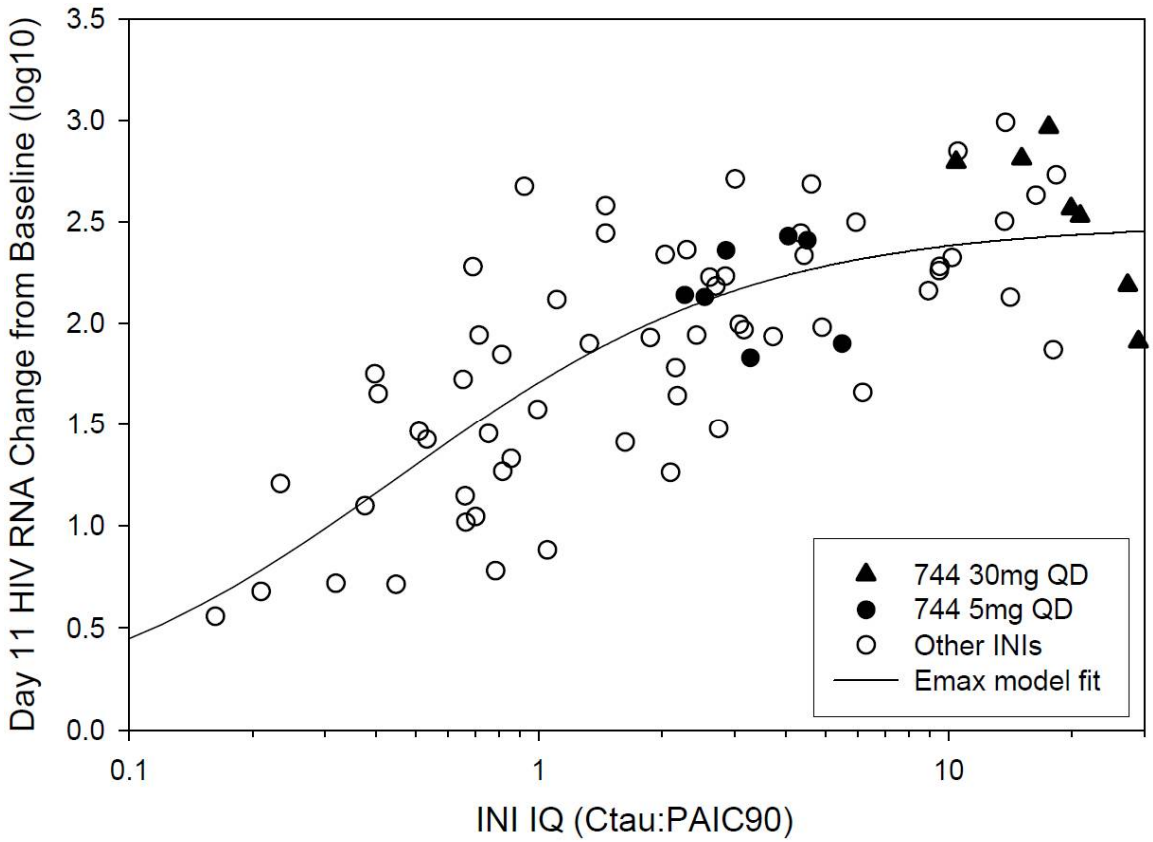
CAB 30 mg + RPV 25 mg once daily (as tablets) has been administered as short-term OLI to assess safety and tolerability prior to IM injections in Phase III Studies 201584 and 201585.

4.1.1.2. Supportive Studies: Study ITZ111451 and ITZ112929

Study ITZ111451 and ITZ112929 were Phase IIa, randomized, double-blind, placebo-controlled, dose-ranging studies conducted to evaluate the dose-response relationship for antiviral activity of CAB monotherapy. HIV-infected, ART-naïve and ART-experienced/INSTI-naïve subjects who were off all ART for at least 12 weeks were randomized to receive oral CAB at a dose level of 30 mg (ITZ111451) or 5 mg (ITZ112929) vs. placebo for 10 days. A brief summary of these studies is provided in the Appendix (Section 7).

Oral CAB monotherapy regimens of 5 mg and 30 mg once daily achieved significant reductions in plasma HIV-1 RNA from Baseline with a mean decrease of >2.1 $\log_{10}$ c/mL on Day 11 [GSK Doc. No. RM2008/00633/00; GSK Doc. No. RM2009/00485/00]. Plasma HIV-1 RNA reduction was evaluated using an Emax model which indicated lack of a strong relationship between the plasma CAB Ctau/PAIC90 ratio and reduction in plasma HIV-1 RNA concentrations given CAB concentrations clustered on the plateau of the dose-response curve (Figure 9). Results from these 2 studies supported dose selection for Study LAI116482, a Phase IIb, dose-ranging, clinical study in treatment-naïve, HIV-infected subjects.

Figure 9 Day 11 HIV RNA Change from Baseline versus IQ (Ct/PA-IC90) following GSK1265744 30 mg and 5 mg Once Daily compared to other INSTIs



Data Source: GSK Doc. No. 2013N168724_00 (LAI116482) Figure 1

4.1.1.3. Oral Lead-in

CAB 30 mg + RPV 25 mg, administered once daily as tablets, is recommended as short-term OLI to assess safety and tolerability prior to IM injections. OLI has been included in Phase III Studies 201584 and 201585, Phase IIIb Study 207966, and Phase IIb Study 200056 (see Section 4.1.1).

4.1.1.4. Oral Therapy for Short-term Use

CAB 30 mg + RPV 25 mg once daily is recommended for short-term oral therapy use for up to 2 consecutive missed injections for patients who will miss planned continuation dosing with CAB LA + RPV LA injections. Oral therapy was permitted in Phase III Studies 201584 and 201585, Phase IIIb Study 207966, Phase IIb Study 200056, and this usage is supported further by long-term safety and efficacy data from Phase IIb Study LAI116482. The Phase IIb and Phase III experience are described in Section 2 and Section 3.

The selection of CAB 30 mg oral dose in combination with oral RPV is discussed in Section 4.1.1.

4.1.2. CAB LA + RPV LA Injection

A monthly or every 2 months CAB LA + RPV LA IM regimen is recommended for the maintenance of virologic suppression in adults with HIV-1 infection. The monthly CAB LA + RPV LA IM dosing regimen begins with initiation doses consisting of 3 mL IM injections of CAB LA 600 mg + RPV LA 900 mg followed by continuation doses consisting of 2 mL IM injections of CAB LA 400 mg + RPV LA 600 mg. The every 2 months CAB LA + RPV LA IM dosing regimen under evaluation consists of 3 mL IM injections of CAB LA 600 mg + RPV LA 900 mg administered on Day 1, 4 weeks later, and every 8 weeks thereafter. Prior to IM administration, administration of oral CAB + oral RPV to assess individual tolerability is recommended and discussed in Section 4.1.1.

CAB LA and RPV LA Q4W dose selection was confirmed by efficacy and safety data from Phase III Studies 201584 and 201585 and supported by the Phase IIb Study 200056 (CAB LA + RPV LA Q4W or Q8W) and the Phase IIb Study LAI116482 (oral CAB 30 mg + oral RPV 25 mg once daily).

CAB LA and RPV LA Q8W dose selection was supported by efficacy and safety data from Phase IIb Study 200056 (CAB LA + RPV LA Q4W or Q8W). Based on the Week 96 results from Study 200056, CAB LA + RPV LA Q8W is being evaluated in comparison to Q4W dosing in Phase IIIb Study 207966. The Q4W dosing for Study 207966 is the same as the Q4W dosing evaluated in the Phase III Studies 201584 and 201585.

4.1.2.1. Phase III Studies 201584 and 201585

The efficacy of CAB + RPV monthly regimen for the maintenance of virologic suppression in ART-naïve and ART-experienced subjects through Week 48 was demonstrated to be non-inferior to standard-of-care oral comparator regimens in 2 individual Phase III studies and in a pooled analysis using 6% and 4% non-inferiority margins, respectively (Table 7).

Plasma CAB geometric mean trough concentrations remained between the geometric mean Cτ values of 10 mg and 30 mg once daily. (Data Source: GSK Doc. No 2017N345267_00 Table 4.5; GSK Doc. No 2018N370336_00 Table 4.4). In the pooled analysis, the proportion of CAB + RPV subjects with plasma HIV-1 RNA ≥50 c/mL at the Week 48 (primary efficacy endpoint) was 1.9% compared with 1.7% for pooled CAR (Table 7).

In the pooled analysis, the rate of CVF was low, 1.2%, across both treatment groups at Week 48 (Table 19). CAB and RPV plasma concentrations for subjects with CVF at the SVF visit overlapped with plasma concentrations of subjects with HIV-RNA <50 c/mL at the corresponding visit, making it is difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. Other factors may be associated with the occurrence of virologic failure.

In both Study 201584 and Study 201585, CAB and RPV concentration-time profiles for subjects with snapshot HIV-1 RNA ≥50 c/mL at Week 48 (n=11 across both studies) were generally below the median but within the 5th and 95th percentile of observed data for the remainder of the population (n=580 across both studies) (Data Source: GSK Doc. No. 2017N345267_00 Figure 5.7, Figure 5.8; GSK Doc. No. 2018N370336_00 Figure 5.7, Figure 5.8). In Study 201585, a multivariable analysis indicated only the last available RPV trough concentration was a statistically significant predictor of Week 48 snapshot failure (HIV-1 RNA ≥50 c/mL) (Data Source: GSK Doc. No. 2018N370336_00 Table 5.3). In Study 201584, a multivariable analysis indicated only HIV-1 subtype and the RPV Week 8 trough concentration remained statistically significant predictors of Week 48 HIV-1 RNA ≥50 c/mL (Data Source: GSK Doc. No. 2017N345267_00 Table 5.2). These analyses should be interpreted with caution and considered as exploratory findings as the low number of subjects with HIV-1 RNA ≥50 c/mL limits the reliability of the multivariable logistic modelling and backwards selection procedure. Not all relevant factors could be measured and included in the multivariable analysis.

4.1.2.2. Phase IIIb Study 207966

Study 207966 was designed to demonstrate non-inferior antiviral activity of CAB LA 600 mg + RPV LA 900 mg administered Q8W compared with CAB LA 400 mg + RPV LA 600 mg administered Q4W over a 48-week treatment period.

Subjects in Study 207966 enrolled either directly from standard oral therapy or from Q4W dosing in Study 201585. The majority of subjects transitioning from Q4W dosing in Study 201585 received injections for more than 1 year, while other subjects remained on CAR during the study and received the OLI followed by Q4W injections, prior to transitioning to Study 207966.

The Q8W regimen has been administered in the ongoing Phase IIb Study 200056 for approximately 3 years, and Week 96 results were supportive of further evaluation of Q8W dosing in Study 207966 [Margolis, 2018]. At Week 160 of the Study 200056 Extension Phase (100 weeks of oral CAB + 2 NRTIs followed by 60 weeks of LA therapy), 33/34 (97%) subjects receiving the optimized Q8W regimen and 10/10 (100%) subjects receiving the optimized Q4W regimen maintained HIV-1 RNA <50 c/mL [GSK Doc. No. 2018N380094_00). The optimized Q4W LA regimen evaluated in Study 207966 also was administered in Phase III Studies 201584 and 201585 (Q4W). At Week 48 of Study 201584 and Study 201585, 265/283 (93.6%) and 285/308 (92.5%) subjects maintained virologic suppression (HIV-1 RNA <50 c/mL), respectively (Table 18). See Section 4.1.2.3 for further details on the optimized LA regimen.

The initial injection dose was CAB LA 600 mg (3 mL) for both regimens in the 200056 Extension Phase and for the Q4W regimen in 201585 and 201584. The geometric mean trough concentrations, 4-weeks following the 600 mg initiation dose, ranged from 1.18 to 1.58 µg/mL across studies and were similar to model-based predictions (CAB 1.4 µg/mL). Geometric mean Week 48 trough concentrations were 1.46 µg/mL following the Q8W regimen in the Study 200056 Maintenance Phase and ranged from

2.58 to 3.13 µg/mL following the Q4W regimen across the 3 clinical studies (see m2.7.2 for further information).

4.1.2.3. Phase IIb Study 200056

Study 200056 was a Phase IIb, dose-ranging, clinical study conducted to support dose selection of IM CAB LA + RPV LA for the maintenance of virologic suppression. The Phase II dose selection strategy for CAB LA was based on maintaining efficacious plasma CAB concentrations beginning with the first injections and throughout the course of therapy. Initial and steady-state exposures of CAB following IM injection were predicted based on population PK modeling of healthy and HIV-infected subject data and supported by the lack of drug-drug interaction following concomitant administration.

The dose and dosing frequency of CAB LA was based on maintaining plasma concentrations at the end of a dosing interval at or above mean exposures following the efficacious 10 mg oral dose observed in LAI116482 (see Section 4.1.1). A higher initiation dose was chosen to quickly achieve target concentrations with a lower continuation dose that was predicted to achieve steady-state mean CAB plasma concentrations ≥1.35 µg/mL (target) in 99.6% and ≥80% of subjects following Q4W and Q8W dosing, respectively.

HIV-infected, ART-naïve subjects received 20 weeks of induction therapy with oral CAB 30 mg once daily + 2 NRTIs (plus oral RPV 25 mg once daily added for the last 4 weeks). Subjects with viral suppression were randomized 2:2:1 on Day 1 to CAB LA + RPV LA either Q4W or Q8W or to continue oral comparator CAB 30 mg + 2 NRTIs for 96 weeks during the Maintenance Period.

Both CAB LA + RPV LA Q4W and Q8W regimens demonstrated high and comparable rates of efficacy to oral CAB at Week 32 and Week 48 [GSK Doc. No. 2015N246053_00; GSK Doc. No. 2016N273084_00]. Plasma CAB geometric mean trough concentrations for both Q4W and Q8W regimens remained between the geometric mean Cτ values of 10 mg and 30 mg once daily.

A higher rate of virologic non-response of 7% in the Q8W arm vs. <1% in the Q4W arm was observed at Week 48, including 1 subject with PDVF with treatment-emergent NNRTI and INSTI genotypic and phenotypic resistance on the Q8W arm [GSK Doc. No. 2016N273084_00]. No additional PDVFs were identified after Week 48. 4 subjects resuppressed to <50 c/mL without a change of therapy by Week 96 [Data Source: GSK Doc. No. 2017N337118_00]. No PK/PD relationship was observed between CAB concentrations and virologic nonresponse at Week 48 because CAB trough concentrations in subjects with virologic non-response were distributed throughout the concentration quartiles.

Results through Week 48 supported progression of the Q4W dosing regimen with continuation doses of CAB LA 400 mg IM + RPV LA 600 mg IM in Phase III studies based on lower virologic non-response rates and similar safety to the Q8W dosing arm. The initiation dose strategy was optimized for the 200056 Extension Phase as well as for the Phase III studies to simplify and align the number and volume of injections at each

dosing visit. CAB LA initiation dose was decreased from 800 mg to 600 mg effectively decreasing the number of injections and injection volume from two-2 mL injections to a single 3 mL IM injection. This change would still maintain mean plasma CAB concentrations comparable to the 10 mg oral dose during the early phase. For RPV LA, an initiation dose of 900 mg (a single 3 mL IM injection) was introduced to achieve RPV plasma concentrations closer to the steady-state values earlier on in the treatment.

Results from 200056 and population PK modelling supported dose selection of an optimized regimen with initiation doses consisting of 3 mL IM injections of CAB LA 600 mg + RPV LA 900 mg followed by continuation doses consisting of 2 mL IM injections of CAB LA 400 mg + RPV LA 600 mg every Q4W for evaluation as maintenance treatment in Phase III studies.

Based on the efficacy and tolerability of CAB + RPV at Week 96 in Study 200056, Q8W LA dosing was selected for further investigation in Phase IIIb Study 207966. In Study 200056, 94% of subjects on the CAB + RPV Q8W dosing arm and 87% of subjects on the Q4W dosing arm maintained virologic suppression (HIV-1 RNA <50 c/mL per Snapshot at Week 96), with both regimens exhibiting acceptable tolerability [GSK Doc. No. 2017N337118_00]. The Q8W regimen consists of 3 mL IM injections of CAB LA 600 mg + RPV LA 900 mg administered as the initiation dose, followed by a second dose in 4 weeks, and every 8 weeks thereafter.

4.2. PK/PD

4.2.1. CAB Oral

In LAI116482, response rate across the 3 dosing arms was similar, when accounting for a higher rate of discontinuations for non-virologic reasons in the 10 mg and 30 mg dosing arm [GSK Doc. No. 2014N216014_00]. In subjects with PDVF, there was a higher rate of treatment-emergent virologic resistance in subjects receiving 10 mg, relative to 30 mg and 60 mg. Steady state CAB trough concentrations for 10 mg, 30 mg, and 60mg oral doses exceeded the in vitro PA-IC90 (0.166 μg/mL) by an average of 8.1-, 25- and 48-fold, respectively. A sustained antiviral response was observed without evidence of INSTI resistance through the Induction Period (oral dosing). The CAB 30 mg dose had sufficient exposure and antiviral activity and was selected for progression to Phase III studies based on these results.

4.2.2. CAB LA and RPV LA

In Study 201584 and Study 201585, geometric mean CAB concentrations were consistent with those observed in Phase II studies [GSK Doc. No. 2017N345267_00, GSK Doc. No. 2018N370336_00]. CAB steady state was confirmed by Week 48. Given the few subjects who experienced CVF on CAB + RPV and the fact that there is a high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it is difficult to establish a relationship between CAB plasma concentrations and the occurrence of virologic failure.

Multiple factors including drug concentrations may be associated with the occurrence of virologic failure.

In an ad-hoc multivariable analysis of Study 200056 Week 48, 3 covariates were identified as statistical predictors of Week 48 Snapshot failure: Day 1 plasma HIV RNA >50 c/mL, time to viral suppression to <50 c/mL of >4 weeks of ART induction (after Week 16), and low RPV trough concentration prior to Week 48 [GSK Doc. No. 2016N273084_00]. Similarly, low RPV concentrations were identified as being associated with HIV-1 RNA ≥50 c/mL in a multivariable analysis of Phase III Studies 201584 and 201585. These analyses should be interpreted with caution and considered as exploratory findings as the low number of subjects with HIV-1 RNA ≥50 c/mL limits the reliability of the multivariable logistic modelling and backwards selection procedure, and not all relevant factors could be measured and included in the multivariable analysis.

In the Phase IIIb Study, 207966, CAB and RPV concentrations were lower at Week 48 for the Q8W regimen as compared to the Q4W regimen, consistent with those observed in Phase IIb (Q8W and Q4W) and III studies (Q4W) [GSK Doc. No. 2017N345267_00, GSK Doc. No. 2018N370336_00]. In Study 207966, the Q8W regimen was determined to be non-inferior to the Q4W regimen, indicating that the exposures for both regimens were effective at maintaining virologic suppression. The rate of CVF was low, 8/522 (1.5%) and 2/523 (0.4%) for Q8W and Q4W, respectively, at Week 48 (Table 19). 7 subjects experiencing CVF had no exposure to CAB + RPV prior to enrollment in Study 207966; 3 subjects experiencing CVF were categorized as having 1 to 24 weeks of prior exposure to the regimen, receiving CAB + RPV for 8, 9, and 13 weeks (OLI + 1-2 injection visits) in Study 201585 prior to Day 1 in Study 207966. Major NNRTI RAMs at Baseline were identified in 5 subjects in the Q8W treatment arm, 1 of whom also had a major INSTI RAM at Baseline. This analysis did not include all factors that were addressed in a post-hoc analysis (see Section 4.2.3).

CAB and RPV plasma concentrations at the SVF visit for subjects with CVF in Study 207966 were within the range of plasma concentrations in subjects with HIV-RNA <50 c/mL for the corresponding visit, making it difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. Median CAB and RPV concentrations for subjects with HIV RNA ≥50 c/mL were similar to those with HIV RNA <50 c/mL for the Q8W regimen and slightly lower for the Q4W regimen (Data Source: GSK Doc No. 2019N406358_01 Figure 5.3, Figure 5.4). Overall, there was not a clear relationship with PK levels and the occurrence of CVF. Given the few numbers of subjects with CVF in Study 207966, it is difficult to establish if PK concentrations, along with other factors, inclusive of pre-existing mutations, contributed to individual CVF.

Univariable and multivariable logistic regression analyses were conducted in Phase IIIb Study 207966 for the population without prior exposure to CAB + RPV and for the overall population. The following factors were evaluated in both analyses: treatment (dosing regimen), age, race, sex, Baseline CD4+ cell count, Baseline HIV-1 RNA, derived Baseline CDC Stage, Baseline BMI, Baseline third agent class, Week 8 RPV

predose concentration, Week 8 CAB predose concentration, length of first RPV injection needle, and length of first CAB injection needle.

For subjects without prior exposure to CAB + RPV in Study 207966, Baseline BMI and Week 8 CAB plasma concentration were identified in the univariable analysis as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL (Data Source: GSK Doc. No. 2019N406358_01 Table 5.1). Only BMI was retained in the multivariable analysis as a statistically significant association of Week 48 HIV RNA ≥50 c/mL (Odds Ratio [95% CI; {p-value}] 5.626 [1.48, 21.4 {0.011}] (Data Source: GSK Doc. No. 2019N406358_01 Table 5.2), without accounting for multiplicity.

For the overall population in Study 207966, Baseline CDC stage of disease, Baseline BMI, and Week 8 CAB plasma concentration were identified in both the univariable analysis and the multivariable analysis as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL (Data Source: GSK Doc. No. 2019N406358_01 Table 5.6). Given the few subjects who were identified as cases of Week 48 HIV RNA ≥50 c/mL or CVF on CAB + RPV and the high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it is difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. Multiple factors, including PK and viral phenotype, may be associated with the occurrence of virologic failure. Additionally, Multivariable and Baseline factors analyses were conducted using data from Studies 201584, 201585, and 207966, and these findings are summarized in Section 4.2.3.

4.2.3. Multivariable and Baseline Factor Analyses of Virologic Outcome – Studies 201584, 201585, 207966

Following the primary reporting of the Phase III and IIIb studies (201584, 201585 and 207966), a post hoc analysis plan was developed to explore potential predictors of virologic outcomes through Week 48 in the pooled CAB + RPV LA treatment group. Specifically, Multivariable and Baseline factor analyses were undertaken to examine the influence of baseline viral factors and subject characteristics, dosage regimen, and post-baseline plasma drug concentrations on CVF using regression modeling with a variable selection procedure. For the primary analysis population, subjects were pooled from Studies 201584, 201585, and 207966 who were naïve to CAB + RPV, eliminating previous exposure as a potential confounding factor. Therefore, subjects from Study 207966 who had transferred from the CAB + RPV arm of Study 201585 were excluded from this analysis. Using these criteria, the MVA population included 1039 HIV-infected adults with no prior exposure to CAB + RPV. Of the 17 subjects noted in Section 3.4.2.3 from the 3 Phase III studies who did not maintain virologic suppression through their first 48 weeks of CAB + RPV treatment (monthly or every 2 months dosing) and who met CFV criteria, 4 were excluded from the MVA population (3 due to prior exposure to CAB + RPV in Study 201585 prior to transferring to Study 207966 and 1 due to the CVF occurring prior to CAB + RPV injections in a subject who had oral lead-in therapy temporarily withheld during a work-up for a false positive pregnancy test). Thus, through Week 48 in these 3 studies, 13/1039 (1.25%) subjects included in the MVA population met CVF criteria while receiving CAB + RPV. Further

details of the MVA population and the methodology used for the analyses are provided in the MVA report [GSK Doc. No. 2020N452718_01].

4.2.3.1. Results of Multivariable Analysis

In the MVA, 4 covariates were significantly associated ($p<0.05$ for each adjusted OR) with increased risk of CVF (Table 38):

- RPV RAMs at Baseline (determined through PBMC-based HIV-1 DNA sequencing in Study 201585 and Study 207966);
- HIV-1 Subtype A6/A1 (associated with integrase L74I polymorphism);
- RPV Ctrough 4 weeks following initial injection dose (per halving concentration);
- BMI (per unit increase in kg/m^2) (associated with CAB PK).

Other variables, including L74I polymorphism, CAB trough concentration at Week 8, pre-specified INSTI mutation, Q4W or Q8W dosing, female sex, or other viral subtypes (non A6/A1) had no significant association with CVF (Table 38). Of note, although L74I polymorphism and CAB trough concentration at Week 8 did not have a significant association with CVF, they are correlated with factors that did have a significant association with CVF; namely HIV Subtype A6/A1 and BMI, respectively. Additionally, although the factor for dosing regimen (i.e., Q8W vs Q4W dosing) was retained in the final model, there was no statistically significant association between dosing regimen and an increased likelihood of CVF ($p=0.156$).

Table 38 Multivariable Logistic Regression Analysis of CVF Through Week 48 (CAB + RPV Naïve Pooled ITTE-LA)

Parameter	Full Model OR (95% CI), p-value[a]	Backwards Elimination Model OR (95% CI), p-value[a]
RPV RAM(s) at baseline	30.23 (6.25–>99), <0.001	40.36 (8.81–>99), <0.001
Log_2 of post hoc Week 8 RPV trough concentration	3.85 (1.15–14.29)[b], 0.029	5.00 (1.79–16.67)[b], 0.002
Baseline ViiV HIV-1 Subtype A6/A1	2.37 (0.34–22.14), 0.394	5.92 (1.62–22.89), 0.008
BMI (kg/m^2) at baseline	1.08 (0.96–1.22), 0.192	1.13 (1.02–1.24), 0.020
Pre-specified INSTI mutation (excluding L74I non-M mixture) at baseline	0.16 (0.01–1.05), 0.057	0.14 (0.01–0.91), 0.038
NNRTI RAM(s) (excluding RPV RAMs) at baseline	2.64 (0.72–9.21), 0.137	2.78 (0.78–9.63), 0.111
Q8W regimen	2.76 (0.65–11.68), 0.164	2.77 (0.67-11.38), 0.156
Log_2 of post hoc Week 8 CAB trough concentration	0.66 (0.25–1.74), 0.395	Eliminated from model
L74I (non-M mixture) INSTI mutation at baseline	2.51 (0.33–13.85), 0.347	Eliminated from model
Female at birth	1.09 (0.26–4.36), 0.899	Eliminated from model

Data Source: GSK Doc. No. 2020N452718_01 Table 5.17

a. OR, 95% penalized profile CI, and penalized likelihood ratio p-values are provided. Backwards elimination used a significance threshold of alpha=0.2.

b. CAB and RPV PK parameters were log_2-transformed; therefore, the corresponding ORs are per halving of each variable. Full Model OR: 0.26 (95% CI: 0.07, 0.87) and Final Model OR: 0.20 (95% CI: 0.06, 0.56); results in table are reciprocal of these so that all ORs are in same direction.

The 13 subjects from the MVA analysis population who met CVF criteria are listed along with examined covariates in Table 39. Only 2 of 13 subjects with CVF had <2 factors associated with CVF; 46% (n=6) had 4 factors.

Overall, the results of the MVA analysis indicate that no covariate alone is associated with a higher likelihood of developing CVF.

Table 39 MVA: Common Covariates in Subjects with CVF and Summary of Covariates Per Individual CVF Case (CAB + RPV Naïve Pooled ITTE-LA)

Study ID	Unique Subject ID	CAB PK ≤Q1	RPV PK ≤Q1	HIV A6/A1	L74I[a]	RPV RAMs	BMI ≥30	NNRTI RAMs[b]	Sex	Regimen	Number of factors (out of 5)[c]
201584	[redacted]	Y	Y	Y	Y	N	Y	Y	M	Q4W	4
201584		Y	Y	Y	Y	N	Y	N	F	Q4W	4
201584		Y	Y	Y	Y	N	Y	N	F	Q4W	4
201585		Y	Y	Y	Y	Y	N	N	F	Q4W	4
201585		Y	Y	N	N	Y	Y	Y	F	Q4W	4
207966		Y	Y	Y	Y	N	Y	N	F	Q8W	4
207966		Y	N	N	Y	Y	Y	Y	F	Q8W	3
207966		N	N	Y	Y	Y	Y	Y	F	Q8W	3
201585		N	Y	Y	Y	N	N	N	M	Q4W	2
207966		N	N	N	N	Y	Y	Y	M	Q8W	2
207966		Y	Y	N	N	N	N	N	M	Q4W	2
201585		N	Y	N	N	N	N	N	M	Q8W	1
207966		N	N	N	N	N	N	Y	M	Q4W	0

Data Source: GSK Doc. No. 2020N452718_01 Listing 1

a. L74I (non-M mixture) INSTI polymorphism at Baseline.

b. NNRTI RAM(s) (excluding RPV RAMs) at Baseline.

c. CAB PK was included as a fifth factor in addition to the 4 covariates that were significantly associated with CVF (RPV PK ≤Q1, HIV A6/A1, RPV RAMs, and BMI ≥30) because of its association with BMI.

4.2.3.2. Results of Baseline Factor Analysis

In the Baseline factors analysis, the same covariates as in the MVA were explored, with the exception of PK parameters. Archived RPV RAMs (per PBMC-based HIV-1 DNA sequencing), HIV-1 Subtype A6/A1, and BMI ≥30 kg/m^2 were selected ($p<0.05$) by the stepwise model selection procedure.

The majority of CVF cases (9 of 13; 69.2%) were multifactorial (≥2 Baseline factors present) [GSK Doc. No. 2020N452718_01]. The results of the Baseline factors analysis support the MVA findings and indicate that no baseline factor alone is associated with a higher likelihood of experiencing CVF. In fact, even in the presence of 2 or more Baseline factors, 25 subjects out of 35 subjects (71%) were able to maintain virologic suppression at Week 48 via the Snapshot algorithm (Table 40). The CVF rate through Week 48 was <0.5% when 0 or 1 Baseline factor(s) were present.

Table 40 Outcomes Analysis by Presence or Absence of Baseline Factors – Overall (CAB + RPV Naïve Pooled ITTE-LA)

	CVF %			RNA <50 [by Snapshot] %		
Factors	**n/N**	**%**	**95% CI**	**n/N**	**%**	**95% CI**
None of 3 factors	**3/732**	**0.4**	**(0.1, 1.2)**	**694/732**	**94.8**	**(92.9, 96.3)**
RPV RAMs alone	0/24		(0.0, 14.2)	24/24	100.0	(85.8, 100.0)
BMI ≥30 kg/m^2 alone	0/153		(0.0, 2.4)	147/153	96.1	(91.7, 98.5)
A6/A1 alone	1/95	1.1	(0.0, 5.7)	90/95	94.7	(88.1, 98.3)
Any 1 BL Factor	**1/272**	**0.4**	**(0.0, 2.0)**	**261/272**	**96.0**	**(92.9, 98.0)**
Combinations of Factors						
RPV RAMs + A6/A1	1/3	33.3	(0.8, 90.6)	2/3	66.7	(9.4, 99.2)
RPV RAMs + BMI ≥30	3/10	30.0	(6.7, 65.2)	7/10	70.0	(34.8, 93.3)
BMI ≥30 + A6/A1	4/21	19.0	(5.4, 41.9)	16/21	76.2	(52.8, 91.8)
All 3 factors	**1/1**	**100.0**	**(2.5, 100.0)**	**0/1**	**-**	**(0.0, 97.5)**
At least 2 factors	**9/35**	**25.7**	**(12.5, 43.3)**	**25/35**	**71.4**	**(53.7, 85.4)**
Total	**13/1039**	**1.3**	**(0.7, 2.1)**	**980/1039**	**94.3**	**(92.7, 95.6)**

Data Source: GSK Doc. No. 2020N452718_01 Table 1.
Note: Confidence intervals are based on the exact method.

4.2.3.3. Summary

In summary, findings from the MVA demonstrate that CVF is an infrequent multifactorial event. Three Baseline factors (archived RPV resistance mutations, A6/A1 subtype, and/or high BMI [≥30 kg/m^2]) when found in combination (2 or more) contributed to a modestly increased risk of CVF.

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

Longer term data (Week 96) from Phase III Study 201584 are presented briefly in this Section. Study 201585 continued in an open-label extension phase, although most subjects have rolled over into Phase IIIb Study 207966. Longer term data on the CAB + RPV 2-drug LA Q8W and Q4W regimens will become available from ongoing Phase IIIb Study 207966.

Longer term data on the LA regimen also are available from the Phase IIb Study 200056 Week 160 analysis. Virologic response rates through Week 160 with the Q8W and Q4W LA regimens provide support for the durability of injection dosing. At Week 160, 83% of subjects receiving CAB + RPV monthly IM dosing (Q4W) and 90% of subjects receiving CAB + RPV bimonthly dosing (Q8W) maintained virologic suppression (HIV-1 RNA <50 c/mL by the Snapshot algorithm) (GSK Doc. No. 2018N380094_00). There were no CVFs in either study arm after Week 48 of dosing. In addition, virologic response rates through Week 144 with once daily oral CAB + RPV provide support for the durability of oral dosing.

5.1. Study 201584 Week 96 Efficacy Results

A secondary efficacy endpoint in this Phase III pivotal study was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 96 (Snapshot Algorithm). The secondary efficacy analysis demonstrated that once-monthly CAB + RPV continued to be non-inferior to CAR in maintaining virologic suppression in HIV-1-infected subjects at Week 96, with few subjects (3.2% in each treatment group) having plasma HIV-1 RNA ≥50 c/mL at Week 96 (ITT-E and PP) (Table 41). The upper bound of 95% CI for the adjusted treatment difference between CAB + RPV and CAR was less than the pre-defined non-inferiority margin of 6%.

Results of the Week 48 primary efficacy analysis are summarized in Study 201584 Week 48 CSR [GSK Doc. No. 2017N345267_00] and in Section 3.4.1.

5.1.1. Proportion of Subjects with Plasma HIV-1 RNA >50 c/mL at Week 96 - Study 201584

Table 41 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 96 (Maintenance Phase) Snapshot Analysis (ITT-E and PP) - Study 201584

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV Q4W	283	9 / 283 (3.2)	0.0 (-2.9, 2.9)	0.0 (-2.9, 2.9)
CAR	283	9 / 283 (3.2)		
PP Population				
CAB + RPV Q4W	278	9 / 278 (3.2)	0.0 (-2.9, 3.0)	0.1 (-2.9, 2.9)
CAR	281	9 / 281 (3.2)		

Data Source: GSK Doc. No. 2019N421511_00 Table 2.1 and Table 2.2

a. Difference: proportion on CAB + RPV - proportion on CAR
b. Based on CMH stratified analysis adjusting for the following Baseline stratification factors: sex at birth (male, female) and Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL)
c. Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

The proportion of subjects with plasma HIV-1 RNA ≥50 c/mL by visit generally was similar for both treatment groups (Data Source: GSK Doc. No. 2019N421511_00 Figure 2.1).

5.1.2. Study Outcomes at Week 96 - Study 201584

Study outcomes based on HIV-1 RNA ≥50 c/mL at Week 96 Snapshot analysis were similar for both treatment groups (Table 42). The majority of subjects remained suppressed with HIV-1 RNA <50 c/mL at Week 96 via Snapshot analysis. A small number of subjects had HIV-1 RNA ≥50 c/mL at Week 96 (CAB + RPV Q4W 9 [3.2%] subjects; CAR 9 [3.2%] subjects; Table 41) or had no virologic data (CAB + RPV Q4W 29 [10.2%] subjects; CAR 21 [7.4%] subjects). Within the Week 96 Snapshot analysis under the category of no virologic data, there were more discontinuations due to AEs in the CAB + RPV Q4W group compared to the CAR group, Table 42).

Table 42 Summary of Study Outcomes (Plasma HIV-1 RNA of 50 c/mL cut off) at Week 96 (Maintenance Phase) Snapshot Analysis (ITT-E Population) - Study 201584

Outcome	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)
HIV-1 RNA <50 c/mL	245 (86.6)	253 (89.4)
HIV-1 RNA ≥50 c/mL	9 (3.2)	9 (3.2)
Data in window not below threshold	3 (1.1)	2 (0.7)
Discontinued for lack of efficacy	6 (2.1)	5 (1.8)
Discontinued for other reason while not below threshold	0	2 (0.7)
Change in background therapy	0	0
No virologic data	29 (10.2)	21 (7.4)
Discontinued study due to AE or death	12 (4.2)[a]	4 (1.4)[b]
Discontinued study for other reasons	16 (5.7)[c]	17 (6.0)[d]
On study but missing data in window	1 (0.4)	0

Data Source: GSK Doc. No. 2019N421511_00 Table 2.3.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

a. 3 injection site pain, 2 Hepatitis C, 1 Hepatitis A, 1 Hepatitis B, 1 transaminases, 1 syphilis,1 depression, 1 adenocarcinoma, 1 nasopharyngitis.
b. 1 tremor, 1 disturbance in attention and dysarthria, 1 renal insufficiency, 1 dizziness, fatigue, nausea.
c. 3 subject relocation, 2 intolerability of injections, 2 lost to follow-up, 2 pregnancy plans, 1 burden of travel, 1 job change, 1 subject unreliable, 1 need for anticoagulation, 1 incarceration, 1 pregnancy, 1 frequency of visits.
d. 4 frequency of visits (subject decision), 3 noncompliance with study treatment and protocol procedures, 2 relocation, 1 subject decision to stop treatment, 1 late to attend visits, 1 lost to follow-up, 1 pregnancy, 1 substance abuse, 1 burden of travel, 1 ViiV Safety and Labelling Committee decision, 1 unspecified.

5.1.3. CVF at Week 96 - Study 201584

The proportion of subjects with CVF was a pre-defined secondary endpoint in Study 201584. CVF was defined as 2 consecutive HIV-1 RNAs ≥200 c/mL after prior suppression to <200 c/mL. At the Week 48 analysis, there were 4 (1.4%) CVFs in the CAB + RPV group and 3 (1.1%) CVFs in the CAR group (Table 19). No CVFs occurred between Week 48 and 96 in the CAB + RPV Q4W treatment group (Table 43). One additional CVF occurred in the CAR group at Week 64. During the Extension Phase, 1 additional CVF was identified in the CAB + RPV Q4W group at Week 108. The proportion of subjects with CVF during the Week 96 analysis (including subjects with dosing beyond Week 96) was low [CAB + RPV (5 subjects, 1.8%); CAR (4 subjects, 1.4%)] (Data Source: GSK Doc. No. 2019N421511_00 Table 2.22, Table 2.23).

Table 43 Cumulative Proportion of Subjects Meeting CVF Criteria by Visit During the Maintenance Phase (Up to Week 100) (ITT-E Population) - Study 201584

SVF Timepoint	CAB + RPV Q4W (N = 283)	CAR (N= 283)
Week 8	1 (0.4)	1 (0.4)
Week 12	1 (0.4)	2 (0.7)
Week 16	1 (0.4)	3 (1.1)
Week 20	2 (0.7)	3 (1.1)
Week 28	3 (1.1)	3 (1.1)
Week 48	4 (1.4)	3 (1.1)
Week 64	4 (1.4)	4 (1.4)
Week 100	4 (1.4)	4 (1.4)

Data Source: GSK Doc. No. 2019N421511_00 Table 2.14, Table 2.21.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.
Note CVF= Rebound is defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.
Note: Displays visits during which at least one new CVF occurs, and End of Maintenance Phase Visit (Week 100).
Note: At Week 108 during the Extension Phase, 1 subject in the CAB + RPV Q4W group met CVF criteria.

5.2. Phase II Studies

Longer term data on the LA regimen are already available from the Phase IIb Study 200056. In this study, no PDVFs were observed in the Q4W arm throughout the study and no additional PDVFs were observed since the Week 48 cut-off (Data Source: GSK Doc. No. 2017N337118_00). Further at Week 160, 83% of subjects receiving CAB + RPV monthly IM dosing (Q4W) and 90% of subjects receiving CAB + RPV dosed every 8 weeks (Q8W) maintained virologic suppression (HIV-1 RNA <50 c/mL) [Data Source: GSK Doc. No. 2018N380094_00]. In the Maintenance and Extension periods, there were 3 PDVFs, 2 in the Q8W arm and 1 in the oral CAB arm.

In the Q8W arm, one subject reached CVF at Week 8. This subject's Baseline, Week 4, and Week 8 RT, PRO, and IN sequence analysis showed no RAMs and no reduced sensitivity to drugs tested (Data Source: GSK Doc. No. 2017N337118_00 Listing 9.1001, Listing 9.1004, Listing 7.1002, Listing 7.1001). This subject discontinued for lack of efficacy at Week 8 due to apparent maladministration of RPV LA (see m2.7.2 Section 2.1.4.4 for additional details). The second subject in the Q8W arm had CVF at the Week 48 retest time point. At SVF (Week 48), NNRTI RAMs, K103N, E138G, and K238T were observed with decreased sensitivity to delavirdine (FC >MAX), EFV (FC=48), NVP (FC>MAX) and RPV (FC=3.34). INSTI RAM, Q148R, was seen with decreased sensitivity to RAL (FC=29), EVG (FC=138) and CAB (FC=5.06). DTG susceptibility was retained (Data Source: GSK Doc No. 2017N337118_00 Listing 9.1001, Listing 9.1004, Listing 7.1002 and Listing 7.1001).

The Phase IIb Study LAI116482 provides longer term evidence for the efficacy of oral CAB + oral RPV. In this study, CAB + RPV demonstrated durable virologic suppression through 144 weeks of treatment (ITT-E population) [GSK Doc. No. 2016N280049_00 (Table 7.2)]. Subjects who entered the open-label phase and switched to CAB 30 mg oral + RPV 25 mg oral continued to remain virologically suppressed, with few non-virologic discontinuations or CVFs [GSK Doc. No. 2016N280049_00 (Table 7.3)]. Virologic response rates through Week 144 with once daily oral CAB + RPV provide support for the durability of oral dosing.

Lastly, HIV antiretroviral drugs are not associated with pharmacological tolerance; however, as HIV-1 is highly mutable, it can develop mutations that confer decreased susceptibility of the virus to 1 or more ARTs. The resistance profile for CAB is discussed in m2.7.2.4.

6. EFFICACY CONCLUSIONS

Comparisons across the 2 pivotal Phase III studies (Study 201584 and Study 201585), the pooled analysis at Week 48, and Phase IIIb Study 207966 show that:

- In Study 201584, Study 201585, and the pooled analysis, the primary efficacy analyses demonstrated that monthly dosing of CAB + RPV is non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E). The adjusted treatment difference between CAB + RPV and CAR for both studies and the pooled analysis met the non-inferiority criterion (upper bound of the 95% CI below 6% for the individual studies and below 4% for the pooled analysis).
- In Study 207966, the primary efficacy analysis demonstrated that the every 2 months dosing of CAB + RPV is non-inferior to the monthly dosing regimen of CAB + RPV on the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48. The adjusted treatment difference between Q8W and Q4W was 0.8 (95% CI –0.6, 2.2) which met the non-inferiority criterion, set below 4% for the primary endpoint (HIV-1 RNA ≥50 c/mL via Snapshot, ITT-E).
- In the ITT-E population (pooled data from Studies 201584 and 201585), the proportion of subjects with HIV-1 RNA ≥50 c/mL among subjects receiving Q4W treatment in the CAB + RPV group (11/591, 1.9%) was similar to the proportion of subjects with HIV-1 RNA ≥50 c/mL receiving CAB + RPV in the Q8W group (9/522, 1.7%) and Q4W group (5/523, 1%) in Study 207966.
- In Study 201584, Study 201585, and the pooled analysis, the key secondary efficacy analyses demonstrated that monthly dosing of CAB + RPV is non-inferior to CAR on the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E). Specifically, both studies and the pooled analysis established non-inferiority to comparator groups (CAR), with a non-inferiority margin of -10%. In Study 207966 at Week 48, 94% of Q8W CAB + RPV subjects and 93% of Q4W CAB + RPV subjects had plasma HIV-1 RNA <50 c/mL (ITT-E). The adjusted treatment difference between Q8W and Q4W was 0.8% (95% CI, -2.1%, 3.7%), which met the non-inferiority criterion for this secondary endpoint.

- At Week 48 for Studies 201584, 201585, and 207966, CVF was an infrequent (~1% across the 3 Phase III/IIIb studies) multifactorial event. Three Baseline factors (archived RPV RAMs, A6/A1 subtype, and/or high BMI [≥30 kg/m^2]) when found in combination (2 or more) represented an increased risk of CVF. When 0 or 1 Baseline factors were present, the Week 48 CVF rate was <0.5%.
- The results from Study 201584, Study 201585 and Study LAI116482 demonstrate that oral once-daily treatment with CAB 30 mg + RPV 25 mg is effective at maintaining virologic suppression prior to initiation of LA dosing. Further, these studies demonstrate that oral once-daily treatment with CAB 30 mg + RPV 25 mg can be successfully used for patients who require a temporary pause in LA dosing.
- The non-inferiority result established in Study 201584 and Study 201585 demonstrated that the length of HIV-1 RNA virologic suppression prior to initiation of CAB + RPV (i.e., <6 months or ≥6 months), did not impact overall response rates.
- In Study 201584, Study 201585, and the pooled analysis, the treatment effect (CAB + RPV vs. CAR) for the primary endpoint was consistent across the randomization stratification factors.
- The treatment effect (Q8W vs Q4W) for the primary endpoint in Study 207966 was consistent across randomization stratification factors of prior exposure to CAB + RPV, 0 weeks, 1-24 weeks, and >24 weeks), supporting the overall conclusions of non-inferiority in the primary and secondary endpoints.
- In the individual Phase III Studies 201584, Study 201585, the pooled analysis, and in Phase IIIb Study 207966, treatment differences within subgroups generally were consistent with the results of the overall analysis.
- In the pooled analysis of Study 201584 and Study 201585, the CAB + RPV group demonstrated greater improvement from Baseline in treatment satisfaction compared with the CAR group using the HIVTSQs. In Study 2076966, the CAB + RPV Q8W group without prior exposure to CAB + RPV demonstrated significantly greater improvement from Baseline in treatment satisfaction compared with the Q4W group using the HIVTSQs. Of respondents with prior exposure to CAB + RPV and randomized to the Q8W arm, preference for Q8W treatment was higher compared with Q4W or oral CAB + RPV; most common reasons were frequency of administration and convenience in terms of ease to integrate into one's daily life.
- Durability of the CAB + RPV LA regimen was demonstrated through 96 weeks in Phase III Study 201584 where once-monthly CAB + RPV continued to be non-inferior to oral CAR with respect to the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL and <50 c/mL at Week 96 (Snapshot Analysis).
- The CAB + RPV LA doses explored in the Phase 3 studies, both monthly and every 2 months dosing, generated statistically non-inferior outcomes against comparative regimens, with low overall HIV-1 RNA ≥50 c/mL event rates. No single identifiable factor, or combination of factors, was associated with a higher risk of an HIV-1 RNA ≥50 c/mL when evaluating individual subjects.

Overall, these results indicate that CAB, when used in combination with RPV as a Q4W or Q8W 2-drug regimen, is effective in the maintenance of plasma HIV-1 RNA

<50 c/mL. The monthly-dosed injectable regimen is non-inferior to oral CAR without increased risk of virologic failure (HIV-1 RNA ≥50 c/mL), and the long-acting, Q8W regimen is non-inferior to the monthly regimen. Overall, these Q4W and Q8W regimens enabling 6-12 injection visits per year, demonstrated no increased risk of virologic failure relative to comparator arms through Week 48.

Module 2.7.4

Summary of Clinical Safety

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8. APPENDIX 202
8.1. Appendix Table 202
8.2. Definition of Adverse Event 202

ABBREVIATIONS

ABC/3TC/DTG	Abacavir/lamivudine/dolutegravir
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AIDS	Acquired immune deficiency syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
ARV	AIDS-related virus
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BSA	Body surface area
c/mL	Copies per milliliter
CAB	Cabotegravir
CAR	Continued/current antiretroviral regimen
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CK	Creatine kinase
Cmax	Maximum plasma drug concentration
cobi	Cobicistat
CSF	Cerebrospinal fluid
CSR	Clinical study report
CT	Computed tomography
CVF	Confirmed Virologic Failure
DAIDS	Division of Acquired Immunodeficiency Syndrome
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DTG	Dolutegravir
ECG	Electrocardiogram
eC-SSRS	Electronic version: Columbia Suicide Severity Rating Scale
ED	Emergency Department
EEG	Electroencephalogram
EFV	Efavirenz
eGFR	Estimated glomerular filtration rate
EOS	End of study
ERCP	Endoscopic retrograde cholangiopancreatography
EU	European Union
EVG	Elvitegravir
FCBP	Females of child-bearing potential
FDC	Fixed-dose combination
FSFV	First subject first visit
FTC	Emtricitabine
GSK	GlaxoSmithKline
HAART	Highly active antiretroviral therapy
HBV	Hepatitis B virus

HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HIV-1	Human Immunodeficiency Virus Type 1
HSR	Hypersensitivity reaction
HSV	Herpes simplex virus
ICU	Intensive care unit
IDMC	Independent Data Monitoring Committee
IFU	Instructions for Use
IM	Intramuscular
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
ISE	Integrated Summary of Efficacy
ISR	Injection site reaction
ISS	Integrated Summary of Safety
ITT-E	Intent-to Treat Exposed Population
IV	Intravenous
LA	Long-acting injectable, extended-release suspension for injection, or prolonged-release suspension for injection
LDL	Low-density lipoprotein
LFT	Liver function test
LOCF	Last observation carried forward
LOQ	Limit of quantification
LSC	Liver stopping criteria
LTFU	Long-term follow-up
MATE	Multidrug and toxin extrusion proteins
MedDRA	Medical Dictionary for Regulatory Activities
MP	Maintenance Phase
MRI	Magnetic resonance imaging
NCEP	National Cholesterol Education Program
NDA	New Drug Application
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NOAEL	No observed adverse effects level
NRTI	Nucleoside reverse transcriptase inhibitor
OCT2	Organic cation transporter 2
OLI	Oral lead-in
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PgP	Permeability glycoprotein
PIN	Perception of Injection
PK	Pharmacokinetic
PO	Per os (by mouth)
PPN	Pre- and Post-Natal
PrEP	Pre-exposure prophylaxis
PRO	Patient-reported outcomes
PSRAE	Possible Suicidality-Related AE
PT	Preferred Term
PTSD	Post-traumatic Stress Disorder

Q4W	Dosing every 4 weeks (monthly)
Q8W	Dosing every 8 weeks (every 2 months)
QTc	QT interval corrected
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
RPV	Rilpivirine
SAE	Serious adverse event
SC	Subcutaneous
sCSR	Synoptic clinical study report
SMQ	Standardized MedDRA Query
SOC	Standard of care
TAF	Tenofovir alafenamide
TDF	Tenofovir disoproxyl fumarate, Viread
TdP	Torsades de pointes
TQTc	Thorough corrected QT interval (study)
UGT	Uridine diphosphate glucuronosyltransferase isozyme
ULN	Upper limit of normal
US	United States
VT	Verbatim text
WNL	Within normal limits

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1. EXPOSURE TO THE DRUG

The purpose of this summary is to provide evidence to support the safety of CAB as part of the new 2-drug regimen of CAB + RPV for the treatment of HIV-1 infection in adults. Two dosing regimens for CAB LA + RPV LA have been evaluated: monthly and every 2 months. This document will summarize the safety findings for monthly dosing from 2 randomized, controlled Phase III studies and the safety findings for dosing every 2 months from 1 randomized, controlled Phase IIIB study. In addition, supplemental data from 2 randomized, controlled Phase IIB studies of CAB + RPV are provided. The safety profile of CAB in these studies supports a favorable benefit-risk assessment in the indicated HIV-1 population for both dosing regimens.

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

The overall objective of the CAB development program is to produce a novel, highly effective, well-tolerated drug component as part of a 2-drug LA injectable regimen for the treatment of HIV-1 infection.

CAB (oral and LA formulations) is in late stage clinical development and has been demonstrated to have an acceptable safety profile in clinical studies. Oral CAB is proposed for short-term use as an OLI and to cover injection interruptions during LA dosing. Subjects participating in the Phase IIB studies, LAI116482 and 200056, had longer-term exposure to oral CAB, which demonstrated an acceptable safety profile.

1.1.1. Strategy for Establishing the Safety Profile for CAB

The overall risk/benefit profile of CAB was established through evaluation of the safety of the CAB + RPV 2-drug regimen and assessment of the safety of CAB with other ARVs.

1.1.1.1. Data from the CAB Development Program

To support the safety profile of CAB, the applicant has undertaken the following studies (further described in Table 1):

Phase III/IIIB

- Monthly dosing
    - **201584** and **201585** – ongoing, pivotal studies in HIV-1-infected adults receiving the CAB + RPV regimen administered monthly; the data package includes individual study data and pooled data from the 2 studies
- Dosing every 2 months
    - 207966 - ongoing Phase IIIB study in HIV-1-infected adults receiving the CAB + RPV regimen administered every 2 months

Phase IIB

- **LAI116482** – completed study in HIV-1-infected adults receiving oral formulations of CAB + RPV once daily
- **200056** – ongoing study in HIV-1-infected adults receiving CAB + RPV administered for at least 160 weeks

To supplement the safety information in the proposed company Reference Safety Information and Country Prescribing Information for CAB, relevant safety data from nonclinical studies and Phase I to IIa clinical trials conducted separately for CAB (and its excipients) are provided in this submission. A pooled analysis of 19 clinical pharmacology studies was performed separately to evaluate the safety profile of CAB, and a summary of this analysis is provided in Section 5.5.

Single-entity data that are considered not relevant to this CAB application, eg, full safety package from the CAB PrEP program, are not provided in this submission.

1.1.2. Nonclinical Data Relevant to Human Safety

Combination toxicity studies are not generally warranted for HIV combination products unless there is a specific cause for concern under clinically relevant conditions; thus, no nonclinical CAB + RPV combination toxicity studies have been conducted. There is no known overlapping toxicity for CAB and RPV based on the comprehensive nonclinical development programs of both agents. A summary of the nonclinical study results supporting the safety and efficacy of CAB is provided in m2.4, and relevant safety data from single entity studies are presented in this section.

1.1.2.1. CAB Nonclinical Data

CAB Pharmacokinetics

Following single IV administration of CAB to dogs and monkeys, the plasma clearance (<2% of hepatic plasma flow) and steady-state volume of distribution (<0.35 L/kg) were low, with half-life values of 4 to 6 hours. Following oral administration as a solution, the oral bioavailability of CAB was acceptable (44% to 83%) and consistent with its high passive permeability. However, when administered as a suspension, or in solid dosage forms, the bioavailability appeared limited by dissolution rate or solubility, which resulted in a less than proportional increase in systemic exposure of CAB relative to dose. In mice, rats, and monkeys, no consistent notable (>2-fold) difference in oral systemic exposure between sexes was observed.

In rats and monkeys given a single SC or IM injection, CAB was slowly released from the injection site with a mean apparent plasma half-life ranging from 12 to 29 days (SC) or from 8 to 12 days (IM).

The protein binding of CAB in rat, dog, monkey, and human plasma and serum was high (>99%). CAB is a substrate for Pgp and BCRP, but due to its high permeability, no alteration in absorption would be expected by coadministration of either Pgp or

BCRP inhibitors. After oral administration of [^{14}C]CAB to rats, radioactivity was slowly absorbed, widely distributed to tissues, and minimally associated with blood cellular components. Elimination of radioactivity was slow with most tissues containing low but quantifiable radioactivity at 28 days. Radioactivity was not observed at the melanin-containing tissues in the eye and skin.

In general, the metabolism of CAB in the nonclinical species reflects that observed in humans, with CAB being the principal component circulating in plasma. The major metabolite of CAB in all species was a glucuronic acid conjugate (GSK3388352), which was eliminated renally and formed primarily by UGT1A1 (with some involvement from UGT1A9). Additional studies in human (IM, SC, and PO) confirmed that the metabolism and excretion of CAB is independent of route of administration. Metabolic conversion of CAB to its stereoisomers was not detected in rat, dog, monkey, or human hepatocytes, or in plasma following repeat oral administration for 14 days.

In vitro studies have been performed to assess the risk of perpetrator PK drug interactions with CAB. No clinical drug interaction risk was identified for co-administered substrates of CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4, UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B4, 2B7, 2B15, and 2B17, P-gp, BCRP, BSEP, OCT1, OCT2, OATP1B1, OATP1B3, MATE1, MATE 2-K, MRP2, or MRP4 at a clinical dose of 30 mg CAB. CAB was shown to be an inhibitor of OAT1 and OAT3 in vitro; however, less than a mean 1.25-fold increase in exposure of OAT1/3 substrates is predicted based on in vitro data, supporting low risk for clinically significant interaction with OAT1 and OAT3 substrates.

There was no observed PK interaction between CAB and RPV when co-administered IM to rats or monkeys.

CAB Toxicology

The toxicology profile of CAB was established following oral administration in safety pharmacology studies in Sprague Dawley rats and cynomolgus monkeys and in repeat-dose oral toxicity studies up to 26 weeks' duration in rats, and up to 39 weeks in monkeys. Two toxicity studies were conducted in rats to characterize toxicity and toxicokinetics of a LA formulation of CAB in order to support clinical studies of CAB prolonged-release suspension for injection: 1) a single-dose study by SC and IM administration followed by a 74- to 86-day non-treatment period, and 2) a 3-month (weekly and monthly administration) SC and IM study followed by a 14-day (SC, weekly administration), 75-day (SC, monthly administration), or 51-day (IM, monthly administration) non-treatment period.

There were no drug-related adverse effects in rats given CAB orally at doses up to 1000 mg/kg/day for 26 weeks. In the 14-day monkey toxicity study, a dose of 1000 mg/kg/day was not tolerated by male monkeys and resulted in morbidity associated with clinical signs suggestive of GI effects, including body weight loss, emesis, loose/watery feces, and moderate to severe dehydration. Microscopic changes occurred in the GI tract and bone marrow with corresponding decreases in peripheral leukocyte, reticulocyte, and platelet counts in males given 1000 mg/kg/day. There were no adverse effects in monkeys given CAB up to 500 mg/kg/day in the 4-week or 39-week toxicity studies. Day 28 exposure at 500 mg/kg/day ($AUC_{0\text{-}24}$ of 902.5 μg.h/mL) was similar to

that achieved in the 14-day study at 1000 mg/kg/day (1051 μg.h/mL in males on Day 1, 961 μg.h/mL in females on Day 1, and 946 μg.h/mL in females on Day 14). This suggests that GI intolerance observed in the 14-day study was the result of local drug administration and not systemic toxicity.

CAB was administered by monthly SC injection (5, 30, and 100 mg/kg/dose), monthly IM injection (2.5, 10, and 75 mg/kg/dose), or bi-weekly SC injection (100 mg/kg/dose) to rats for up to 3 months, followed by non-dose periods of up to 75 days. There were no adverse effects noted and no new target organ toxicities identified versus what was seen in the oral toxicity studies. Therefore, the NOAEL values for monthly administration were 100 mg/kg/dose SC and 75 mg/kg/dose IM. Exposure at the NOAELs ($AUC_{1440\text{-}2160h} = AUC_{60\text{-}90days}$) corresponds to ~38 to 48× the human $AUC_{(0\text{-}t)}$ for a 400-mg IM dose (2461 μg.h/mL) or ~21 to 26× the human $AUC_{(0\text{-}t)}$ for an 800-mg IM dose given once every 12 weeks (4417 μg.h/mL).

In vitro and in vivo genetic toxicity studies have also been conducted. Carcinogenicity studies in mice and rats were conducted to assess the tumorigenic potential of CAB and immunotoxicology studies in rats have been performed to assess the effects of CAB on the antibody response to the T cell-dependent antigen. Overall, the CAB toxicology package supports the registration of CAB. See m2.4 for details.

Pre- and Postnatal Studies with CAB

Reproductive and developmental toxicity studies have been conducted following oral administration to Sprague Dawley rats and Dutch Belted rabbits. The weight of non-clinical evidence from the rat PPN studies and rat and rabbit embryo-fetal development studies indicate that CAB had no direct effect on embryo-fetal development and survival. However, there appears to be an effect on labor and delivery in the rat that may be related to a delay in the onset of parturition that led to higher post-natal mortality in rat pups (see m2.6.6, Section 6.4). Non-clinical data demonstrated decreased survival of rat pups exposed to high doses of CAB (>30-fold exposure), which may be related to a delay in parturition in dams. There was no risk to fetal survival in rats delivered by cesarean delivery. Lactational exposure to CAB did not cause harm to the growth, neurodevelopment, or reproductive development of the offspring.

The clinical significance in humans of the non-clinical PPN findings is unclear. There is a ~14-fold margin of safety when patients discontinue CAB LA in the first trimester with levels of CAB expected to decrease as pregnancy progresses (reference NOAEL Toxicokinetic PK data and clinical exposure PK data). Overall, the embryofetal development toxicity studies in rat and rabbit do not indicate a risk to the human fetus.

1.1.3. Overview of the Clinical Development Program

ViiV Healthcare in partnership with Janssen are developing the CAB + RPV regimen for the treatment of HIV-1 infection. ViiV Healthcare is the Sponsor of the CAB + RPV clinical program. The overall clinical development and reporting strategy for the CAB program is summarized in m2.5 Section 1.2.

1.1.4. Description of Clinical Studies

The 2 Phase III studies (201584 and 201585) for which data are presented in this module compared CAB + RPV Q4W with other treatments for HIV-1-infected adults (Table 1). The Phase IIIB study, 207966, compared 2 dosing regimens of CAB + RPV (Q8W vs. Q4W).

As needed to support discussions, supplemental data are included from 2 Phase IIB studies in HIV-1-infected adults (LAI116482 and 200056), 2 Phase I PK studies in healthy adults (LAI115428 and LAI116181), and QT prolongation studies with CAB. Data not presented in this module can be found in the individual study reports.

Table 1 Summary of Design, Population, and Treatment Details for Key Clinical Studies Evaluating Safety in the CAB Program

Study	Study Design	Population	Treatment Details[1]
201584 (FLAIR) GSK Document #s 2017N345267_00 2019N421511_00 Status: Ongoing; Week 48 CSR completed; Week 96/100 CSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on DTG/ABC/3TC	HIV-1 infected ARV treatment-naïve adult subjects	**Induction Phase (20 weeks):** Oral ABC/DTG/3TC FDC (NRTI substitution allowed) **Maintenance Phase (MP) (100 weeks):** CAB + RPV Q4W group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the initial dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs) **Extension Phase:** If on CAB LA + RPV LA during MP, continue receiving CAB + RPV in Extension Phase. If on ABC/DTG/3TC, either complete study at end of MP or transition to CAB LA + RPV LA in Extension Phase.
201585 (ATLAS) GSK Document #s 2018N370336_00 2019N399072_00 Status: Ongoing; Week 48 CSR completed; Week 96 sCSR completed	Open-label, randomized, Phase III trial to demonstrate non-inferior antiviral activity of switching to CAB LA in combination with RPV LA compared with remaining on current ARV regimen	HIV-1-infected ARV-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (MP) (52 Weeks):** CAB + RPV Q4W group: Oral CAB 30 mg + RPV 25 mg once daily for 4-5 weeks, followed by IM CAB LA 600 mg + RPV LA 900 mg for the initial dose and then CAB LA 400 mg + RPV LA 600 mg every 4 weeks Control group: 2 NRTIs + INSTI or 2 NRTIs + PI or 2 NRTIs + NNRTI. **Extension Phase:** At the end of the MP, subjects could choose to transition to Study 207966, stay in Study 201585 and enter the Extension Phase, or withdraw from the study. Upon entering the Extension Phase: If on CAB LA + RPV LA, continue regimen. If on CAR, must transition to CAB LA + RPV LA to continue in study.

Study	Study Design	Population	Treatment Details[1]
207966 (ATLAS-2M) GSK Document #s: 2019N406358_01 Status: Ongoing; Week 48 CSR completed	Open-label, randomized, Phase IIIB study to demonstrate non-inferiority of LA CAB + LA RPV Q8W compared with LA CAB + LA RPV Q4W	HIV-1-infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (MP) (100 Weeks):** CAB + RPV Q4W group: CAB LA 600 mg + RPV LA 900 mg initial dose*, CAB LA 400 mg + RPV LA 600 mg every 4 weeks (±7 days) CAB + RPV Q8W group: CAB LA 600 mg + RPV LA 900 mg initial dose* and CAB LA 600 mg + RPV LA 900 mg initial dose* administered 4 weeks after the first dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks (±7 days) *Note: Subjects were either transitioned from Study 201585 (CAB + RPV Q4W or SOC) or from their current SOC. Those transitioning from SOC (201585 or current treatment) received oral CAB 30 mg + RPV 25 mg once daily for 4 to 5 weeks followed by appropriate initial doses. Those transitioning from CAB + RPV Q4W received OLI and initial doses during their participation in Study 201585 and started continuation doses on Day 1 of Study 207966 according to their randomization assignment. **Extension Phase and beyond:** Details are provided in CSR.
LAI116482 (LATTE) GSK Document #s 2013N168724_00 2014N216014_00 2016N280049_00 2019N404586_00 Status: Completed; Week 24 CSR completed, Week 96 CSR completed; Week 144 sCSR completed; Final (EOS) CSR completed	Open-label, randomized, dose ranging, Phase IIb trial evaluating oral CAB in combination with oral RPV	HIV-1 infected ARV treatment-naïve adult subjects	**Induction Phase (24 weeks):** CAB group: Oral CAB 10, 30, or 60 mg + ABC/3TC or TDF/FTC once daily Control group: EFV + ABC/3TC or TDF/FTC **Maintenance Phase (MP) (72 weeks):** CAB + RPV group: Oral CAB 10, 30, or 60 mg + oral RPV 25 mg once daily Control group: EFV + ABC/3TC or TDF/FTC **Open-Label Phase (post 96 weeks):** CAB 30 mg + RPV 25 mg

Study	Study Design	Population	Treatment Details[1]
200056 (LATTE-2) GSK Document #s 2015N246053_00 2016N273084_00 2017N337118_00 2018N360914_00 2018N380094_00 Status: Ongoing; Week 32 CSR completed, Week 48 CSR completed, Week 96 CSR completed, Week 128 sCSR completed; Week 160 aCSR completed	Open-label, randomized, dose ranging, Phase IIb trial evaluating CAB LA in combination with RPV LA compared with oral CAB in combination with 2 NRTIs to maintain virologic suppression	HIV-1 infected ARV treatment-naïve adult subjects	**Induction Phase (20 weeks):** Oral CAB 30 mg + ABC/3TC once daily, with oral RPV 25 mg once daily for last 4 weeks **Maintenance Phase (96 weeks):** CAB + RPV Q4W group: CAB LA 800 mg + RPV LA 600 mg initial dose, CAB LA 400 mg + RPV LA 600 mg every 4 weeks CAB + RPV Q8W group: CAB LA 800 mg + RPV LA 900 mg initial dose, CAB LA 600 mg initial dose, CAB LA 600 mg + RPV LA 900 mg every 8 weeks Control group: Oral CAB 30 mg + ABC/3TC once daily **Extension Phase:** If on CAB LA + RPV LA, continue from MP (either Q4W or Q8W). If on oral CAB + ABC/3TC, transition to chosen optimized IM dosing regimen (CAB LA + RPV Q4W or Q8W).

[1]See also Table 3.

In addition, there is a separate pooled safety analysis that included data from 19 Phase I/IIa clinical studies for CAB (Table 96).

1.1.4.1. Data Cut-off Dates

Table 2 Data Cut-off Dates for Studies 201584, 201585, 207966, LAI116482, and 200056

Study	Data Analysis Timepoint	Data Cut-off Date
Pooled Studies 201584 and 201585	Week 48	[redacted]
201584	Week 100	[redacted]
201585	Week 96	[redacted]
207966	Week 48	[redacted]
LAI116482	End of Study	End of Study[a]
200056	Week 160	[redacted]

a. Last subject last visit was 15 January 2019.

1.1.5. Description of Populations

As appropriate, results (eg, demographics, baseline characteristics) are presented for the ITT-E Population (all randomized subjects who received at least 1 dose of study drug; subjects were assessed according to their randomized treatment, regardless of the treatment received).

In Phase IIB Study 200056, the ITT-ME population was used (all randomized subjects who received at least 1 dose of study drug during the MP; subjects were assessed according to their randomized treatment, regardless of the treatment received).

1.1.5.1. Safety Data: Phase III/IIIB Studies 201584, 201585, and 207966 – Week 48

All randomized subjects who received at least 1 dose of study drug in these studies were included in the Safety Population for each respective study; subjects were assessed according to the actual treatment received.

1.1.5.2. Safety Data: Longer-term Phase III Studies 201584 and 201585

The MP for Study 201584 ended at Week 100 for safety data, while the MP for Study 201585 ended at Week 52 (Table 3). Subjects in Study 201585 could transition to Study 207966 at Week 52 of Study 201585, and most subjects did (Table 5). Therefore, populations for longer-term data for Study 201585 are smaller than those for Study 201584.

Study 201584

The main presentation of safety data in this document is for the Safety Population (Section 1.1.5.1) at the end of the MP (100 weeks). Some safety data (eg, SAEs and AEs leading to withdrawal) are presented for the Safety Population for the Maintenance and Extension Phases combined and for the Extension-switch Q4W group (Extension Switch Population), which consisted of all randomized subjects from the CAR arm who received at least 1 dose of CAB and/or RPV during the Extension Phase of the study.

Study 201585

In addition to the Safety Population (Section 1.1.5.1) for the Maintenance and Extension Phases combined (up to 100 weeks), some safety data are presented for the Extension Switch to CAB + RPV Q4W group (Extension Switch Population), which consisted of all randomized subjects from the CAR arm who received at least 1 dose of CAB and/or RPV during the Extension Phase of the study.

1.1.5.3. Safety Data: Phase IIB Studies LAI116482 and 200056

Study LAI116482

Unless otherwise specified, safety results from Study LAI116482 are presented for the Safety Maintenance Population, which consisted of all subjects who entered the MP and received at least one dose of study drug. Subjects were analyzed according to the actual treatments received. Results for the Safety Maintenance Population included data for the Maintenance and Open-label Phases (Weeks 24 to 312) when subjects were on oral CAB + oral RPV or EFV + 2 NRTIs (subjects randomized to the EFV arm completed the study at the end of the MP, Week 96). Results for the Safety Population covered Day 1 to Week 312; however, this population also included data from the Induction Phase

(Day 1 to Week 24) when subjects were taking CAB + 2 NRTIs. These data are available in the Study LAI116482 CSR.

Other considerations for presenting these study results include:

- When appropriate, results for EFV + 2 NRTIs are presented for balance; however, these subjects completed the study at Week 96 while the subjects on CAB + RPV continued for up to 312 weeks (EOS).
- When possible, results from the 3 CAB + RPV groups are combined; in these cases, the nomenclature for these results will be CAB +RPV group (singular).

Study 200056

Safety results from Study 200056 are presented for the Safety Maintenance Population, which consisted of all subjects who entered the MP and received at least one dose of study drug. Subjects were analyzed according to the actual treatments received. Some results are also presented for the Extension Switch Population, which included all subjects originally randomized to the oral CAB 30 mg + ABC/3TC arm in the MP who switched to, and received at least one dose of, the optimized IM dosing regimen of their choice (either Q8W or Q4W) in the Extension Period.

1.1.6. Statistical Methods

1.1.6.1. Week 48 Phase III/IIIB Results

Pooled Analysis of Studies 201584 and 201585 for Week 48 - Maintenance Phase

Safety profiles of CAB and RPV were consistent across Studies 201584 and 201585. Therefore, unless otherwise specified, the safety results presented in this submission for those 2 studies for the Week 48 analysis are data pooled from them for the MP (Section 1.1.6.5 and Table 3), cumulative through the Week 48 database, which included information beyond Week 48 where available.

Demographic, study population, and health outcomes results are for the ITT-E Population, and all safety analyses are performed for the Safety Population (Section 1.1.5.1), as defined in the RAP and SDAP documents.

Safety analyses include summaries of extent of exposure, AEs including special interest categories, laboratory tests, vital signs, and ECGs.

The AE data for Studies 201584 and 201585 used MedDRA version 21.0. The GSKDrug dictionary was used for concomitant medications.

A post-hoc Bonferroni procedure was used to control type I error at the 5% significance level within each study and within the pooled analysis as the testing framework for PROs. See m2.7.3 Section 1.6.1.4.1 for details.

For complete details of data handling and analysis for the individual studies, please refer to the RAP for each CSR; for the pooled safety analysis, please refer to the SDAP for CAB + RPV.

Study 207966

For Study 207966, safety data analyses were also at Week 48 for the MP (Section 1.1.6.5 and Table 3) and included data beyond 48 weeks where available.

Demographic, study population, and health outcomes results are for the ITT-E Population, and all safety analyses are performed for the Safety Population (Section 1.1.5.1), as defined in the RAP.

Safety analyses include summaries of extent of exposure, AEs including special interest categories, laboratory tests, vital signs, and ECGs.

The AE data for Study 207966 used MedDRA version 22.0. The GSKDrug dictionary was used for concomitant medications.

For complete details of data handling and analysis, please refer to the RAP for the CSR.

1.1.6.2. Longer-term Phase III Results

Longer-term safety data for Studies 201584 and 201585 (see Table 3) are presented by the individual study. For complete details of data handling and analysis, please refer to the RAP for each CSR.

1.1.6.3. Phase IIB Results

Data for Studies LAI116482 and 200056 are presented by the individual study. For complete details of data handling and analysis, please refer to the RAP for each CSR.

1.1.6.4. Pooled Clinical Pharmacology Safety Analysis for CAB

Results of the pooled Phase I/IIa safety analyses are presented in Section 5.5. For complete details of data handling and analysis, please refer to the SDAP (m5.3.5.3).

1.1.6.5. Treatment Phase Definitions

Definitions used to determine the treatment phases of AEs and laboratory assessments are described in the individual study RAPs.

For Studies 201584, 201585, and 207966, Baseline referred to assessments and randomization occurring on Day 1.

Durations for study phases differed among some of the studies (Table 3). See Table 1 for study design summary.

Table 3 Treatment Phase Definitions for Phase IIB and III/IIIB Studies

Study	Maintenance Phase	Extension Phase	LTFU Phase[a]
Phase III/IIIB			
201584[b]	Day 1 through Week 100[c]	Post Week 100	Day of last study drug dose to 52 weeks post-dose
201585	Day 1 to Week 52[c]	Post Week 52[d]	Day of last study drug dose to 52 weeks post-dose
207966	Day 1 through Week 100[c]	Post Week 100	Day of last study drug dose to 52 weeks post-dose
Phase IIB			
LAI116482[e]	Week 24 through Week 96	Post Week 96[f]	Not applicable
200056[g]	Day 1 through Week 96	Post Week 96[h]	Day of last study drug dose to 52 weeks post-dose

a. Subjects were to be on suppressive HAART.
b. Induction Baseline referred to assessments occurring at Week -20 prior to subjects receiving CAR.
c. Included OLI.
d. Following Week 52 visit, could transition to Study 207966, continue in study on CAR + RPV, or withdraw.
e. MP was preceded by Induction Phase from Day 1 through Week 24.
f. For this study only, this was the Open-Label Phase.
g. MP was preceded by Induction Period from Week -20 to Day 1 (randomization).
h. Following Week 96 visit, subjects switched to selected IM dosing regimen (CAB + RPV Q4W or Q8W).

The LTFU Phase started after the last dose of the study treatment. Therefore, AEs starting after the last dose of study treatment and before the start of LTFU Phase HAART would be considered in both the Maintenance Phase and LTFU Phase.

Available data (SAEs) from the LTFU Phase are included in this application.

1.1.7. Independent Data Monitoring Committees

An IDMC was formed for Studies 201584 and 201585 and for Study 207966 to evaluate the efficacy, tolerability, safety, and PK of the CAB + RPV 2-drug regimen and to identify any unexpected safety issues and/or lack of efficacy early in the studies. The IDMC consisted of 2 independent physicians and an independent statistician.

An interim futility analysis was performed by an independent statistical and data analysis center on the data from the individual studies when approximately 50% of subjects were expected to have reached their Week 24 Maintenance Phase visit. This timing was to allow the IDMC sufficient opportunity to review data prior to subjects reaching the Week 48 visit for the respective study in case any modification to the study was warranted. The Sponsor remained blinded to this analysis. Based on their review, the IDMC recommended to continue each study as planned.

1.1.8. Subject Disposition

1.1.8.1. Week 48 Phase III/IIIB Results

In Studies 201584, 201585, and 207966, the Safety Population was the same as the ITT-E Population (pooled Studies 201584 and 201585: CAB + RPV Q4W , 591 subjects and CAR, 591 subjects [total of 1182 subjects]; Study 207966: Q8W, 522 subjects and Q4W, 523 subjects [total of 1045 subjects]). Overall and for the individual studies, the number of subjects randomized and treated was similar across treatment groups.

In pooled Studies 201584 and 201585, similar proportions of subjects in each treatment group (CAB + RPV Q4W : 9%; CAR: 7%) withdrew from the study at the Week 48 analysis, although a greater number of subjects in the CAB + RPV Q4W group withdrew due to AEs (22 [4%] vs. 9 [2%] subjects) (m2.7.3 in-text Table 3). Of note, Study 201584 had a longer MP (up to Week 100) whereas the majority of subjects in Study 201585 transitioned to Study 207966 after completing the MP at Week 52; therefore, the number of completers was higher in Study 201585.

In Study 207966, most subjects in both treatment groups (Q8W: 93%; Q4W: 92%) were ongoing in the MP at the data cutoff (Section 1.1.4.1) (m2.7.3 in-text Table 3). For the Q8W group, the most common reasons for withdrawal were AEs and lack of efficacy (n=12 and n=9, respectively; 2% each). For the Q4W group, the most common reasons for withdrawal were withdrawal by subject (n=21; 4%) and AEs (n=13; 2%). All other reasons for withdrawal were reported by ≤1% of subjects in either group.

1.1.8.2. Longer-term Phase III Results

For Study 201584, Week 100 was the end of the MP. At least 86% of subjects in each treatment group completed the MP, and the majority of completers entered the Extension Phase (Table 4). A similar proportion of subjects in each treatment group withdrew during the MP; the most common reason for withdrawal by treatment group was AE and withdrawal by subject (5% for each reason) for CAB + RPV Q4W and withdrawal by subject (4%) for CAR.

Table 4 Subject Disposition in Study 201584 at Week 100 (ITT-E Population)

	CAB + RPV Q4W (N=283)	CAR (N=283)
Completed Maintenance Phase Through Week 100, n (%)	244 (86)	253 (89)
Entered Extension Phase, n	243	232
Withdrawn During Maintenance Phase Through Week 100, n (%)	39 (14)	30 (11)
Primary reason for withdrawal, n (%)		
AE	14 (5)	4 (1)
Lack of efficacy	6 (2)	5 (2)
Protocol deviation	0	2 (<1)
Withdrawal by subject	14 (5)	10 (4)
Lost to follow-up	2 (<1)	3 (1)
Physician decision	3 (1)	6 (2)

Data Source: GSK Doc. # 2019N421511_00 in-text Figure 2 and in-text Table 2.

In Study 201585 at Week 96, 51 subjects were ongoing in the Extension Phase (Table 5).

Table 5 Subject Disposition in Study 201585 at Week 96 (ITT-E Population)

	CAB + RPV Q4W N=308	Extension Switch to CAB + RPV Q4W N=308
Withdrawn During Maintenance Phase Through Week 52, n	26	18[a, b]
Withdrawn During Extension Phase, n	4	8
Ongoing at Week 96, n	23	28
Transitioned to Study 207966[c], n	253	251[a]
Completed Maintenance Phase, Did Not Transition to Study 207966, and Did Not Enter Extension Phase, n	2	5

Data Source: GSK Doc. # 2019N399072_00 in-text Table 6.

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.

a. Two subjects were included in both categories, because they deviated from Protocol, i.e. withdrew at Week 48 and transitioned to Study 207966 prior to the completion of Maintenance Phase (i.e. Week 52 visit).
b. 18 subjects who were receiving CAR and withdrew during the Maintenance Phase are listed in Extension Switch to CAB + RPV group.
c. Transition option was available after subjects completed Maintenance Phase.

1.1.8.3. Phase IIB Results

The majority of subjects (62%) completed Study LAI116482 (Table 6). The most common reason for withdrawal was lost to follow-up, followed by AE.

Table 6 Summary of Subject Accountability: Study LAI116482 Conclusion (End of Study) Record (ITT-E Population)

	CAB 10 mg + RPV N=60	CAB 30 mg + RPV N=60	CAB 60 mg + RPV N=61	EFV 600 mg + 2 NRTIs 600 mg N=62	Total N=243
Completion Status, n (%)					
Completed	30 (50)	36 (60)	44 (72)	41 (66)	151 (62)
Withdrew	30 (50)	24 (40)	17 (28)	21 (34)	92 (38)
Primary reason for withdrawal, n (%)					
Adverse event	4 (7)	3 (5)	5 (8)	9 (15)	21 (9)
Lack of efficacy	9 (15)	3 (5)	2 (3)	6 (10)	20 (8)
Protocol deviation	3 (5)	2 (3)	1 (2)	0	6 (2)
Study closed/terminated	1 (2)	0	0	0	1 (<1)
Lost to follow-up	8 (13)	6 (10)	6 (10)	4 (6)	24 (10)
Investigator discretion	0	3 (5)	1 (2)	1 (2)	5 (2)
Withdrew consent	5 (8)	7 (12)	2 (3)	1 (2)	15 (6)

Data Source: GSK Doc. # 2019N404586_00 Table 6.2.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96.

Disposition in Study 200056 at the Week 160 data cutoff is presented in Table 7.

Table 7 Summary of Subject Accountability: Maintenance and Extension Period Conclusion Records in Study 200056 at Week 160 (ITT-ME and Extension Switch Populations)

	Randomized			Optimized		
	CAB + RPV Q8W IM[b] (N=115)	CAB + RPV Q4W IM[c] (N=115)	CAB + RPV IM Total (N=230)	CAB + RPV Q8W IM[d] (N=34)	CAB + RPV Q4W IM[e] (N=10)	CAB + RPV IM Total (N=44)
Completion Status, n (%)						
Completed Maintenance Period[a]	110 (96)	101 (88)	211 (92)	-	-	-
Prematurely discontinued Maintenance Period	5 (4)	14 (12)	19 (8)	-	-	-
Prematurely discontinued Extension Period	3 (3)	7 (6)	10 (4)	1 (3)	1 (10)	2 (5)
Ongoing at time of analysis	104 (90)	94 (82)	198 (86)	33 (97)	9 (90)	42 (95)
Primary reason for withdrawal, n (%)						
Adverse event	1 (<1)	12 (10)	13 (6)	0	1 (10)	1 (2)
Lack of efficacy	1 (<1)	0	1 (<1)	1 (3)	0	1 (2)
Protocol-specified withdrawal criterion met		1 (<1)	1 (<1)	-	-	-
Protocol deviation	1 (<1)	3 (3)	4 (2)	-	-	-
Withdrawal by subject	4 (3)	4 (3)	8 (3)	-	-	-
Lost to follow-up	0	1 (<1)	1 (<1)	-	-	-
Physician decision	1 (<1)	0	1 (<1)	-	-	-

Data Source: GSK Doc. # 2018N380094_00 in-text Table 2.

Note: All subjects received 20 weeks oral CAB in the Induction Period. At start of the Maintenance Period, eligible subjects were randomized to: Q8W IM, Q4W IM, or Oral CAB. Subjects randomized to Q8W/Q4W IM continued to receive their Maintenance Period IM dosing regimen in the Extension Period and are denoted as 'Randomized' in this table. Subjects who successfully completed 96 weeks of oral CAB in the Maintenance Period had the option of continuing study participation in the Extension Period by switching to an optimized IM dosing regimen of their choice and are denoted as 'Optimized' in this table. Data for subjects receiving oral comparator are not summarized.

a. 3 subjects from the randomized Q8W IM arm completed Maintenance and did not enter Extension.
b. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W).
c. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W).
d. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension.
e. Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension.

1.2. Overall Extent of Exposure

1.2.1. Program-wide Exposure

Overall, 2141 subjects were exposed to oral and/or LA CAB + RPV during ViiV Healthcare-sponsored HIV treatment clinical studies in Phase IIB and Phase III/IIIB (LA116482, 200056, 201584, 201585, and 207966) as of 18-OCT-2019.

As stated in Section 1.1.1.1, CAB LA + RPV LA have been evaluated in 2 dosing regimens: monthly dosing and dosing every 2 months. When assessing the safety of the 2 dosing regimens, the following should be borne in mind to understand similarities and differences between the 2 regimens with regards to exposure. Plasma CAB Cmax is approximately 8.0 mg/mL with CAB oral therapy (30 mg PO once daily), twice the Cmax observed with CAB LA regimens (m2.7.2 Section 3.1.3). At Week 48, plasma CAB Cmax values are similar for the CAB LA 400 mg IM monthly and CAB LA 600 mg IM every 2 months injection schedules, with values of approximately 4.2 and 4.0 mg/mL, respectively. Consistent with the lower dose over a dosing interval, plasma CAB AUC(0-τ) for CAB LA 400 mg IM monthly (2415 mg.h/mL) is lower than for CAB LA 600 mg IM every 2 months (3764 mg.h/mL). Consistent with the relatively higher dose over a 2-month period, plasma CAB AUC(0-1440h) for CAB LA 400 mg IM monthly (800 mg over 2 months; 4830 mg.h/mL) is higher than for CAB LA 600 mg IM every 2 months (3764 mg.h/mL).

1.2.2. Week 48 Phase III/IIIB Results

As of the reporting date (see Section 1.1.4.1 for individual study cut-off dates), the median time of exposure of HIV-1 infected subjects (N=591) to CAB LA + RPV LA Q4W in pooled Studies 201584 and 201585 was 392 days (56 weeks) (Table 8). The majority of subjects in Study 201585 transitioned to Study 207966 after completing MP at Week 52; therefore, the extent of exposure represented in these data was higher in Study 201584.

In Study 207966, the median time of exposure from Baseline to LA CAB + RPV was similar between treatment groups (Table 8). Subjects have been exposed to LA CAB + RPV for up to about 1.5 years (582 days).

Table 8 Summary of Overall Exposure (Days) in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283)	CAR (N=283)	CAB + RPV Q4W (N=308)	CAR (N=308)	CAB + RPV Q4W (N=591)	CAR (N=591)	CAB + RPV Q8W (N=522)	CAB + RPV Q4W (N=523)
Overall Exposure (Days)								
n	282	283	308	308	590	591	522	523
Mean	429.2	395.5	358.1	356.6	392.0	375.2	416.4	424.3
SD	88.83	85.01	69.45	42.74	86.84	69.15	81.89	85.10
Median	435.0	393.0	374.0	364.0	382.0	366.0	447.0	445.0
Q1	407.0	390.0	372.0	364.0	372.0	364.0	393.0	399.0
Q3	488.0	449.0	380.0	366.0	434.0	393.0	457.0	462.0
Min	3	29	7	45	3	29	19	19
Max	551	512	417	394	551	512	579	582

Data Source: ISS/ISE Table 3.03 and 2019N406358_01 Table 3.1.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
CAB + RPV: From Day 1, subjects started oral CAB 30 mg + RPV 25 mg once daily for 4 weeks. At Week 4b, subjects had the 1st CAB LA + RPV LA IM. After Week 4b, the IM injection was performed at every 4 weeks.
Overall Exposure for CAB LA + RPV LA arm = (Date of last IP injection + 35 days) - Oral lead-in CAB + RPV Start Date + 1 day.

Overall exposure by weeks is presented for Studies 201584 and 201585 in Table 9 and for Study 207966 in Table 10.

Table 9 Summary of Overall Exposure by Weeks in Studies 201584, 201585, and 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283)	CAR (N=283)	CAB + RPV Q4W (N=308)	CAR (N=308)	CAB + RPV Q4W (N=591)	CAR (N=591)
Overall Exposure, n (%)						
n	282	283	308	308	590	591
<2 weeks	2 (<1)	0	1 (<1)	0	3 (<1)	0
2 to <4 weeks	0	0	1 (<1)	0	1 (<1)	0
4 to <8 weeks	1 (<1)	3 (1)	3 (<1)	1 (<1)	4 (<1)	4 (<1)
8 to <12 weeks	3 (1)	3 (1)	0	1 (<1)	3 (<1)	4 (<1)
12 to <16 weeks	0	0	6 (2)	1 (<1)	6 (1)	1 (<1)
16 to <20 weeks	3 (1)	2 (<1)	5 (2)	1 (<1)	8 (1)	3 (<1)
20 to <24 weeks	2 (<1)	5 (2)	1 (<1)	4 (1)	3 (<1)	9 (2)
24 to <28 weeks	1 (<1)	1 (<1)	3 (<1)	0	4 (<1)	1 (<1)
28 to <32 weeks	1 (<1)	0	0	2 (<1)	1 (<1)	2 (<1)
32 to <36 weeks	1 (<1)	2 (<1)	0	1 (<1)	1 (<1)	3 (<1)
36 to <40 weeks	1 (<1)	0	0	0	1 (<1)	0
40 to <44 weeks	0	0	3 (<1)	3 (<1)	3 (<1)	3 (<1)
44 to <48 weeks	3 (1)	11 (4)	1 (<1)	0	4 (<1)	11 (2)
48 to <52 weeks	2 (<1)	35 (12)	4 (1)	53 (17)	6 (1)	88 (15)
52 to <64 weeks	148 (52)	130 (46)	280 (91)	241 (78)	428 (72)	371 (63)
64 to <76 weeks	104 (37)	91 (32)	0	0	104 (18)	91 (15)
≥76 weeks	10 (4)	0	0	0	10 (2)	0

Data Source: ISS/ISE Table 3.03.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
CAB + RPV: From Day 1, subjects started oral CAB 30mg + RPV 25mg once daily for 4 weeks. At Week 4b, subjects had the 1st CAB LA + RPV LA IM. After Week 4b, the IM injection will be performed at every 4 weeks.
Overall Exposure for CAB LA + RPV LA arm = (Date of last IP injection + 35 days) - Oral lead-in CAB + RPV Start Date + 1 day.

Table 10 Summary of Overall Exposure by Weeks in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Overall Exposure (Weeks)		
n	522	523
<2 weeks	0	0
2 to <4 weeks	1 (<1%)	1 (<1%)
4 to <8 weeks	5 (<1%)	6 (1%)
8 to <12 weeks	1 (<1%)	1 (<1%)
12 to <16 weeks	2 (<1%)	3 (<1%)
16 to <20 weeks	3 (<1%)	4 (<1%)
20 to <24 weeks	2 (<1%)	4 (<1%)
24 to <28 weeks	7 (1%)	1 (<1%)
28 to <32 weeks	2 (<1%)	3 (<1%)
32 to <36 weeks	1 (<1%)	1 (<1%)
36 to <40 weeks	0	4 (<1%)
40 to <44 weeks	2 (<1%)	4 (<1%)
44 to <48 weeks	5 (<1%)	0
48 to <52 weeks	48 (9%)	11 (2%)
≥52 weeks	443 (85%)	480 (92%)

Data Source: GSK Doc. # 2019N406358_01 Table 3.1.

OLI

The median time of exposure to oral CAB + RPV from the OLI period of the MP (Week 48 analysis) of pooled Studies 201584 and 201585 was 5.3 weeks (Data Source: ISS/ISE Table 3.01). The median time of exposure to oral CAB + RPV from the OLI period of the MP of Study 207966 was 39 days (5.6 weeks) in both the Q8W and Q4W groups (Data Source: GSK Doc. # 2019N406358_01 Table 3.1).

In Study 207966, 655 subjects received OLI during transition from SOC to treatment with LA CAB + RPV (Data Source: GSK Doc. # 2019N406358_01 Table 1.12). When combined with the 590 subjects who received OLI during Studies 201584 and 201585 (ISS/ISE Table 3.01), a total of 1245 subjects have received oral CAB + RPV as OLI across these studies.

1.2.2.1. Prior Treatment (CAB + RPV or CAR) for Subjects in Study 207966

As presented in Table 1, both rollover and de novo subjects were eligible to enter Study 207966. Subjects either could have rolled over from Study 201585 (treated with either CAB + RPV Q4W or CAR) or entered de novo and transitioned from their current SOC.

An important consideration for interpretation of the safety results for Study 207966 is that assessments at Baseline for this study included data for over one-third of subjects who had prior exposure to CAB + RPV Q4W during Study 201585. At the Week 48 analysis for Study 207966, 253 subjects from Study 201585 (Q4W dosing with CAB + RPV) had rolled over and had received at least 96 weeks of treatment with injectable CAB + RPV Q4W (Data Source: GSK Doc. # 2019N406358_01 Table 1.12). Treatment groups were well balanced with regards to prior exposure to CAB + RPV Q4W; therefore, overall prior exposure is summarized here (Data Source: GSK Doc. # 2019N406358_01 Table 1.22):

- 24% had >48 weeks of prior exposure to CAB + RPV Q4W,
- <1% had >24 to ≤48 weeks of prior exposure to CAB + RPV Q4W,
- 13% had 1 to 24 weeks of prior exposure to CAB + RPV Q4W, and
- 63% had no prior exposure to CAB + RPV.

In Study 201585 (the study from which subjects could have rolled over), the median time since the first ART until the start of the Maintenance Phase in that study was 52 months in both the CAB + RPV Q4W and SOC (CAR) treatment groups (Data Source: GSK Doc. # 2018N370336_00 Table 1.31).

1.2.3. Longer-term Phase III Results

At the end of the MP in Study 201584, subjects have been exposed to CAB + RPV Q4W for up to 737 days (about 105 weeks) (Table 11). In Study 201585, subjects have been exposed to CAB + RPV Q4W for up to 911 days (about 130 weeks) in the Maintenance + Extension Phases. For subjects originally randomized to CAB + RPV Q4W (ie, not switched), median time of exposure has increased since the medians at the Week 48 data cutoff (Table 8).

Table 11 Summary of Overall Exposure (Days): End of Maintenance Phase (Week 100) in Study 201584 (Safety Population) and Maintenance + Extension Phases (Week 96) in Study 201585 (Safety and Extension Switch Populations)

	Study 201584	Study 201585	
	CAB + RPV Q4W (N=283)	CAB + RPV Q4W Day 1 to Week 96 (N=308)	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 (N=174)
Overall Exposure (Days)			
Mean	661.9	437.6	146.7
SD	151.16	142.49	138.54
Median	709.0	416.5	85.0
Q1	707.0	407.0	72.0
Q3	714.0	443.0	128.0
Min	1	9	7
Max	737	911	524

Data Source: GSK Doc. # 2019N421511_00 Table 3.1 and 2019N399072_00 Table 13.1.
Note: CAB + RPV: From Day 1, subjects started oral CAB 30 mg + RPV 25 mg once daily for 4 weeks. At Week 4b, subjects had the 1st CAB LA + RPV LA IM. After Week 4b, the IM injection was performed at every 4 weeks.
Overall Exposure for CAB LA + RPV LA arm = (Date of last IP injection + 35 days) - Oral lead-in CAB + RPV Start Date + 1 day.

In Study 201584 for the Safety Population in the cumulative Maintenance + Extension Phases (n=283), median (IQR1, IQR3) duration of exposure was 782 (746, 825) days (about 111 weeks); for the Extension Switch Population (n=232), median (IQR1, IQR3) duration of exposure was 91 (59, 140) days (13 weeks) (Data Source: GSK Doc. # 2019N421511_00 Table 3.2 and Table 3.3).

1.2.4. Phase IIB Results

At EOS in Study LAI116482, median exposure to oral CAB was 2179 days (311 weeks or almost 6 years) and median exposure to oral RPV was 2014 days (about 288 weeks or about 5.5 years) (Data Source: GSK Doc. # 2019N404586_00 Table 8.1 and Table 8.74).

In Study 200056, with the exception of Week 4 for the Q8W IM arm, all injection visits included the administration of both CAB and RPV injections. The median number of injections was 25 and 46, respectively, for the randomized Q8W IM and randomized Q4W IM treatment groups (Data Source: GSK Doc. # 2018N380094_00 Section 5.5). The median number of injections was 11 and 20 for the optimized Q8W IM and optimized Q4W IM arms, respectively, during the Extension Period.

1.3. Demographic and Other Characteristics of Study Population

1.3.1. Demographic Characteristics

1.3.1.1. Phase III/IIIB Results

Demographic characteristics were generally similar across treatment groups overall and in the individual studies (m2.7.3 in-text Table 4). In Studies 201584 and 201585, 27% and 28% of subjects were women in the pooled analysis in the CAB + RPV Q4W and CAR groups, respectively. Further, 17% and 21% of subjects were 50 years of age or older in the CAB + RPV Q4W and CAR groups, respectively. The median age across the study populations was 38 years. The majority of subjects in both studies were White/Caucasian (72% in the CAB + RPV Q4W group and 68% in the CAR group).

In Study 207966, demographic characteristics were similar to those in Studies 201584 and 201585 and generally similar between the Q8W and Q4W groups (m2.7.3 in-text Table 4). Although the majority of subjects were male, the study enrolled 27% females. Median (range) age was 42.0 years (19-83 years). Over one-quarter of the subjects (27%) were ≥50 years old, and 3% (n=28) were ≥65 years old. The majority of subjects in both groups were White/Caucasian (70% in the Q8W group and 74% in the Q4W group). Median weight (Q8W: 77.50 kg; Q4W: 78.00 kg) and BMI categorization (Q8W: 25.724; Q4W: 25.923) were similar between treatment groups.

1.3.1.2. Phase IIB Results

In Study LAI116482, demographic characteristics were well balanced across the treatment groups (Data Source: GSK Doc. # 2019N404586_00 in-text Table 8). Most (96%) subjects were male. Median (range) age was 33.0 years (18-70 years). Most subjects (62%) were White/Caucasian.

In Study 200056, demographic characteristics were similar between the randomized groups (Data Source: GSK Doc. # 2018N380094_00 in-text Table 8). Most (82%) subjects were male. Median (range) age was 35.0 years (19-56 years). Most subjects (68%) were White/Caucasian.

1.3.2. Baseline Characteristics

1.3.2.1. Phase III/IIIB Results

In Studies 201584, 201585, and 207966, Baseline disease characteristics were similar across treatment groups overall and in the individual studies (Table 12). Subjects in Study 201584 were treatment naïve at the initiation of the Induction Phase. Subjects in Study 201585 were virologically suppressed prior to study entry and both arms had been receiving ART for a median of 52 months prior to randomization (GSK Doc. # 2018N370336_00 Section 5.5). Subjects in Study 207966 were on a stable ART regimen, either SOC or at least 52 weeks of CAB + RPV Q4W in Study 201585.

Overall, most subjects were in CDC Stage 1. Baseline plasma HIV-1 RNA and CD4+ counts were similar between treatment groups. HIV risk factors at Baseline were similar between the treatment groups in each respective study (Data Source: GSK Doc. # 2017N345267_00 Section 5.4.2.9; GSK Doc. # 2018N370336_00 Section 5.4.2.4; GSK Doc. # 2019N406358_01 Table 1.23).

Table 12 Summary of Baseline Characteristics for Studies 201584, 201585, 201584+201585 Pooled, and 207966 (ITT-E Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283)	CAR (N=283)	CAB + RPV Q4W (N=308)	CAR (N=308)	CAB + RPV Q4W (N=591)	CAR (N=591)	CAB + RPV Q8W (N=522)	CAB + RPV Q4W (N=523)
Adults CDC Category, n (%)								
HIV Infection Stage 1	200 (71)	196 (69)	229 (74)	224 (73)	429 (73)	420 (71)	391 (75)	407 (78)
HIV Infection Stage 2	78 (28)	82 (29)	78 (25)	83 (27)	156 (26)	165 (28)	129 (25)	113 (22)
HIV Infection Stage 3 (AIDS)	5 (2)	5 (2)	1 (<1)	1 (<1)	6 (1)	6 (1)	2 (<1)	3 (<1)
Baseline CD4+ (cells/mm^3), n (%)								
<350	19 (7)	27 (10)	23 (7)	27 (9)	42 (7)	54 (9)	35 (7)	27 (5)
350 to <500	64 (23)	60 (21)	56 (18)	57 (19)	120 (20)	117 (20)	96 (18)	89 (17)
≥500	200 (71)	196 (69)	229 (74)	224 (73)	429 (73)	420 (71)	391 (75)	407 (78)
Mean	666.4	645.7	678.5	692.8	672.7	670.2	681.8	729.8
SD	272.14	253.44	257.11	288.74	264.26	273.20	259.91	298.57
Median	624.0	625.0	653.5	652.5	645.0	641.0	642.0	688.0
Q1	473.0	472.0	497.0	488.0	487.0	480.0	499.0	523.0
Q3	839.0	799.0	816.0	843.5	824.0	821.0	827.0	878.0
Min, Max	109, 1889	66, 1558	185, 1903	150, 2543	109, 1903	66, 2543	163, 1737	114, 2929

Data Source: ISS/ISE Table 1.08, ISS/ISE Table 1.09, GSK Doc. # 2019N406358_01 Table 1.19 and Table 1.21.

Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Across Studies 201584 and 201585, 41 (7%) subjects in the CAB + RPV Q4W group and 40 (7%) subjects in the CAR groups were considered to have had HCV at Screening (GSK Doc. # 2017N345267_00 Section 5.4.2; GSK Doc. # 2018N370336_00 Section 5.4.2). Additionally, 1 subject in the CAB + RPV Q4W group (Study 201584) had HCV and had serology and virology results consistent with prior HBV infection, with no evidence of active infection.

Hepatitis status at study entry in Study 207966 (Data Source: GSK Doc. # 2019N406358_01 Table 1.18) was as follows:

- Positive for Hepatitis C only; Q8W: 5 subjects (<1%); Q4W: 6 subjects (1%)
- Positive for Hepatitis B only (not active infection; GSK Doc # 2019N406358_01 Section 5.5.2.2); Q8W: 2 subjects (<1%); Q4W: 1 subject (<1%)

1.3.2.2. Phase IIB Results

Most subjects were CDC Category A in the Phase IIB studies (Table 13).

Table 13 Summary of Baseline Characteristics for Studies LAI116482 and 200056 (ITT-E Population)

	Study LAI116482 N=243	Study 200056 N=309
CDC Classification, n (%)		
A: Asymptomatic or lymphadenopathy or acute HIV	229 (94)	286 (93)
B: Symptomatic, not AIDS	11 (5)	20 (6)
C: AIDS	3 (1)	3 (<1)
Baseline CD4+ (cells/mm^3)		
<200, n (%)	9 (4)	6 (2)
200 to 350, n (%)	66 (27)	66 (21)
>350, n (%)	168 (69)	237 (77)
Median	416	484
Q1	323	355
Q3	552	618

Data Source: GSK Doc. # 2019N404586_00 in-text Table 9; GSK Doc. # 2015N246053_00 in-text Table 10.

In Study LAI116482, all subjects (100%) were negative (non-reactive) for HBV infection and 96% were negative (non-reactive) for HCV (Data Source: GSK Doc. # 2019N404586_00 in-text Table 9). The rest of subjects (4%) were reactive for HCV.

In Study 200056, all subjects (100%) were negative for HBV and 95% were negative for HCV (Data Source: GSK Doc. # 2015N246053_00 in-text Table 10). The rest of subjects (4%) were reactive for HCV or the test result was missing (<1%).

1.3.3. Concomitant and Prior ART Medications

1.3.3.1. Phase III/IIIB Results

For Studies 201584 and 201585, prior medications, including those taken during the Screening and/or Induction Phase, are presented in ISS/ISE Table 1.14.

In Study 201584, subjects were ART-naïve at Screening and then received 20 weeks of ABC/DTG/3TC (or DTG + 2 NRTIs) during the Induction Phase. Subsequently, subjects were randomized to continue CAR or switch to CAB + RPV Q4W.

In Study 201585, 50% of subjects in both groups were receiving NNRTIs, 17% of subjects in the CAB + RPV Q4W group and 18% of subjects in the CAR group were receiving PIs, and 33% in the CAB + RPV Q4W group and 32% of subjects in the CAR group were receiving INSTIs at Screening. Of the subjects in CAB + RPV Q4W group, 13% were taking RPV at Screening (Data Source: GSK Doc. # 2018N370336_00 Table 1.29).

For Studies 201584 and 201585, at least 1 concomitant medication was used during the MP (Week 48 analysis) by most subjects (CAB + RPV Q4W: 84%; CAR: 76%) (ISS/ISE Table 1.15). Analgesics were the only medications used by >20% of subjects in either treatment group (paracetamol - CAB + RPV Q4W: 31%; CAR: 17% and ibuprofen - CAB + RPV Q4W: 29%; CAR: 14%).

In Study 207966, treatment groups were similar with regards to use of prior ART medications (Data Source: GSK Doc. # 2019N406358_01 Table 1.28). Almost all subjects (>99% overall) had taken an NRTI prior to the study, 72% overall had taken an NNRTI (including RPV, 51% overall), and 65% overall had taken an INSTI (including CAB, 37% overall) (subjects may have rolled over from Study 201585 in which they could have been administered LA CAB + RPV Q4W; Table 1). Most subjects (Q8W: 89%; Q4W: 90%) had concomitant use of non-ART medications; analgesics (ibuprofen and paracetamol) were the only medications used by >20% of subjects in either treatment group (Data Source: GSK Doc. # 2019N406358_01 Table 1.29). Non-ART medications were used by a similar proportion of subjects in each treatment group.

1.3.3.2. Phase IIB Results

Subjects in Studies LAI16482 and 200056 were ART-naïve (Table 1).

In Study LAI16482 at Week 96, most subjects (CAB 10 mg: 93%; CAB 30 mg: 83%; CAB 60 mg: 98%; EFV: 92%) had used at least 1 concomitant medication (Data Source: GSK Doc. # 2014N216014_00 Table 6.12). Medications taken by >20% of all subjects were paracetamol, vitamins not otherwise specified, ibuprofen, azithromycin, and influenza vaccine.

In Study 200056 at Week 160, most subjects (Q8W: >99%; Q4W: 97%) had used at least 1 concomitant medication (Data Source: GSK Doc. # 2018N380094_00 Table 6.1019).

Medications taken by >20% of all subjects were paracetamol, ibuprofen, amoxicillin, influenza vaccine, azithromycin, and pneumococcal vaccine.

2. ADVERSE EVENTS

Week 48 Phase III/IIIB Results

- The overall AE profile across the Phase III/IIIB studies was similar for subjects who received CAB + RPV Q4W. The most common AEs were ISRs (mostly pain and nodules), nasopharyngitis, upper respiratory tract infection, and headache. At least 1 SAE was reported for 4% to 5% of subjects/treatment group in the pooled studies (201584 and 201585) and in Study 207966; however, <1%/treatment group were assessed by the investigator as related to study drug. The proportion of subjects who withdrew due to injection intolerability was 1% (pooled Studies 201584 and 201585), 1% (Study 207966, Q8W group), and 2% (Study 207966, Q4W group). Three deaths were reported in the Safety Population for the Phase III/IIIB studies: 1 in the Induction Phase in Study 201584 (homicide) and 2 in the MP of studies; 1 in the CAR group in Study 201585 (methamphetamine overdose) and 1 in the Q8W group in Study 207966 (sepsis) (Section 2.1.2).

  Studies 201584 and 201585

  - No clinically significant new safety issues were identified in subjects administered CAB LA + RPV LA in Studies 201584 and 201585 relative to the findings from Phase IIB studies and the known safety profile of approved RPV. The safety results observed for CAB + RPV Q4W in Studies 201584 and 201585 are acceptable for the intended population and proposed indication.
  - AEs reported by ≥10% of subjects in the CAB + RPV Q4W groups in pooled Studies 201584 and 201585 were injection site pain, nasopharyngitis, injection site nodule, injection site induration, upper respiratory tract infection, and headache.

  Study 207966

  - Based on analyses of AEs in Study 207966, safety data for the Q8W treatment group were generally similar to safety data for the Q4W treatment group. Overall, injections for Q8W CAB LA + RPV LA were well tolerated with few withdrawals due to injection intolerability (1% in Q8W group and 2% in Q4W group). The most common AEs in both treatment groups were mild/moderate ISRs. AEs reported by ≥10% of subjects in Study 207966 in either the Q8W or Q4W group were injection site pain, nasopharyngitis, injection site nodule, and upper respiratory tract infection. SAEs reported as possibly drug related occurred with a frequency of <1% in either group. Three SAEs of systemic post-injection reactions were observed in Study 207966, 1 in the Q8W group and 2 in the Q4W group; see Section 2.1.7 for additional information.

Longer-term Phase III Results

- No clinically significant new safety issues were identified in longer-term exposure to CAB LA + RPV LA in Studies 201584 (Week 96/100) and 201585 (Week 96). AEs reported by ≥10% of subjects in either treatment group at the end of the MP in Study 201584 were injection site pain, nasopharyngitis, upper respiratory tract infection, headache, diarrhea, influenza, injection site nodule, back pain, injection site induration, pyrexia, and injection site swelling. AEs reported by ≥10% of subjects in Study 201585 in either Extension Phase population were injection site pain, nasopharyngitis, injection site nodule, upper respiratory tract infection, headache, and injection site induration.

Phase IIB Results

- Subjects in the Phase IIB studies have had long-term exposure to CAB (Section 1.2.4). There has been 1 report of systemic post-injection reaction (see Section 2.1.7); otherwise, no new safety issues have been observed during these studies.

2.1. Analysis of Adverse Events

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, an overall trend for increased drug-related AEs, including ISRs, was observed for CAB + RPV Q4W compared with CAR (Table 14); however, these were not made up of SAEs or Grade 3 to 5 AEs. Within Study 207966, the proportions of subjects in the overview of AE categories were similar between the Q8W and Q4W groups.

In Studies 201584 and 201585, non-ISR AEs were reported in 86% of subjects in the pooled CAB + RPV Q4W group and 75% of subjects in the pooled CAR group (Table 15). Excluding ISRs, Grade 3 to 5 AEs, AEs leading to withdrawal, and SAEs were generally comparable between treatment groups. One fatal SAE occurred, which was a subject in the CAR group and was not considered study drug related. It should be noted that subjects in the CAR group had been established on their regimen prior to randomization.

Within Study 207966, the proportions of subjects in the overview of AE categories were similar between the Q8W and Q4W groups. One fatal SAE (sepsis) occurred in the Q8W group.

Table 14 Overview of All AEs in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Any AE	**267 (94)**	**225 (80)**	**294 (95)**	**220 (71)**	**561 (95)**	**445 (75)**	**473 (91)**	**482 (92)**
Any Grade 3/4/5 AE	31 (11)	11 (4)	35 (11)	24 (8)	66 (11)	35 (6)	41 (8)	49 (9)
Any drug-related AE	236 (83)	28 (10)	255 (83)	8 (3)	491 (83)	36 (6)	400 (77)	399 (76)
Any Grade 3/4/5 drug-related AE	14 (5)	0	14 (5)	1 (<1)	28 (5)	1 (<1)	16 (3)	26 (5)
Any AEs leading to withdrawal	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	9 (2)	12 (2)	13 (2)
Any SAE	**18 (6)**	**12 (4)**	**13 (4)**	**14 (5)**	**31 (5)**	**26 (4)**	**27 (5)**	**19 (4)**
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)	1 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0

Data Source: ISS/ISE Table 3.05; GSK Doc. # 2019N406358_01 in-text Table 25, Table 3.6, Table 3.13, Table 3.16, Table 3.19, Table 3.22, and Table 3.26.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: Drug-related is based on investigator assessment.

Table 15 Overall Summary of Non-ISR AEs in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Any AE	**246 (87)**	**225 (80)**	**264 (86)**	**220 (71)**	**510 (86)**	**445 (75)**	**403 (77)**	**441 (84)**
Any Grade 3/4/5 AE	22 (8)	11 (4)	25 (8)	24 (8)	47 (8)	35 (6)	29 (6)	30 (6)
Any drug related AE	79 (28)	28 (10)	87 (28)	8 (3)	166 (28)	36 (6)	109 (21)	125 (24)
Any Grade 3/4/5 drug related AE	4 (1)	0	4 (1)	1 (<1)	8 (1)	1 (<1)	4 (<1)	5 (<1)
Any AEs leading to withdrawal	8 (3)	4 (1)	9 (3)	5 (2)	17 (3)	9 (2)	7 (1)	10 (2)[a]
Any SAE	**18 (6)**	**12 (4)**	**13 (4)**	**14 (5)**	**31 (5)**	**26 (4)**	**26 (5)**	**19 (4)**
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	2 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	0	1 (<1)	1 (<1)	0
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0

Data Source: ISS/ISE Table 3.07; GSK Doc. # 2019N406358_01 Table 3.7, Table 3.14, Table 3.19, Listing 15, Listing 16, and Listing 17.

Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Note: Drug-related is based on investigator assessment.

a. 2 additional subjects who discontinued due to AE had multiple AEs with an action taken as "drug withdrawn," including ISR AEs and non-ISR AEs.

Injection site pain was the most common AE reported in the CAB + RPV Q4W group in pooled Studies 201584 and 201585 and was also the most common AE reported in Study 207966 (Section 2.1.1.1). Additional details are provided in Section 2.1.6.1.

AEs of special interest that were evaluated during the CAB + RPV development program, including a section for ISRs, are presented in detail in Section 2.1.6.

The definition of an AE is provided in the Appendix (Section 8.2). For Studies 201584 and 201585, analysis of AEs followed a general tiered approach: Tier 1 to 3; refer to the SDAP (m5.3.5.3) for the pre-specified list of PTs analyzed and for further details. Unless otherwise specified, the term "drug related" refers to the independent assessment of the investigator regarding the relationship of the AE to the study drug (CAB + RPV).

Longer-term Phase III Results

No new trends or unexpected safety findings occurred during the MP in Study 201584 (through 100 weeks) and during the Maintenance + Extension Phases in Study 201585 (Table 16 and Table 17, respectively).

Table 16 Overall Summary of AEs During Maintenance Phase (Through 100 Weeks) in Study 201584 (Safety Population)

	CAB + RPV Q4W N=283 n (%)	CAR N=308 n (%)
Any AE	274 (97)	242 (86)
Any SAE	24 (8)	22 (8)
Any Fatal SAE	0	0
Any Drug-related SAE	1 (<1)	0
Any Grade 3-4 AE	40 (14)	16 (6)
Any AE Leading to Withdrawal	14 (5)	4 (1)

Data Source: GSK Doc. # 2019N421511_00 in-text Table 24.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

Table 17 Overall Summary of AEs During the Maintenance (up to Week 52) + Extension (Post-Week 52) Phases in Study 201585 at Week 96 (Safety and Extension Switch Populations)

	CAB + RPV Q4W Day 1 to Week 52 N=308 n (%)	CAR Day 1 to Week 52 N=308 n (%)	CAB + RPV Q4W Day 1 to Week 96 N=308 n (%)	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 N=174 n (%)
Any AE	294 (95)	220 (71)	295 (96)	105 (60)
Any SAE	13 (4)	14 (5)	15 (5)	2 (1)
Any Fatal SAE	0	1 (<1)[a]	0	0
Any Drug-related SAE	0	1 (<1)	0	0
Any Grade 3-5 AE	35 (11)	23 (7)	37 (12)	7 (4)
Any AE Leading to Withdrawal	13 (4)	5 (2)	16 (5)	1 (<1)

Data Source: GSK Doc. # 2019N399072_00 in-text Table 13.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.
a. Not related to study drug (methamphetamine overdose; see Section 2.1.2).

Phase IIB Results

An overall summary of AEs at EOS for Study LAI116482 is presented in Table 18.

Table 18 Overall Summary of AEs in Study LAI116482 at End of Study (Safety Population)

	CAB 10 mg + RPV (N=60) n (%)	CAB 30 mg + RPV (N=60) n (%)	CAB 60 mg + RPV (N=61) n (%)	CAB + RPV Subtotal (N=181) n (%)	EFV 600 mg + 2 NRTIs (N=62) n (%)
Any AE	57 (95)	57 (95)	60 (98)	174 (96)	60 (97)
Any SAE	13 (22)	12 (20)	11 (18)	36 (20)	4 (6)
Any Fatal SAE	0	1 (2)	1 (2)	2 (1)[a]	0
Any Drug-related SAE	0	1 (2)	1 (2)	2 (1)	1 (2)
Any AE Leading to Withdrawal	4 (7)	4 (7)	4 (7)	12 (7)	9 (15)

Data Source: GSK Doc. # 2019N404586_00 Table 8.3, Table 8.13, Table 8.14, Table 8.15, and Listing 8.4.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.
a. Neither (gastrointestinal hemorrhage and cardiac arrest) considered related to study drug; see Section 2.1.2.

An overall summary of AEs at the Week 160 cutoff for Study 200056 is presented in Table 19.

Table 19 Overall Summary of AEs in Maintenance and Extension Phases in Study 200056 at Week 160 Analysis (Safety Maintenance and Extension Switch Populations)

	CAB + RPV Q8W IM[a] (N=115) n (%)	CAB + RPV Q4W IM[b] (N=115) n (%)	CAB + RPV IM Total (N=230) n (%)	CAB + RPV Optimized Q8W IM[a] (N=34) n (%)	CAB + RPV Optimized Q4W IM[b] (N=10) n (%)	CAB + RPV Optimized IM Total (N=44) n (%)
Any AE	115 (100)	115 (100)	230 (100)	34 (100)	9 (90)	43 (98)
Any SAE	17 (15)	21 (18)	38 (17)	2 (6)	0	2 (5)
Fatal SAE	0	2 (2)[a]	0	0	0	0
Drug-related SAEs	0	1 (1)	1 (<1)	0	0	0
AEs Leading to Withdrawal	3 (3)	12 (10)	15 (7)	0	1 (10)	1 (2)

Data Source: GSK Doc. # 2018N380094_00 Table 8.1001, Table 8.1010, Table 8.1021, Table 8.1027, Table 8.1024, Table 8.1030, Listing 8.1004, and Section 7.3.1.

a. One assessed as related to study drug by the investigator; see Section 2.1.2.

2.1.1. Common Adverse Events

2.1.1.1. Common (≥5%) Adverse Events

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, the most commonly reported AEs (occurring in ≥5% of subjects in either treatment group) were generally similar (Table 20). The 3 most commonly reported AEs for the CAB + RPV Q4W and CAR groups were injection site pain (77% vs. 0), nasopharyngitis (18% vs. 15%), and upper respiratory tract infection (12% vs. 9%). Non-ISR AEs more commonly reported (≥5% difference) in the CAB + RPV Q4W group compared with the CAR group were headache and pyrexia.

Table 20 Most Common AEs (Reported in At Least 5% of Subjects in Either Treatment Group) by PT for Studies 201584, 201585 and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

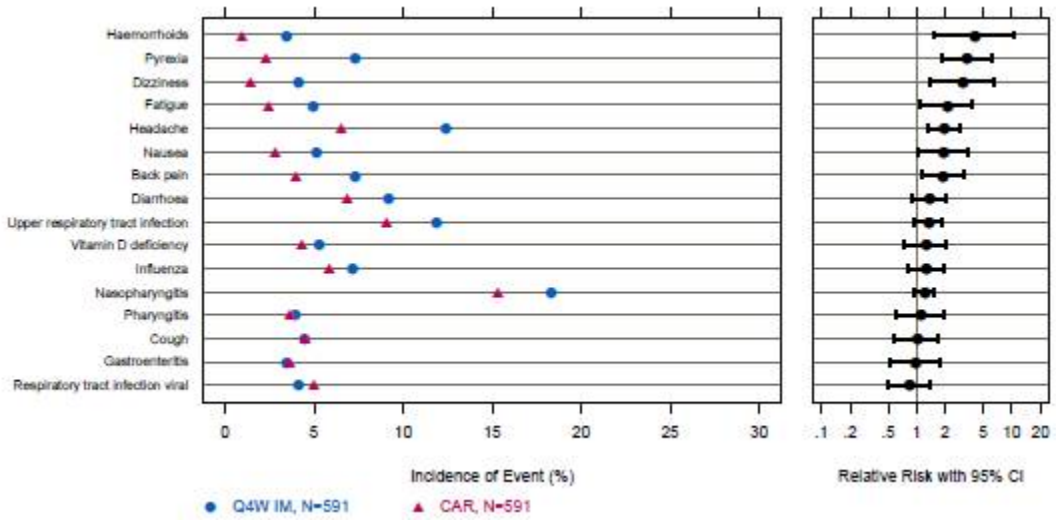
	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
Preferred Term	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)
ANY EVENT	**267 (94)**	**225 (80)**	**294 (95)**	**220 (71)**	**561 (95)**	**445 (75)**
Injection site pain	227 (80)	0	231 (75)	0	458 (77)	0
Nasopharyngitis	56 (20)	48 (17)	52 (17)	42 (14)	108 (18)	90 (15)
Upper respiratory tract infection	38 (13)	28 (10)	32 (10)	25 (8)	70 (12)	53 (9)
Headache	39 (14)	21 (7)	34 (11)	17 (6)	73 (12)	38 (6)
Diarrhea	32 (11)	25 (9)	22 (7)	15 (5)	54 (9)	40 (7)
Injection site nodule	44 (16)	0	37 (12)	0	81 (14)	0
Influenza	25 (9)	20 (7)	17 (6)	14 (5)	42 (7)	34 (6)
Injection site induration	38 (13)	0	30 (10)	0	68 (12)	0
Back pain	22 (8)	13 (5)	21 (7)	10 (3)	43 (7)	23 (4)
Pyrexia	22 (8)	4 (1)	21 (7)	9 (3)	43 (7)	13 (2)
Vitamin D deficiency	23 (8)	13 (5)	8 (3)	12 (4)	31 (5)	25 (4)
Respiratory tract infection viral	13 (5)	12 (4)	11 (4)	17 (6)	24 (4)	29 (5)
Cough	10 (4)	12 (4)	16 (5)	14 (5)	26 (4)	26 (4)
Injection site swelling	23 (8)	0	23 (7)	0	46 (8)	0
Nausea	16 (6)	11 (4)	14 (5)	5 (2)	30 (5)	16 (3)
Pharyngitis	15 (5)	9 (3)	8 (3)	12 (4)	23 (4)	21 (4)
Fatigue	7 (2)	8 (3)	22 (7)	6 (2)	29 (5)	14 (2)
Gastroenteritis	15 (5)	11 (4)	5 (2)	10 (3)	20 (3)	21 (4)
Dizziness	15 (5)	3 (1)	9 (3)	5 (2)	24 (4)	8 (1)
Hemorrhoids	16 (6)	3 (1)	4 (1)	2 (<1)	20 (3)	5 (<1)
Injection site pruritus	16 (6)	0	7 (2)	0	23 (4)	0

Data Source: ISS/ISE Table 3.17.

Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

For common non-ISR AEs, the relative risk of having hemorrhoids, pyrexia, dizziness, fatigue, headache, nausea, or back pain was higher in the CAB + RPV Q4W group compared with the CAR group (Figure 1).

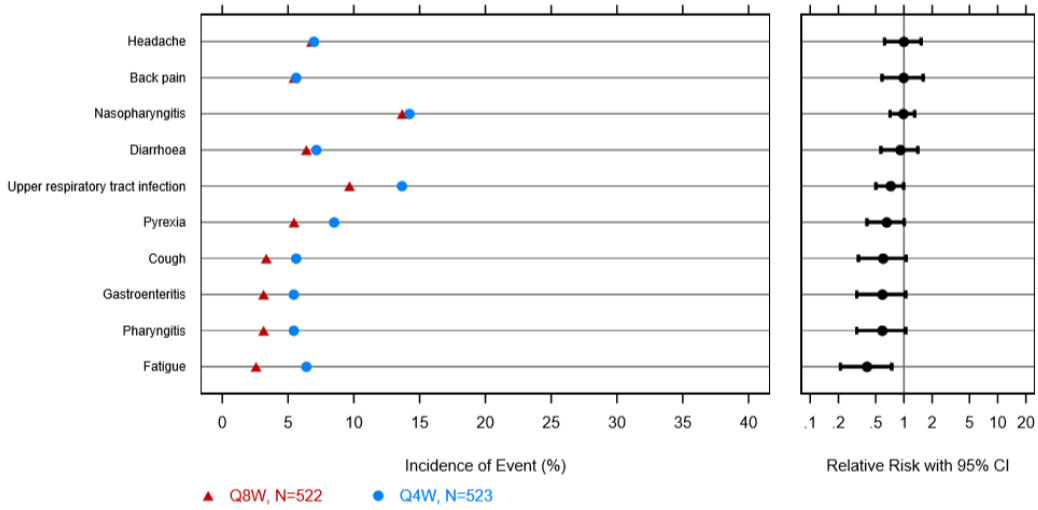
Figure 1 Plot of Common (At Least 5% of Subjects in Either Treatment Group) Non-ISR AEs and Relative Risk for CAB + RPV Q4W vs. CAR in Studies 201584+201585 Pooled – Week 48 Analysis – Maintenance Phase (Safety Population)



Data Source: ISS/ISE Figure 3.01.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, for common non-ISR AEs the relative risk of having one of these events was similar in each treatment group with the exception of fatigue; the relative risk of fatigue was lower in the Q8W group compared with the Q4W group (Figure 2).

Figure 2 Plot of Common (At Least 5% of Subjects in Either Treatment Group) Non-ISR AEs and Relative Risk for Q8W vs. Q4W in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 3.1.

Furthermore, in Study 207966 the proportion of subjects reporting at least 1 AE (Q8W: 91%; Q4W: 92%) as well as the frequency of individual common AEs (≥5% in either group) was comparable between the 2 treatment groups with the exception of injection site nodule, reported by a higher proportion of subjects in the Q4W group (Q8W: 10%; Q4W: 17%) (Data Source: GSK Doc. # 2019N406358_01 Table 3.10). AEs reported in ≥10% of subjects in either treatment group were injection site pain (Q8W: 71%; Q4W: 69%), nasopharyngitis (Q8W: 14%; Q4W: 14%), injection site nodule (Q8W: 10%; Q4W: 17%), and upper respiratory tract infection (Q8W: 10%; Q4W: 14%). Headache (Q8W: 7%; Q4W: 7%) and pyrexia (Q8W: 5%; Q4W: 8%) were reported by similar proportions of subjects in each treatment group.

For ISRs overall, 76% of subjects in the Q8W group and 75% of subjects in the Q4W group reported at least 1 ISR AE (Data Source: GSK Doc. # 2019N406358_01 Table 3.29). Additional details for ISR AEs are provided in Section 2.1.6.1.

Longer-term Phase III Results

At the end of the MP in Study 201584, the percentage of subjects reporting at least 1 AE was higher in the CAB + RPV Q4W group compared with the CAR group (Table 21). This was at least in part attributable to the occurrence of ISRs in the CAB + RPV Q4W group (which were obviously absent in the CAR group). The frequency of individual common (≥5%) AEs was similar in the 2 treatment groups, with the exception of ISR events. For non-ISR AEs, the relative risk of having asthenia, pyrexia, dizziness, dyspepsia, oral herpes, hemorrhoids, vomiting, myalgia, oropharyngeal pain, back pain, or headache was higher in the CAB + RPV Q4W group compared with the CAR group (Data Source: GSK Doc. # 2019N421511_00 Figure 3.1).

Table 21 Summary of Common AEs (At Least 5% in Either Treatment Group) in Study 201584 at Week 100 – Maintenance Phase (Safety Population)

PT	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)
Any AE	**274 (97)**	**242 (86)**
Injection site pain	235 (83)	0
Nasopharyngitis	78 (28)	63 (22)
Upper respiratory tract infection	47 (17)	41 (14)
Headache	50 (18)	33 (12)
Diarrhoea	43 (15)	38 (13)
Influenza	37 (13)	29 (10)
Injection site nodule	58 (20)	0
Back pain	34 (12)	18 (6)
Vitamin D deficiency	25 (9)	21 (7)
Injection site induration	44 (16)	0
Gastroenteritis	22 (8)	20 (7)
Pyrexia	30 (11)	7 (2)
Bronchitis	18 (6)	17 (6)
Syphilis	18 (6)	17 (6)
Cough	15 (5)	19 (7)
Pharyngitis	20 (7)	13 (5)
Arthralgia	16 (6)	15 (5)
Nausea	18 (6)	13 (5)
Injection site swelling	30 (11)	0
Abdominal pain	16 (6)	11 (4)
Anogenital warts	16 (6)	10 (4)
Hemorrhoids	20 (7)	6 (2)
Injection site pruritus	26 (9)	0
Myalgia	18 (6)	7 (2)
Anxiety	16 (6)	8 (3)
Oropharyngeal pain	17 (6)	7 (2)
Oral herpes	18 (6)	5 (2)
Dizziness	17 (6)	4 (1)
Vomiting	16 (6)	5 (2)
Dyspepsia	16 (6)	4 (1)
Asthenia	16 (6)	2 (<1)
Injection site erythema	17 (6)	0

Data Source: GSK Doc. # 2019N421511_00 Table 3.14

Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

In Study 201584, the number (%) of subjects who reported at least 1 AE remained at 274 (97%) for the CAB + RPV Q4W group in the cumulative Maintenance and Extension Phases (Data Source: GSK Doc. # 2019N421511_00 Table 3.9). At least 1 AE

was reported by 74% of the Extension-switch Q4W group (Data Source: GSK Doc. # 2019N421511_00 Table 3.10). Injection site pain and injection site induration were the only AEs reported by ≥5% of subjects.

In Study 201585, the frequency and type of common (≥5%), non-serious AEs were similar among CAB + RPV Q4W subjects in the Extension Phase compared with subjects randomized to CAB + RPV Q4W during the first 48 weeks (Table 22). The only difference in the CAB + RPV Q4W group between Maintenance and Maintenance + Extension Phase results was that 1 new subject had an AE of insomnia during the Extension Phase, so insomnia was considered a 'common' AE in the Maintenance + Extension Phase. The frequency and type of common, non-serious AEs in the Extension Switch to CAB + RPV Q4W group were consistent with AEs observed in the CAB + RPV Q4W group during Maintenance Phase; no new safety trends were observed during the Extension Phase. Overall, ISRs (predominantly injection site pain) accounted for the most commonly reported AEs.

Table 22 Summary of Subjects and Number of Common (At Least 5%) Non-serious AEs by System Organ Class for Maintenance (up to Week 52) + Extension (Post Week 52) Phases in Study 201585 at Week 96 (Safety and Extension Switch Populations)

System Organ Class Preferred Term	CAB + RPV Q4W Day 1 to Week 52 N=308 n (%)	CAR Day 1 to Week 52 N=308 n (%)	CAB + RPV Q4W Day 1 to Week 96 N=308 n (%)	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 N=174 n (%)
Any Event	**263 (85)**	**117 (38)**	**265 (86)**	**82 (47)**
General Disorders and Administration Site Conditions				
Injection Site Pain	231 (75)	0	231 (75)	78 (45)
Injection Site Nodule	37 (12)	0	38 (12)	2 (1)
Injection Site Induration	30 (10)	0	32 (10)	8 (5)
Fatigue	22 (7)	6 (2)	23 (7)	5 (3)
Injection Site Swelling	23 (7)	0	23 (7)	1 (<1)
Pyrexia	21 (7)	9 (3)	21 (7)	6 (3)
Infections and Infestations				
Nasopharyngitis	52 (17)	42 (14)	59 (19)	10 (6)
Upper Respiratory Tract Infection	32 (10)	25 (8)	36 (12)	2 (1)
Influenza	17 (6)	14 (5)	18 (6)	8 (5)
Respiratory Tract Infection Viral	11 (4)	17 (6)	14 (5)	4 (2)
Nervous System Disorders				
Headache	34 (11)	17 (6)	35 (11)	4 (2)
Gastrointestinal Disorders				
Diarrhea	22 (7)	15 (5)	24 (8)	6 (3)
Musculoskeletal and Connective Tissue Disorders				
Back Pain	20 (6)	10 (3)	22 (7)	2 (1)
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	16 (5)	14 (5)	18 (6)	4 (2)
Psychiatric Disorders				
Insomnia	15 (5)	4 (1)	16 (5)	0

GSK Doc. # 2019N399072_00 in-text Table 14.

Note: Common (≥5%) refers to incidence of event in either treatment group.

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.

Phase IIB Results

At the end of Study LAI116482, the most commonly (≥20% of subjects) reported AEs among subjects receiving CAB were upper respiratory tract infection (36%), diarrhea

(29%), nausea (26%), and headache (25%) (GSK Doc. # 2019N404586_00 Section 7.1.1).

In Study 200056, overall in the Maintenance and Extension Periods, injection site pain (97% of subjects) was the most commonly reported AE from Day 1 in the randomized IM dosing arms (GSK Doc. # 2018N380094_00 Section 7.1). Other commonly reported ISRs included injection site nodule (34% of subjects) and injection site swelling (31% of subjects). The most commonly reported non-ISR events included nasopharyngitis (38%), diarrhea (22%), and headache (22%) across both randomized IM dosing arms. During the Extension Period, injection site pain (84% of subjects) was the most commonly reported AE through 60 weeks of LA therapy in the optimized IM arms. Other commonly reported ISRs included injection site nodule (27% of subjects) and injection site swelling (16% of subjects). The most commonly reported non-injection site AEs included nasopharyngitis (14%), back pain (11%), and influenza (11%) across both optimized IM dosing arms.

2.1.1.2. Adverse Events by System Organ Class

Week 48 Phase III/IIIB Results

Overall, in the pooled analysis for Studies 201584 and 201585 aside from ISRs, more AEs were reported for several of the System Organ Classes in the CAB + RPV Q4W group compared with the CAR group, most notably in Infections and infestations (65% vs. 57%), Gastrointestinal disorders (31% vs. 20%), Musculoskeletal and connective tissue disorders (23% vs. 15%), Nervous system disorders (22% vs. 12%), Skin and subcutaneous tissue disorders (14% vs. 9%), Investigations (13% vs. 8%), and Psychiatric disorders (12% vs. 9%) (Data Source: ISS/ISE Table 3.12). Several differences in individual AE PTs reported within these System Organ Classes contributed to these results. The differences in individual AE terms was generally small, with very few terms occurring >1% more frequently in the CAB + RPV Q4W arm relative to CAR. The largest differences are shown below.

- For Infections and infestations, the largest differences in incidences of AEs of nasopharyngitis (CAB + RPV Q4W 108/591 [18%], CAR 90/591 [15%]) and upper respiratory tract infection (CAB + RPV Q4W 70/591 [12%], CAR 53/591 [9%]).
- For Gastrointestinal disorders, the largest differences in incidences of AEs occurred for diarrhea (CAB + RPV Q4W 54/591 [9%], CAR 40/591 [7%]) and nausea (CAB + RPV Q4W 30/591 [5%], CAR 16/591 [3%]).
- For Musculoskeletal and connective tissue disorders, the largest differences in incidences of AEs occurred for back pain (CAB + RPV Q4W 43/591 [7%], CAR 23/591 [4%]) and myalgia (CAB + RPV Q4W 24/591 [4%], CAR 8/591 [1%]).
- For Nervous system disorders, the largest differences in incidences of AEs occurred for headache (CAB + RPV Q4W 73/591 [12%], CAR 38/591 [6%]) and dizziness (CAB + RPV Q4W 24/591 [4%], CAR 8/591 [1%]).
- For Skin and subcutaneous tissue disorders, the largest differences in incidences of AEs occurred for rash (CAB + RPV Q4W 17/591 [3%], CAR 12/591 [2%]) and eczema (CAB + RPV Q4W 11/591 [2%], CAR 7/591 [1%]).

- For Investigations, the largest differences in incidences of AEs occurred for blood creatine phosphokinase increased (CAB + RPV Q4W 15/591 [3%], CAR 10/591 [2%]) and lipase increased (CAB + RPV Q4W 10/591 [2%], CAR 6/591 [1%]).
- For Psychiatric disorders, the largest differences in incidences of AEs occurred for anxiety (CAB + RPV Q4W 21/591 [4%], CAR 13/591 [2%]) and insomnia (CAB + RPV Q4W 22/591 [4%], CAR 8/591 [1%]).

The difference in number of subjects reporting events in other System Organ Classes between the treatment groups (e.g., respiratory disorders, reproductive system disorders, neoplasms, renal and urinary disorders, vascular disorders, ear and labyrinth disorders, immune system disorders, hepatobiliary disorders, and cardiac disorders) represented <1%.

In Study 207966, the top 3 System Organ Classes under which AEs were reported in either treatment group were General disorders and administration site conditions (Q8W: 78%; Q4W: 77%), Infections and infestations (Q8W: 53%; Q4W: 60%), and Gastrointestinal disorders (Q8W: 20%; Q4W: 26%) (Data Source: GSK Doc. # 2019N406358_01 Table 3.5). Among the System Organ Classes, there were no new trends observed among the individual PTs. The proportions of subjects with AEs coding to specific SOCs was similar between the 2 treatment groups with the exception of 3 System Organ Classes in which AEs were reported by ≥5% higher proportion of subjects in the Q4W group (Infections and infestations, Q8W: 53%; Q4W: 60%; Gastrointestinal disorders, Q8W: 20%; Q4W: 26%; and Injury, poisoning and procedural complications, Q8W: 10%; Q4W: 16%).

2.1.1.3. Adverse Events by Maximum Intensity

Week 48 Phase III/IIIB Results

Of subjects who reported at least 1 AE in Studies 201584 or 201585, few subjects reported an AE with a maximum intensity of Grade 3 or 4 (Table 23). The majority of subjects had an AE with a maximum intensity of Grade 1 or 2 in both treatment groups (Data Source: ISS/ISE Table 3.20). The proportions of subjects who reported AEs with a maximum intensity of Grade 3 or 4 were slightly higher for CAB + RPV Q4W compared with CAR; however, when excluding ISR AEs, the proportions of subjects who reported AEs with a maximum intensity of Grade 3 or 4 was similar between the treatment groups. This slight difference between treatment groups also may be partially attributable to the higher incidence of acute viral hepatitis, ISRs, and AEs of lipase abnormalities and CPK and AST elevations in the CAB + RPV Q4W group.

There was 1 fatal (Grade 5) AE; 1 subject in the CAR group died due to methamphetamine overdose. See Section 2.1.2 for more information.

Table 23 Summary of AEs That Were Grade 3 to 5 in Maximum Intensity in Studies 201584, 201585 and 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)
Any Grade 3-5 AE	**31 (11)**	**11 (4)**	**35 (11)**	**24 (8)**	**66 (11)**	**35 (6)**
Any Grade 3 AE	23 (8)	10 (4)	27 (9)	19 (6)	50 (8)	29 (5)
Any Grade 4 AE	8 (3)	1 (<1)	8 (3)	4 (1)	16 (3)	5 (<1)
Any Grade 5 AE	0	0	0	1 (<1)	0	1 (<1)
Any Grade 3-5 non-ISR AE	**19 (7)**	**11 (4)**	**25 (8)**	**24 (8)**	**44 (7)**	**35 (6)**

Data Source: ISS/ISE Table 3.06 and Table 3.20.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Of subjects who reported at least 1 AE in Study 207966, few subjects reported an AE with a maximum intensity of Grade 3 or 4 (Table 24). The proportions of subjects who reported AEs with a maximum intensity of Grade 3 or 4 was similar between treatment groups for all AEs, as well as for all non-ISR AEs.

There was 1 fatal (Grade 5) AE; 1 subject in the Q8W group died due to sepsis as a result of complications of acute pancreatitis. See Section 2.1.2 for more information.

Table 24 Summary of AEs That Were Grade 3 to 5 in Maximum Intensity in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	All AEs		All non-ISR AEs	
	CAB + RPV Q8W (N=522) N (%)	CAB + RPV Q4W (N=523) N (%)	CAB + RPV Q8W (N=522) N (%)	CAB + RPV Q4W (N=523) N (%)
Any Grade 3 AE	38 (7)	43 (8)	26 (5)	24 (5)
Any Grade 4 AE	2 (<1)	6 (1)	2 (<1)	6 (1)
Any Grade 5 AE	1 (<1)[a]	0	1 (<1)[a]	0

Data Source: GSK Doc. # 2019N406358_01 Table 3.6 and Table 3.7.
a. This subject also had Grade 4 AEs and is the first subject in the Q8W group in Table 28.

Grade 3 AEs

There were 7 non-ISR Grade 3 AEs in pooled Studies 201584 and 201585 that were reported by ≥2 subjects in either treatment group (Table 25). Lipase increased was the only PT reported by >2 subjects in either the CAB + RPV Q4W or CAR treatment group

and was the most frequently reported Grade 3 non-ISR AE (4 subjects in CAB + RPV Q4W group and 2 subjects in CAR group). Grade 3 blood CK increased and Grade 3 headache were each reported by 2 subjects in the CAB + RPV Q4W group and by no subjects in the CAR group.

Table 25 Non-ISR AEs With Maximum Grade 3 Reported by At Least 2 Subjects in Either Treatment Group in Studies 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)

	Pooled Studies 201584 and 201585	
	CAB + RPV Q4W	CAR
System Organ Class PT Reported by ≥2 Subjects	Grade 3 n (%)	Grade 3 n (%)
Infections and Infestations		
Anal abscess	0	2 (<1)
Gastrointestinal Disorders		
Colitis	1 (<1)	2 (<1)
Nervous System Disorders		
Headache	2 (<1)	0
Investigations		
Blood creatine phosphokinase increased	2 (<1)	0
Lipase increased	4 (<1)	2 (<1)
Blood glucose increased	0	2 (<1)
Metabolism and Nutrition Disorders		
Hypertriglyceridemia	0	2 (<1)

Data Source: ISS/ISE Table 3.20.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, of the 26 subjects in the Q8W group and the 24 subjects in the Q4W group who reported a non-ISR AE with a maximum intensity of Grade 3 (Table 24), there were seven Grade 3 AEs reported by at least 2 of these subjects in either treatment group (Table 26).

Table 26 Non-ISR AEs That Were Grade 3 in Maximum Intensity and Reported by At Least 2 Subjects in Either Treatment Group in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

PT Reported by ≥2 Subjects	CAB + RPV Q8W N=522 n (%)	CAB + RPV Q4W N=523 n (%)
Appendicitis	2 (<1)	0
Intervertebral disc protrusion	2 (<1)	0
Low density lipoprotein increased	2 (<1)	0
Hyperglycemia	2 (<1)	0
Acute hepatitis C	0	2 (<1)
Myalgia	0	2 (<1)
Aspartate aminotransferase increased	0	2 (<1)

Data Source: GSK Doc. # 2019N406358_01 Table 3.7.

There were no Grade 3 non-ISR AEs reported by ≥2 subjects that occurred in both the pooled studies and in Study 207966 (Table 25 and Table 26).

Grade 4 AEs

There were 18 non-ISR Grade 4 AEs in pooled Studies 201584 and 201585 (Table 27). Two of these 18 PTs (hepatis A and lipase increased) were reported in both the CAB + RPV Q4W and CAR groups. Three of these 18 PTs (hepatitis A, blood creatine phosphokinase increased, and lipase increased) were reported by >1 subject overall.

Table 27 Non-ISR AEs With Maximum Intensity of Grade 4 in Studies 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)

	Pooled Studies 201584 and 201585	
	CAB + RPV Q4W	CAR
System Organ Class Preferred Term	**Grade 4 n (%)**	**Grade 4 n (%)**
Infections and Infestations		
Hepatitis A	2 (<1)	1 (<1)
Acute hepatitis C	1 (<1)	0
Pyelonephritis acute	1 (<1)	0
Gastrointestinal Disorders		
Large intestine perforation	0	1 (<1)
Rectal fissure	0	1 (<1)
Investigations		
Blood creatine phosphokinase increased	3 (<1)	0
Lipase increased	3 (<1)	1 (<1)
Aspartate aminotransferase increased	1 (<1)	0
Transaminases increased	1 (<1)	0
Blood bilirubin increased	1 (<1)	0
Weight decreased	1 (<1)	0
Injury, Poisoning, and Procedural Complications		
Laceration	1 (<1)	0
Road traffic accident	0	1 <1)
Diabetic ketoacidosis	1 (<1)	0
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)		
Squamous cell carcinoma	0	1 (<1)
Blood and Lymphatic System Disorders		
Neutropenia	0	1 (<1)
Renal and Urinary Disorders		
Hyperbilirubinemia	1 (<1)	0
Hepatobiliary Disorders		
Hepatocellular injury	1 (<1)	0

Data Source: ISS/ISE Table 3.20.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, 11 Grade 4 AEs were reported for 3 subjects in the Q8W group, and seven Grade 4 AEs were reported for 6 subjects in the Q4W group (Data Source: GSK Doc. # 2019N406358_01 Table 3.6); reports by subject are presented in Table 28. There were no apparent patterns with regards to types of Grade 4 AEs. Two subjects had Grade 4 CPK elevations associated with AST and/or ALT elevations (Data Source: GSK Doc. # 2019N406358_01 Listing 19). Neither subject had concurrent myalgia or any other AE possibly indicative of rhabdomyolysis.

Table 28 Non-ISR AEs That Were Grade 4 in Maximum Intensity in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

Placeholder ID Number	Grade 4 AE(s) Reported for Each Subject
CAB + RPV Q8W	
Subject [redacted] of [redacted][a]	pancreatitis acute, cardio-respiratory arrest, urinary tract infection, septic shock, pulmonary embolism, deep vein thrombosis, acute kidney injury, and disseminated intravascular coagulation
Subject [redacted] of [redacted]	epiglottitis obstructive, overdose[b]
Subject [redacted] of [redacted]	diffuse large B-cell lymphoma
CAB + RPV Q4W	
Subject [redacted] of [redacted]	acute hepatitis B
Subject [redacted] of [redacted]	blood creatinine phosphokinase increased
Subject [redacted] of [redacted]	blood creatinine phosphokinase increased
Subject [redacted] of [redacted]	glioblastoma
Subject [redacted] of [redacted]	arteriosclerosis coronary artery, coronary artery stenosis
Subject [redacted] of [redacted]	neutropenia

Data Source: GSK Doc. # 2019N406358_01 Table 3.7, Listing 13, and Listing 19.
Note: Each row represents 1 subject.
a. Subject had a maximum AE of Grade 5; see Section 2.1.2, Subject also had Grade 4 AEs as listed in this table. The subject having a maximum AE of Grade 5 means that source Table 3.7 shows only 2 subjects with maximum AEs of Grade 4 in this group.
b. Verbatim text was "[redacted]."

Blood creatine phosphokinase increased was the only Grade 4 non-ISR AE reported in both pooled Studies 201584 and 201585 and in Study 207966 among subjects treated with CAB + RPV(Table 27 and Table 28). Grade 4 neutropenia was reported in the CAR group in pooled Studies 201584 and 201585 and in the CAB + RPV Q4W group in Study 207966.

Longer-term Phase III Results

At the end of the MP in Study 201584, the majority of subjects in both treatment groups reported AEs with a maximum intensity of Grade 1 or 2 (GSK Doc. #2019N421511_00 Section 7.2.3). There were no Grade 5 AEs. The overall incidence of subjects reporting Grade 3 or 4 AEs was low, but Grade 3 AEs occurred at a higher incidence in the CAB + RPV Q4W group compared with the CAR group (11% of CAB + RPV Q4W subjects and 4% of CAR subjects). Grade 4 AEs occurred at a similar incidence in both treatment groups (3% of CAB + RPV Q4W subjects and 2% of CAR subjects).

In Study 201584, non-ISR Grade 3 and 4 AEs occurred in 7% and 3% of CAB + RPV Q4W subjects and 4% and 2% of CAR subjects, respectively.

In Study 201584, no individual non-ISR AE term for the Grade 3 or 4 events involved more than 1 subject with the exceptions of hepatitis A (Grade 4: 2 [<1%] subjects), blood creatine phosphokinase (Grade 3: 2 (<1%) subjects; Grade 4: 3 [1%] subjects) and lipase increased (Grade 3: 3 [1%] subjects; Grade 4: 1 [<1%] subject) in the CAB + RPV Q4W

group, and lipase increased (Grade 4: 2 [<1%] subjects) in the CAR group. Of these Grade 3 or 4 AEs in the CAB + RPV Q4W group, 2 blood creatine phosphokinase AEs (Grade 3: 1; Grade 4: 1) and 2 lipase increased AEs (Grade 3: 2) occurred since the Week 48 analysis.

In the Maintenance + Extension Phase for Study 201585, the majority of subjects continued to have AEs with a maximum intensity of Grade 1 or 2 for the CAB + RPV Q4W group (Data Source: GSK Doc. # 2019N399072_00 Table 13.5). Since the Week 48 analysis (Data Source: 2018N370336_00 Table 3.8), 2 additional subjects reported an AE with a maximum intensity of Grade 3 (acute hepatitis B and hypophosphatemia), and no additional subjects reported an AE with a maximum intensity of Grade 4.

In the Extension Switch to CAB + RPV Q4W Population in Study 201585, the majority of subjects who switched from CAR to CAB + RPV Q4W reported AEs with a maximum intensity of Grade 1 or 2 (Data Source: GSK Doc. # 2019N399072_00 Table 13.6). Including all AEs, 3% of subjects had a Grade 3 AE and 1% of subjects had a Grade 4 AE. The only Grade 3 AE reported by >1 subject was injection site pain (3 subjects). The only Grade 4 AE reported was lipase increased, which was reported for 2 subjects.

Phase IIB Results

At the end of Study LAI116482, the majority of subjects reported AEs that were considered Grade 1 or Grade 2 in maximum intensity (Table 29). AEs with a maximum intensity of Grade 3 that were reported by >1 subject in the CAB + RPV groups combined included blood CK increased (n=4), cellulitis (n=3), chest pain (n=3), colitis (n=2), depression (n=2), and systemic inflammatory response syndrome (n=2). AEs with a maximum intensity of Grade 4 that were reported by >1 subject in the CAB + RPV groups combined were appendicitis (n=2).

Table 29 Summary of AEs in Study LAI116482 at End of Study by Maximum Intensity (Safety Maintenance Population)

Maximum Grade	CAB 10 mg+ RPV N=52 n (%)	CAB 30 mg + RPV N=53 n (%)	CAB 60 mg + RPV N=55 n (%)	EFV 600 mg + 2 NRTIs N=47 n (%)
Grade 1	12 (23)	8 (15)	13 (24)	19 (40)
Grade 2	22 (42)	31 (58)	25 (45)	13 (28)
Grade 3	9 (17)	10 (19)	14 (25)	2 (4)
Grade 4	3 (6)	4 (8)	1 (2)	1 (2)

Data Source: GSK Doc. # 2019N404586_00 Table 8.122.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

In Study 200056 overall, the majority of subjects reported AEs were considered Grade 2 or Grade 3 in maximum intensity (Table 30).

Table 30 Summary of AEs in Maintenance and Extension Phases in Study 200056 at Week 160 by Maximum Intensity (Safety Maintenance Population)

Maximum Grade Safety Maintenance Population	CAB + RPV Q8W IM N=115 n (%)	CAB + RPV Q4W IM N=115 n (%)	CAB + RPV IM Total N=230 n (%)
Maintenance and Extension Period Total	**115 (100)**	**115 (100)**	**230 (100)**
Grade 1	17 (15)	16 (14)	33 (14)
Grade 2	67 (58)	69 (60)	136 (59)
Grade 3	26 (23)	24 (21)	50 (22)
Grade 4	5 (4)	6 (5)	11 (5)

Data Source: GSK Doc. # 2018N380094_00 in-text Table 24.

In the optimized IM arms, the majority of subjects reported AEs that were considered Grade 1 or Grade 2 in maximum intensity and were driven primarily by ISRs (Table 31). There was only 1 maximum Grade 4 AE (optimized Q4W, lipase increase).

Table 31 Summary of AEs in Maintenance and Extension Phases in Study 200056 at Week 160 by Maximum Intensity (Extension Switch Population)

Maximum Grade Safety Maintenance Population	CAB + RPV Optimized Q8W IM N=34 n (%)	CAB + RPV Optimized Q4W IM N=10 n (%)	CAB + RPV Optimized IM Total N=44 n (%)
Extension Period Total	**34 (100)**	**9 (90)**	**43 (98)**
Grade 1	9 (26)	2 (20)	11 (25)
Grade 2	21 (62)	5 (50)	26 (59)
Grade 3	4 (12)	1 (10)	5 (11)
Grade 4	0	1 (10)	1 (2)

Data Source: GSK Doc. # 2018N380094_00 in-text Table 25.

2.1.1.4. Drug-related Adverse Events

Whether an event was considered drug related (reasonable possibility yes/no) is based on the investigator assessment.

Week 48 Phase III/IIIB Results

In pooled Studies 201584 and 201585, for non-ISR AEs, no individual terms for AEs considered to be drug related were reported for >10 subjects per group with the exceptions of headache (CAB + RPV Q4W: 25 subjects, 4%; CAR: 4 subjects, <1%),

pyrexia (CAB + RPV Q4W: 25 subjects, 4%; CAR: 0 subjects), nausea (CAB + RPV Q4W: 15 subjects, 3%; CAR: 6 subjects, 1%), fatigue (CAB + RPV Q4W: 15 subjects, 3%; CAR: 5 subjects, <1%), asthenia (CAB + RPV Q4W: 13 subjects, 2%; CAR: 0 subjects), and body temperature increased (CAB + RPV Q4W: 12 subjects, 2%; CAR: 0 subjects) (Data Source: ISS/ISE Table 3.26).

The overall proportions of subjects reporting at least one Grade 3 to 5 non-ISR AE considered to be drug related were low in both treatment groups (Table 32).

Table 32 Summary of AEs That Were Grade 3 to 5 in Maximum Intensity and Considered to be Drug Related in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

	All drug-related AEs		All drug-related non-ISR AEs[1]	
	CAB + RPV Q4W N (%)	CAR N (%)	CAB + RPV Q4W N (%)	CAR N (%)
201584	**(N=283)**	**(N=283)**	**(N=283)**	**(N=283)**
Any Grade 3 to 5 AE	14 (5)	0	4 (1)	0
Any Grade 3 AE	13 (5)	0	3 (1)[2]	0
Any Grade 4 AE	1 (<1)	0	1 (<1)[2]	0
Any Grade 5 AE	0	0	0	0
201585	**(N=308)**	**(N=308)**	**(N=308)**	**(N=308)**
Any Grade 3 to 5 AE	14 (5)	1 (<1)	4 (1)	1 (<1)
Any Grade 3 AE	13 (4)	1 (<1)	3 (1)[2]	1 (<1)
Any Grade 4 AE	1 (<1)	0	1 (<1)[2]	0
Any Grade 5 AE	0	0	0	0
Pooled 201584+201585	**(N=591)**	**(N=591)**	**(N=591)**	**(N=591)**
Any Grade 3 to 5 AE	28 (5)	1 (<1)	8 (1)	1 (<1)
Any Grade 3 AE	26 (4)	1 (<1)	6 (1)	1 (<1)
Any Grade 4 AE	2 (<1)	0	2 (<1)	0
Any Grade 5 AE	0	0	0	0

Data Source: ISS/ISE Table 3.06 and ISS/ISE Table 3.27.

1. Only the overall line (Any Grade 3 to 5 AE) was summarized for non-ISR AEs for these studies. Therefore, results for each grade level for non-ISR AEs for CAB + RPV were inferred based on that line of data plus data from ISS/ISE Table 3.27. All AEs from the CAR groups are non-ISR AEs.
2. Lipase increased was the only drug-related Grade 4 AE and is a non-ISR AE. Therefore, there must be 3 subjects with non-ISR Grade 3 AEs to make the total line (Any Grade 3 to 5 AE) from Table 3.06.

In Study 207966, for non-ISR AEs, no individual terms for AEs considered to be drug related were reported for >10 subjects per treatment group with the exceptions of pyrexia (Q8W: 19 subjects, 4%; Q4W: 25 subjects, 5%), asthenia (Q8W: 12 subjects, 2%; Q4W: 6 subjects, 1%), fatigue (Q8W: 7 subjects, 1%; Q4W: 19 subjects, 4%), nausea (Q8W: 5 subjects, <1%; Q4W: 12 subjects, 2%), and headache (Q8W: 10 subjects, 2%; Q4W: 11 subjects, 2%) (Data Source: GSK Doc. # 2019N406358_01 Table 3.14).

The overall proportions of subjects reporting at least one Grade 3 to 5 AE considered to be drug related, both for all AEs as well as non-ISR AEs, were similar between treatment groups (Table 33).

Table 33 Summary of AEs That Were Grade 3 to 5 in Maximum Intensity and Considered to be Drug Related in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

	All drug-related AEs		All drug-related non-ISR AEs	
	CAB + RPV Q8W (N=522) N (%)	CAB + RPV Q4W (N=523) N (%)	CAB + RPV Q8W (N=522) N (%)	CAB + RPV Q4W (N=523) N (%)
Any Grade 3 AE	15 (3)	25 (5)	3 (<1)	4 (<1)
Any Grade 4 AE	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Any Grade 5 AE	0	0	0	0

Data Source: GSK Doc. # 2019N406358_01 Table 3.13 and Table 3.14.

One Grade 4 SAE (pancreatitis acute) considered to be drug related by the investigator was reported for 1 subject in the Q8W group (see Section 2.1.2), and one Grade 4, nonserious AE considered to be drug related (blood creatine phosphokinase increased) was reported for 1 subject in the Q4W group (see GSK Doc. # 2019N406358_01 Section 7.1.5.3.9) (Data Source: GSK Doc. # 2019N406358_01 Table 3.14).

Patterns noted for Grade 3 drug-related AEs included ISRs (mostly injection site pain; Section 2.1.6.1) and post-injection reactions (Section 2.1.7).

Longer-term Phase III Results

At the end of the MP in Study 201584, the incidence of subjects with drug-related AEs was higher in the CAB + RPV Q4W group (87%) compared with the CAR group (12%) (GSK Doc # 2019N421511_00 Section 7.2.2). This difference was largely attributable to the incidence of ISRs in the CAB + RPV Q4W group. The most frequently reported non-ISR drug-related AEs were pyrexia (6%), headache (5%), asthenia (3%), and body temperature increased (3%) in the CAB + RPV Q4W group and headache (1%), fatigue (2%), and nausea (2%) in the CAR group. The majority of non-ISR drug-related AEs in the CAB + RPV Q4W group were Grade 1 or 2, and no new Grade 3 or 4 non-ISR drug-related AEs were reported since the Week 48 analysis.

In Study 201585, no new subjects in the CAB + RPV Q4W group had drug-related AEs during the Extension Phase (Data Source: GSK Doc. # 2019N399072_00 Table 13.8); therefore, the number of subjects with drug-related AEs for Maintenance + Extension Phase are the same as those reported for the Maintenance Phase. The most frequently reported non-ISR, drug-related AEs for the CAB + RPV Q4W group during the Maintenance + Extension Phase were fatigue (4%), pyrexia (4%), nausea (4%), and headache (4%).

In the Extension Switch to CAB + RPV Q4W Population in Study 201585, the most frequently reported non-ISR, drug-related AEs were pyrexia (3%) and diarrhea (2%) (Data Source: GSK Doc. # 2019N399072_00 Table 13.9). All other non-ISR, drug-related AEs were reported at ≤1%. Non-ISR, drug-related AEs in the Extension Switch to CAB + RPV Q4W group were all Grade 1 or Grade 2 except for one Grade 4 AE of lipase increased. No Grade 3 or Grade 5 non-ISR, drug-related AEs were reported.

Phase IIB Results

At EOS in Study LAI116482, at least 1 AE considered related to study medication was reported by 52% of CAB + RPV subjects (GSK Doc. # 2019N404586_00 Section 7.2.1). The AEs considered related to study medication and reported by ≥10% of subjects were nausea (17%), headache (15%), and diarrhea (10%).

In Study 200056 during the Maintenance and Extension Periods, injection site pain (97%) was the most commonly reported drug-related AE in the randomized IM arms (GSK Doc. # 2018N380094_00 Section 7.2). Other commonly reported ISRs included injection site nodule (33%) and injection site swelling (31%). The most commonly reported non-ISR drug-related (per investigator) AEs included pyrexia (5%), headache (3%), fatigue (3%), and influenza like illness (3%) across both IM dosing arms. There were no clear differences in incidence of drug-related AEs suggesting a regimen-specific trend. In the Extension Period, injection site pain (84%) was the most commonly reported drug-related AE in the optimized IM arms. Other commonly reported ISRs included injection site nodule (27%) and injection site swelling (16%). The most commonly reported drug-related (per investigator) AEs, excluding ISRs, included asthenia, fatigue, musculoskeletal stiffness, and palpitations, each occurring as isolated events only. The sample size and numbers of events was insufficient to allow any comparison of the relative frequency of drug-related AEs in the Extension Switch Population.

2.1.1.5. Analysis of Common AEs for Pooled Studies 201584 and 201585 (Week 48 Analysis)

For pooled Studies 201584 and 201585, statistical comparisons were conducted to evaluate potential associations of CAB + RPV Q4W treatment with the incidence of common AEs (≥5%) (Data Source: ISS/ISE Table 3.155), according to the methodology described in the SDAP. A statistical association was identified for ISRs, pyrexia, hemorrhoids, headache, dizziness, fatigue, and back pain. An analysis of common non-ISR AEs and relative risk for CAB + RPV Q4W vs. CAR presented in Figure 1 appears to indicate a similar trend of statistical association for pyrexia, hemorrhoids, headache, dizziness, fatigue, and back pain, and nausea.

Partially due to ISRs, there were a statistically significant greater number of AEs for the System Organ Class of General disorders and administration site conditions in the CAB + RPV Q4W group compared with the CAR group ($p<0.001$) (Data Source: ISS/ISE Table 3.155). Details of ISRs are presented in Section 2.1.6.1.

Other System Organ Classes that were represented by a statistically significant greater number of AEs in the CAB + RPV Q4W group compared with the CAR group were Nervous system disorders ($p=0.002$), GI disorders ($p=0.009$), and Musculoskeletal and connective tissue disorders ($p=0.027$) (Data Source: ISS/ISE Table 3.155). There were no System Organ Classes with a statistically significant higher number of AEs in the CAR group. Statistical comparisons were performed only for the common (≥5% in either treatment group) AEs.

2.1.2. Deaths

A total of 10 deaths (9 in the Safety Population) have been reported in Studies 201584, 201585, 207966, LAI116482, and 200056 (see Appendix Table). All were considered by the investigators to be unrelated to study drug with the exception of a case of fatal myocardial infarction (Study 200056) for which the investigator could not rule out the possibility of relationship to study drug. A subject in the Q8W group in Study 207966 died due to sepsis, a complication of acute pancreatitis. Acute pancreatitis was considered related to study drug by the investigator.

Study 201584

- Subject was a 30- to 40-year-old male in the CAR group who died due to a reported homicide during the Induction Phase (GSK Document # 2017N345267_00 Section 16). The event was reported as a '[redacted]' and not considered related to study treatment.

Study 201585

- Subject was a 40- to 50-year old female in the CAR group who died due to a methamphetamine overdose during the Maintenance Phase (GSK Doc. # 2018N370336_00 Section 15). This event was not considered related to study drug by the investigator.

Study 207966 (GSK Doc. # 2019N406358_01 Section 13)

- Subject was a 40- to 50-year-old male who was randomized to the Q8W group. The subject had previously participated in Study 201585 and had received CAB + RPV LA for 17 months prior to the SAE. The subject presented with an SAE of severe acute pancreatitis 2 weeks after the Week 16 visit in Study 207966. The subject was hospitalized and subsequently experienced cardiopulmonary arrest 2 days after admission. The subject required a prolonged hospital admission over 14 weeks during which over 2 weeks were spent in the ICU. During this time period, the subject experienced multiple serious complications that were also reported as SAEs and culminated in death from sepsis. Death occurred 522 days after the first dose of CAB + RPV and 98 days after the last dose of study medication. The subject had a history of post-endoscopic retrograde cholangiopancreatography pancreatitis, gallstones, and biliary sludge 13 years prior. This subject also had a history of hyperlipidemia that was being treated with rosuvastatin, which is rarely associated with pancreatitis as an ADR. The investigator considered the pancreatitis possibly related to study drugs as it was not possible to exclude a causative association. Based upon the long latency period and these possible confounders, the Sponsor does not believe the evidence supports the study medication being causative in this instance.
- Subject was a 30- to 40-year-old male. The subject was screened de novo for Study 207966 but did not receive a dose of study drug and therefore was not included in the Safety Population. The cause of death was a hemorrhage from a cerebral aneurysm.

Study 200056

- Subject was a 30- to 40-year-old in the oral CAB group who died due to a road traffic accident that occurred during the Induction Phase of the study (GSK Document # 2015N246053_00 Section 13). The event was not considered related to study treatment.
- Subject was a 40- to 50-year-old male in the CAB + RPV group who died due to myocardial infarction (GSK Document # 2018N380094_00 Section 12) after approximately 3 years of CAB + RPV exposure. The subject was found dead. The subject was a non-smoker with no history of drug use. The subject had cardiovascular risk factors of a BMI of 40 kg/m^2, adipositas (obesity), and hypertension. Otherwise, there was no history of heart failure or use of heart medication. An autopsy was performed but the complete results have not been made available to the study. It was reported in the autopsy that there were signs of chronic heart failure. In spite of potential confounders, the investigator could not exclude that this may have been caused by study drug.
- Subject was a 30- to 40-year-old male in the CAB + RPV group who died due to acute onset refractory epilepsy (GSK Document Number 2018N380094_00 Section 12). The event occurred 48 weeks following initial CAB administration and 32 weeks following initial RPV administration. The subject developed acute onset status epilepticus lasting for approximately 6 hours while alone in his apartment, leading to anoxic brain injury and death. The cause of death was brain death following cerebral edema secondary to refractory epilepsy. An autopsy was not conducted at the family's request. Social history and papaverine detected on urine spectroscopy suggested recreational drug use. The subject had no known prior history of seizure disorder. The event was not considered related to study treatment.
- An additional death was reported after the data cutoff date. Subject was a 50- to 60-year-old female who died due to toxicity to various agents (cocaine). The subject had been in the study for over 4 years and was receiving Q4W CAB + RPV at the time of death. The subject had a medical history of diabetes and mild dyslipidemia (elevated total and LDL cholesterol, normal triglycerides). The subject was found dead at home in bed. An autopsy was performed, and the cause of death was reported as cocaine toxicity with atherosclerotic heart disease as a contributory cause. The manner of death was classified as accidental. The event was not considered related to study treatment.

Study LAI116482 (GSK Doc. # 2019N404586_00 Section 12)

- Subject was a 50- to 60-year old male in the CAB 30 mg + RPV group who died due to gastrointestinal hemorrhage per the autopsy report (initial cause of death was unknown). The subject had a medical history of peptic ulcer disease and prior tobacco use. The subject had been in the study for over 3 years and was found dead at home. The event was not considered related to study treatment.
- Subject was a 40- to 50-year old male in the CAB 60 mg + RPV group who died after a cardiac arrest while undergoing elective shoulder repair. The subject had been in the study for over 3 years. While under anesthesia for elective shoulder repair, the subject had cardiac arrest, was asystolic for 35 minutes, and was

successfully resuscitated. An EEG 2 days later showed no brainwave activity. The subject was removed from life support per the family's wishes. The event was not considered related to study treatment.

2.1.3. Other Serious Adverse Events

2.1.3.1. Week 48 Phase III/IIIB Results

During the MP (Week 48 analysis) in pooled Studies 201584 and 201585, 31 subjects in the CAB + RPV Q4W group had a total of 37 SAEs and 26 subjects in the CAR group had a total of 33 SAEs (ISS/ISE Table 3.33). The incidence of subjects developing at least 1 SAE was low and similar between treatment groups (CAB + RPV Q4W 5%; CAR 4%). The most frequently reported SAEs were hepatitis A (reported in 4 subjects in the CAB + RPV Q4W group and 2 subjects in the CAR group), colitis (reported in 1 subject in the CAB + RPV Q4W group and 2 subjects in the CAR group), anal abscess (reported in 0 subjects in the CAB + RPV Q4W group and 2 subjects in the CAR group), and anogenital warts (reported in 1 subject in the CAB + RPV Q4W group and 2 subjects in the CAR group). Other SAEs were reported in ≤1 subject per treatment group. Drug-related SAEs are summarized in Section 2.1.4.

During the CAB + RPV OLI period of the MP in pooled Studies 201584 and 201585, 4 subjects had SAEs (1 SAE per subject) (Data Source: ISS/ISE Table 3.34). These SAEs during OLI were enterocolitis, pyrexia, hepatitis A, and abortion missed (nonviable pregnancy was terminated). The SAE of pyrexia was considered a Jarisch-Herxheimer reaction secondary to treatment of syphilis with IM penicillin G, which required hospitalization. None of these SAEs were considered to be drug related.

During the MP (Week 48 analysis) in Study 207966, the frequency of subjects reporting at least 1 SAE was similar in the 2 treatment groups (Q8W: 5%; Q4W: 4%) (Data Source: GSK Doc. # 2019N406358_01 Table 3.26). No patterns of clinical concern for non-fatal SAEs were noted; individual non-fatal SAEs occurred across diverse System Organ Classes and PTs for both treatment groups. In the Q8W group, 44 SAEs were reported for 27 subjects (13 of the 44 SAEs were reported for 1 subject with acute pancreatitis who died due to sepsis; see Section 2.1.2) (Data Source: GSK Doc. # 2019N406358_01 Table 3.26 and Listing 16), and in the Q4W group, 22 SAEs were reported for 19 subjects. Three SAEs were reported in more than 1 subject in either treatment group: pneumonia (Q8W: 2 subjects; Q4W: 2 subjects), appendicitis (Q8W: 2 subjects; Q4W: 0 subjects), and hemorrhoids (Q8W: 2 subjects; Q4W: 0 subjects) (Data Source: GSK Doc. # 2019N406358_01 Table 3.16). There were also subjects who had an SAE considered to be a post-injection reaction (Section 2.1.7). Otherwise, all SAEs were reported for single subjects in 1 or both treatment groups (ie, ≤2 subjects overall). There was 1 ISR SAE (injection site abscess) in a subject randomized to the Q8W group (Section 2.1.6.1).

During the CAB + RPV OLI period of the MP in Study 207966, 1 subject (<1%) in the Q8W group had 1 SAE (intervertebral disc protrusion) and 4 subjects (1%) in the Q4W group had SAEs (pneumonia, sialoadenitis, sinusitis, and abortion spontaneous) (Data Source: GSK Doc. # 2019N406358_01 Table 3.18).

Full narratives for SAEs are presented in GSK Doc. # 2017N345267_00 Section 17, GSK Doc. # 2018N370336_00 Section 15 (Case Narratives), and GSK Doc. # 2019N406358_01 Section 13.

2.1.3.2. Longer-term Phase III Results

At the end of the MP in Study 201584, the incidence of non-fatal SAEs was similar in the 2 treatment groups (8% in both the CAB + RPV Q4W [n=24] and the CAR [n=22] groups; GSK Doc. # 2019N421511_00 Section 7.3.2). No patterns of clinical concern for nonfatal SAEs were noted as individual nonfatal SAEs occurred across diverse System Organ Classes and PTs for both treatment groups. Hepatitis A, anogenital warts (both CAB + RPV Q4W), and anal abscess (CAR) were the only nonfatal SAEs occurring in more than 1 subject.

In Study 201584, the cumulative rate for SAEs in the CAB + RPV Q4W group was 11% (n=31) during the Maintenance + Extension Phases (Data Source: GSK Doc. # 2019N421511_00 Section 7.8.3 and Table 3.22). Therefore, 7 additional subjects in the CAB + RPV Q4W group had at least 1 SAE during the Extension Phase and 1 subject who had an SAE in the MP also had an SAE in the Extension Phase: headache, hypoesthesia, and paresthesia in 1 subject; pyrexia in 1 subject (also had infectious mononucleosis in MP); rib fracture in 1 subject; herpes zoster in 1 subject; intervertebral disc protrusion in 1 subject; anorectal disorder in 1 subject; dysfunctional uterine bleeding in 1 subject; and depression in 1 subject) (Data Source: GSK Doc. # 2019N421511_00 Section 7.8.3 and Listing 19).

In Study 201584, in the Extension-switch Q4W group, 5 subjects reported at least 1 SAE; the PTs were colitis, hiatus hernia, herpes simplex, Parkinson's disease, and Hodgkin's disease mixed cellularity stage unspecified (Data Source: GSK Doc. # 2019N421511_00 Table 3.2.3).

In Study 201585, the frequency of SAEs was similar in the CAB + RPV Q4W group during the Extension Phase compared with those observed during the Maintenance Phase. No patterns of clinical concern for SAEs were noted as individual SAEs were reported across diverse System Organ Classes and PTs for both treatment groups.

During the Extension Phase in Study 201585, 2 SAEs were reported in the CAB + RPV Q4W group; neither were fatal nor drug-related (Data Source: GSK Doc. # 2019N399072_00 Table 13.10, Listing 107, Listing 147).

- Subject had Grade 3 acute hepatitis B and met protocol-defined LSC at the Week 80 visit. The subject had liver enzyme results that were Grade 3 and 4 intensity (ALT=1500 U/L, AST = 770 U/L, total bilirubin = 0.5 mg/dL). The SAE was considered not related to study drug. The study drug was discontinued due to the SAE.
- Subject had Grade 3 hypertension for which he was hospitalized. The subject was receiving medication for hypertension during the study. The SAE was considered not related to study drug and no change was made to the study drug regimen. The hypertension resolved after 26 days.

In the Extension Switch to CAB + RPV Q4W group in Study 201585, 2 subjects had SAEs; neither were fatal, nor drug related (Data Source: GSK Doc. # 2019N399072_00 Table 13.11, Listing 107).

- Subject had a Grade 3 femur fracture due to a fall while riding a bicycle, for which he was hospitalized. The SAE was considered not related to study drug and no change was made to the study drug regimen. The femur fracture resolved after 45 days.
- Subject had a Grade 2 hemorrhagic stroke during the MP and was subsequently hospitalized. The SAE resolved after 11 days when the subject was discharged from the hospital. The next day, the subject had the Week 52 visit and started oral CAB + RPV in the Extension Phase. 12 days later, the subject had another Grade 2 hemorrhagic stroke and was hospitalized; this stroke resolved after 3 days. Neither SAE was considered to be related to study drug and no change was made to the study drug regimen for either incident.

Case narratives for 3 subjects are provided in GSK Doc. # 2019N399072_00. The 4th narrative for the subject with hemorrhagic stroke in the Extension Switch to CAB + RPV Q4W group was provided in GSK Doc. # 2018N370336_00 because one of the hemorrhagic strokes was reported at the end of the MP and follow up information included the second SAE that was reported after Week 52.

2.1.3.3. Phase IIB Results

At EOS in Study LAI116482, 36 (20%) CAB +RPV subjects and 4 (6%) EFV subjects had reported a SAE (Data Source: GSK Doc. # 2019N404586_00 Table 8.13). SAEs reported by >1 subject in the CAB +RPV groups combined were cellulitis (n=4); appendicitis, pneumonia, and suicide attempt (n=3 each); shigella infection, major depression, suicidal ideation, colitis, and systemic inflammatory response syndrome (n=2 each).

Through 160 weeks of treatment, 38 (17%) subjects reported a SAE in Study 200056. (GSK Doc. # 2018N380094_00 Section 7.3). SAEs reported by >1 subject were suicide attempt (3 subjects), anogenital warts, cardiogenic shock (sequelae of other SAEs; suicide attempt in 1 subject and urosepsis in 1 subject), headache, hypertension, intervertebral disc protrusion, overdose, umbilical hernia, and viral infection (2 subjects each).

2.1.4. Drug-Related Serious Adverse Events

2.1.4.1. Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, 2 SAEs that were considered study drug-related were reported at the Week 48 analysis. 1 subject in the CAB + RPV Q4W treatment group had an SAE of right knee mono-arthritis (Study 201584), and 1 subject in the CAR treatment group had an SAE of suicidal ideation (Study 201585) (Data Source: ISS/ISE Table 3.33).

- A subject in the CAB + RPV Q4W group in Study 201584 had an SAE of right knee monoarthritis. A 50- to 60-year-old male on CAB + RPV Q4W with no history of arthritis presented with acute pain and swelling of the right knee with no other joints involved and no pyrexia. Joint aspirations were found to have a leukocytosis, but cultures were sterile. There was an absence of microcrystals and autoimmune screen was negative. The patient was treated with antibiotics, colchicine and infiltration of the right knee with betamethasone. CAB + RPV Q4W was continued and the event resolved after 102 days. The investigator could not exclude a causal relationship with CAB + RPV Q4W.
- A subject in the CAR group in Study 201585 had an SAE of suicidal ideation. A 50-to-60-year-old male with no history of suicidal ideation presented himself to a psychiatric hospital and was admitted with suicidal ideation. The investigator considered the event of suicidal ideation as possibly related to treatment with efavirenz + emtricitabine + tenofovir disoproxil fumarate, based on prescribing information for efavirenz. The subject was withdrawn from study and current ART was changed. The event of suicidal ideation resolved after 3 days from onset.

In Study 207966, 3 subjects (<1%) in the Q8W group had 3 SAEs considered to be drug related, and 1 subject (<1%) in the Q4W group had 1 SAE considered to be drug related (Data Source: GSK Doc. # 2019N406358_01 Table 3.19). SAEs considered to be drug related were pancreatitis acute (Section 2.1.2 and Section 2.1.6.10), injection site abscess (Section 2.1.6.1), and presyncope (Section 2.1.7) in the Q8W group and hypersensitivity (Section 2.1.7) in the Q4W group. Case narratives for subjects with SAEs are provided in GSK Doc. # 2019N406358_01 Section 13.

2.1.4.2. Longer-term Phase III Results

No additional drug-related SAEs were reported in the Safety Population since the Week 48 analysis of Study 201584 (Data Source: GSK Doc. # 2019N404586_00 Section 7.3.2 and Table 3.27). None of the SAEs reported in the Extension-switch Q4W group were assessed as drug related (Data Source: GSK Doc. # 2019N404586_00 Table 3.28).

No drug-related SAEs were reported in the Extension Phase of Study 201585 (Data Source: GSK Doc. # 2019N399072_00 Table 13.13; Table 13.14).

2.1.4.3. Phase IIB Results

In Study LAI111682, there were 3 drug-related SAEs in 2 subjects in the CAB + RPV group: suicidal ideation and depression (CAB 30 mg; both in same subject) and seizure (CAB 60 mg) (GSK Doc. # 2019N404586_00 Section 7.4.3).

In Study 200056, 1 subject in the CAB + RPV treatment group had a fatal SAE of myocardial infarction (see Section 2.1.2; Data Source: GSK Doc. # 2018N380094_00 Section 7.3).

2.1.5. Other Significant Adverse Events

2.1.5.1. Adverse Events Leading to Withdrawal

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, 22 (4%) subjects in the CAB + RPV Q4W group had 36 AEs and 9 (2%) subjects in the CAR group had 15 AEs leading to withdrawal/permanent discontinuation of study drug (Table 34). Additionally, 1 subject in the CAB + RPV Q4W group (Study 201585) was discontinued due to meeting the protocol-defined LSC, which was not considered as an AE leading to withdrawal (Data Source: ISS/ISE Table 1.05). In the CAB + RPV Q4W group, most (17 of 22) subjects who withdrew due to an AE withdrew due to a non-ISR AE. Non-ISR AEs leading to withdrawal were most frequently reported in the Infections and infestations (CAB + RPV Q4W, n=9 [8 acute viral hepatitis; 1 acute hepatitis A with secondary syphilis]; CAR, n=0) and Nervous system disorders (CAB + RPV Q4W, n=3 [headache, n=2; memory impairment]; CAR, n=4 [amnesia, disturbance in attention, dizziness, dysarthria]) System Organ Classes. With the exception of acute viral hepatitis, all non-ISR AEs leading to withdrawal had an incidence of <1%.

Table 34 Summary of AEs Leading to Withdrawal/Permanent Discontinuation of Study Drug in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

System Organ Class PT	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) N (%)	CAR (N=283) N (%)	CAB + RPV Q4W (N=308) N (%)	CAR (N=308) N (%)	CAB + RPV Q4W (N=591) N (%)	CAR (N=591) N (%)
Any AE leading to withdrawal, including ISRs	**9 (3)**	**4 (1)**	**13 (4)**	**5 (2)**	**22 (4)**	**9 (2)**
Any AE leading to withdrawal, excluding ISRs	**8 (3)**	**4 (1)**	**9 (3)**	**5 (2)**	**17 (3)**	**9 (2)**
General disorders and administration site conditions						
Asthenia	0	0	1 (<1)	0	1 (<1)	0
Discomfort	1 (<1)	0	0	0	1 (<1)	0
Fatigue	0	1 (<1)	0	0	0	1 (<1)
Infections and infestations[a]						
Hepatitis A	2 (<1)	0	2 (<1)	0	4 (<1)	0
Acute hepatitis B	2 (<1)	0	1 (<1)	0	3 (<1)	0
Acute hepatitis C	1 (<1)	0	0	0	1 (<1)	0
Secondary syphilis	1 (<1)	0	0	0	1 (<1)	0
Nervous system disorders						
Headache	0	0	2 (<1)	0	2 (<1)	0
Amnesia	0	1 (<1)	0	0	0	1 (<1)
Disturbance in attention	0	1 (<1)	0	0	0	1 (<1)
Dizziness	0	1 (<1)	0	0	0	1 (<1)
Dysarthria	0	1 (<1)	0	0	0	1 (<1)
Memory impairment	0	0	1 (<1)	0	1 (<1)	0
Gastrointestinal disorders						
Diarrhea	1 (<1)	0	1 (<1)	0	2 (<1)	0
Nausea	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Colitis	0	0	0	1 (<1)	0	1 (<1)
Vomiting	1 (<1)	0	0	0	1 (<1)	0
Psychiatric disorders						
Anxiety	0	0	1 (<1)	0	1 (<1)	0
Anxiety disorder	0	0	0	1 (<1)	0	1 (<1)
Depression	0	0	0	1 (<1)	0	1 (<1)
Depression suicidal	0	0	1 (<1)	0	1 (<1)	0
Suicidal ideation	0	0	0	1 (<1)	0	1 (<1)
Suicide attempt	0	1 (<1)	0	0	0	1 (<1)
Investigations						
Blood creatinine increased	0	0	0	1 (<1)	0	1 (<1)
Liver function test abnormal	0	0	1 (<1)	0	1 (<1)	0
Transaminases increased	1 (<1)	0	0	0	1 (<1)	0
Renal and urinary disorders						
Renal failure	0	1 (<1)	0	0	0	1 (<1)
Renal impairment	0	0	0	1 (<1)	0	1 (<1)
Hepatobiliary disorders						
Hepatocellular injury	0	0	1 (<1)	0	1 (<1)	0
Hyperbilirubinemia	0	0	1 (<1)	0	1 (<1)	0
Injury, poisoning and procedural complications						
Overdose	0	0	0	1 (<1)	0	1 (<1)
Musculoskeletal and connective tissue disorders						
Myalgia	0	0	1 (<1)	0	1 (<1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)						
Adenocarcinoma of colon	1 (<1)	0	0	0	1 (<1)	0

Data Source: ISS/ISE Table 3.06 and ISS/ISE Table 3.36.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: ISR PTs are not presented in this table.
a. For details of subjects who withdrew due to acute viral hepatitis, see Table 44.

Injection site pain led to withdrawal in 6 subjects (1%); additional information on ISRs leading to withdrawal is summarized in Section 2.1.6.1.

Injection site pain, headache, and diarrhea are all ADRs for CAB. Additional AEs leading to withdrawal reported in >1 CAB + RPV Q4W subject were hepatitis A and hepatitis C. All other AEs leading to withdrawal in Studies 201584 and 201585 were reported in single subjects in 1 or both treatment groups.

In Study 207966, the frequency of subjects reporting at least 1 AE leading to withdrawal was low (2% in both treatment groups; Data Source: GSK Doc. # 2019N406358_01 Table 3.22). In the Q8W group, 18 AEs leading to withdrawal were reported for 12 subjects, and in the Q4W group, 21 AEs leading to withdrawal were reported for 13 subjects.

A total of 3 AEs leading to withdrawal were reported for more than 1 subject in either treatment group:

- injection site pain (Q8W: 1 subject; Q4W: 4 subjects),
- fatigue (Q8W: 1 subject; Q4W: 2 subjects; all considered related to study drug; see GSK Doc # 2019N406358_01 in-text Table 30), and
- abnormal dreams (Q8W: 0 subjects; Q4W: 2 subjects; considered related to study drug; see GSK Doc # 2019N406358_01 in-text Table 30).

Injection site pain, fatigue, and abnormal dreams are all ADRs for CAB. All other AEs leading to withdrawal were reported in single subjects in 1 or both treatment groups in Study 207966.

Additional results for non-ISR AEs leading to withdrawal are summarized in GSK Doc. # 2019N406358_01 Section 7.1.4.

Withdrawals During the OLI Period in Studies 201584, 201585, and 207966

During the OLI period in Studies 201584 and 201585, 6 subjects (3 in each study) withdrew due to AEs (Data Source: ISS/ISE Table 3.37). The AEs that occurred in Study 201584 were acute hepatitis C (Grade 2), hepatitis A (Grade 4), and transaminases increased, probably related to chronic hepatitis C infection, illicit drug use, and inorganic solvent abuse (Grade 3). None of these AEs were considered to be related to study drug (Data Source: GSK Doc. # 2017N345267_00 Listing 19). AEs leading to withdrawal in Study 201585 were asthenia (Grade 1), myalgia (Grade 1), headache (Grade 3), and depression suicidal (Grade 2). All 4 AEs were considered to be related to study drug (Data Source: GSK Doc. # 2018N370336_00 Listing 17).

During the CAB + RPV OLI period in Study 207966, 2 subjects (<1%) in the Q8W group withdrew due to an AE (asthenia, skin lesion) and 2 subjects (<1%) in the Q4W group withdrew due to an AE (fatigue, transaminases increased, depression) (Data Source: GSK Doc. # 2019N406358_01 Table 3.23). With the exception of skin lesion, all of these AEs are either ADRs or directly related to an ADR (transaminases increased related to DILI, an ADR) for CAB + RPV. Skin lesion was not considered related to study drug (Data Source: GSK Doc. # 2019N406358_01 Table 3.12).

Longer-term Phase III Results

At the end of the MP in Study 201584, AEs leading to withdrawal were reported by 5% of the CAB + RPV Q4W group and 1% of the CAR group (GSK Doc. # 2019N421511_00 Section 7.2.4). This included 5 additional subjects in the CAB + RPV Q4W group who withdrew since the Week 48 analysis due to hepatitis A, hepatitis C, injection site pain, or depression (2 subjects). Depression and injection site pain were considered related to study drug by the investigator.

During the Extension Phase in Study 201584, 1 CAB + RPV Q4W subject in the Safety Population withdrew due to overdose (paracetamol) (GSK Doc. # 2019N421511_00 Section 7.8.4). In the Extension-switch Q4W group, 2 subjects withdrew; 1 due to injection site pain and 1 due to weight increased. All 3 of these AEs were considered related to study drug by the investigator.

In Study 201585, during the Extension Phase, 2 subjects in the CAB + RPV Q4W group had AEs leading to withdrawal of study drug (AEs of hepatitis B [serious, Grade 3, not related to study treatment] and fear [nonserious, Grade 1, related to study treatment]) (Data Source: GSK Doc. # 2019N399072_00 Table 13.15, Listing 108). In the Extension Switch to CAB + RPV Q4W group, 1 subject had an AE (injection site pain) that led to withdrawal from the study drug (Data Source: GSK Doc. # 2019N399072_00 Table 13.16; Listing 108).

Phase IIB Results

For both studies, all AEs leading to withdrawal for CAB subjects had an incidence of <1%.

At EOS in Study LAI116482, 12 (7%) subjects in the CAB + RPV group and 9 (15%) subjects in the EFV group experienced at least 1 AE leading to withdrawal/permanent discontinuation of study drug (Data Source: GSK Doc. # 2019N404586_00 Table 8.15). All AEs were reported by single subjects.

Through 160 weeks of study treatment, 15 (7%) subjects in Study 200056 experienced at least 1 AE leading to withdrawal/permanent discontinuation of study drug (Data Source: GSK Doc. # 2018N380094_00 Section 7.4). Injection site pain and hepatitis C were the only AEs leading to withdrawal/permanent discontinuation of study drug reported by >1 subject.

2.1.6. Adverse Events of Special Interest for CAB and RPV

AEs of special interest have been identified for CAB + RPV (oral and LA) based on their relevance in the target population, nonclinical and/or clinical safety data for CAB and RPV (oral and LA), labeling and/or regulatory authority interest, known association for approved INSTIs, and/or regulatory authority requirements.

There are no expected or observed additive or synergistic effects on AESIs in subjects taking CAB + RPV beyond those effects associated with the individual components.

For Phase III/IIIB studies, in each AESI category, MedDRA PTs were selected (search terms are listed in the SDAP for Studies 201584 and 201585, m5.3.5.3 and the RAP for Study 207966). This was based on whether a MedDRA SMQ was available specific to the AESI and practical to apply to the data. If a MedDRA SMQ was not available or if there were additional PTs that the Sponsor considered were relevant to the AESI, these were selected as grouped PTs (favored) or using individual PTs (less favored). Further details can be found in the SDAP and RAP. For pooled Studies 201584 and 201585, results from small numbers of AEs for a particular term are not informative and therefore were not analyzed if the incidence of a given AESI was <20 subjects, as specified in the SDAP.

For topics for which results from pooled Studies 201584 and 201585 are summarized, results for individual studies are available in the CSRs.

2.1.6.1. Injection Site Reactions From Study Drug Injections

ISRs were only recorded from study drug (CAB + RPV) injections and are expected with IM injections.

Subject-level Data

Overview of ISRs

Week 48 Phase III/IIIB Results

In pooled Studies 201584 and 201585, 84% of subjects experienced at least 1 ISR (Table 35). Most subjects had ISRs that resolved within 14 days. No Grade 4 or 5 ISRs occurred. Most subjects had AEs with a maximum intensity of Grade 1 or Grade 2. 21 (4%) subjects had injection site pain ISRs that were Grade 3. 2 (<1%) subjects had injection site induration ISRs that were Grade 3. None of the ISRs were considered to be serious and 10 (<1%) ISRs led to withdrawal (Data Source: ISS/ISE Table 3.110). Nonserious complications such as injection site abscess and cellulitis were observed but occurred in less than 1% of subjects for each event (Data Source: ISS/ISE Table 3.50).

In Study 207966, the overall frequency, intensity, duration, and rates of withdrawal for study drug ISRs were generally similar between the Q8W and Q4W treatment groups. An exception was that a lower proportion of subjects in the Q8W group had an ISR with a maximum duration of >14 days compared with subjects in the Q4W group. The maximum intensity of ISRs was similar between the treatment groups, with most subjects in either treatment group developing ISRs with a maximum intensity of Grade 1. There

were no Grade 4 or 5 ISRs. There was 1 ISR SAE; a subject in the Q8W group had an injection site abscess at the site of the RPV injection; a summary of the SAE follows the table.

Table 35 Summary of Subject-level Characteristics of ISR AEs in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584 CAB + RPV Q4W (N=283) n (%)	Study 201585 CAB + RPV Q4W (N=308) n (%)	Pooled Studies 201584 and 201585 CAB + RPV Q4W (N=591) n (%)	Study 207966 CAB + RPV Q8W (N=522) n (%)	Study 207966 CAB + RPV Q4W (N=523) n (%)
Number of Subjects with Injection	278 (98)	303 (98)	581 (98)	516 (99)	517 (99)
Number of Subjects with ISR Event	239 (86)	250 (83)	489 (84)	392 (76)	390 (75)
Any Grade					
Grade 1 Events	222 (80)	215 (71)	437 (75)	364 (71)	362 (70)
Grade 2 Events	101 (36)	110 (36)	211 (36)	140 (27)	143 (28)
Grade 3 Events	11 (4)	11 (4)	22 (4)	14 (3)	21 (4)
Not applicable[a]	1 (<1)	0	1 (<1)	0	0
Maximum Grade or Intensity					
Mild or Grade 1	135 (49)	137 (45)	272 (47)	246 (48)	237 (46)
Moderate or Grade 2	93 (33)	102 (34)	195 (34)	132 (26)	132 (26)
Severe or Grade 3	11 (4)	11 (4)	22 (4)	14 (3)	21 (4)
Maximum Duration, days					
1-7	133 (48)	158 (52)	291 (50)	281 (54)	250 (48)
8-14	51 (18)	44 (15)	95 (16)	57 (11)	58 (11)
>14	53 (19)	48 (16)	101 (17)	51 (10)	78 (15)
Not applicable/Missing	2 (<1)	0	2 (<1)	3 (<1)	4 (<1)
Event Characteristics					
Serious	0	0	0	1 (<1)	0
Drug-related	233 (84)	244 (81)	477 (82)	384 (74)	384 (74)
Leading to Withdrawal/Study Drug Withdrawn	2 (<1)	4 (1)	6 (1)	5 (<1)	5 (<1)
Outcome					
Recovered/Resolved	236 (85)	249 (82)	485 (83)	387 (75)	386 (75)
Recovering/Resolving	9 (3)	2 (<1)	11 (2)	4 (<1)	6 (1)
Not Recovered/Not Resolved	7 (3)	2 (<1)	9 (2)	16 (3)	12 (2)
Recovered/Resolved with Sequelae	12 (4)	13 (4)	25 (4)	19 (4)	19 (4)

Data Source: ISS/ISE Table 3.113; GSK Doc. # 2019N406358_01 Table 3.29.

Note: All percentages based on the number of subjects with at least one injection. For Any Grade, Event Characteristics and Outcome, the sum in a column may be greater than number of subjects, because each event is assessed independently, so a subject could be counted in more than one category.

a. Grade was missing.

The subject with the ISR SAE in Study 207966 recovered after hospitalization for drainage of the abscess and antibiotic treatment; a case narrative is presented in GSK Doc. # 2019N406358_01 Section 13, and a summary is provided as follows.

- Subject was a 20- to 30-year-old female who was randomized to the Q8W group. The subject previously received CAR in Study 201585. The subject reported no issues through Week 16 of Study 207966. At Week 22 the subject presented to the ED with buttock swelling and pain. Ultrasound and CT confirmed a 12 x 9 cm right gluteal abscess. The subject was admitted to the hospital. The abscess was incised and drained, and the subject received antibiotic treatment (amoxicillin and clavulanate). Investigations including cultures and hematology were normal. The gluteal wound healed well with no complications, and the subject was discharged from the hospital 8 days later. The SAE resulted in withdrawal of the subject from the study. The event was considered possibly related to RPV because the gluteal abscess appeared on the same site where RPV was administered by IM injection.

ISRs and Injection Tolerability AEs Leading to Withdrawal

In Studies 201584 and 201585, 6 subjects withdrew due to 11 ISRs, including injection site pain (n=8; 6 AEs were Grade 2, 2 AEs were Grade 3), discomfort (n=1, Grade 2), injection site nodule (n=1, Grade 2), and injection site swelling (n=1, Grade 2) (Table 36; Data Source: GSK Doc. # 2018N370336_00 Listing 17; GSK Doc. # 2017N345267_00 Listing 19). All of the ISR AEs were considered to be related to study drug. Two additional subjects withdrew from Study 201584 citing intolerability of injections but did not name a specific ISR AE term that led to withdrawal (Data Source: ISS/ISE Table 1.02). Therefore, the total number of withdrawals due to injection intolerability was 8 subjects (1%).

Table 36 Summary of ISR AEs Leading to Withdrawal/Permanent Discontinuation of Study Drug in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
PT	CAB + RPV Q4W (N=283)	CAR (N=283)	CAB + RPV Q4W (N=308)	CAR (N=308)	CAB + RPV Q4W (N=591)	CAR (N=591)
Injection site pain. n (%)	2 (<1)	0	4 (1)	0	6 (1)	0
Injection site nodule, n (%)	0	0	1 (<1)	0	1 (<1)	0
Discomfort, n (%)	1 (<1)	0	0	0	1 (<1)	0
Injection site swelling	0	0	1 (<1)	0	1 (<1)	0

Data Source: ISS/ISE Table 3.36.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Regarding withdrawals due to ISRs in Study 207966:

- 5 subjects in the Q8W group reported 7 ISRs (injection site pain, injection site injection site swelling, injection site discoloration, injection site discomfort, injection

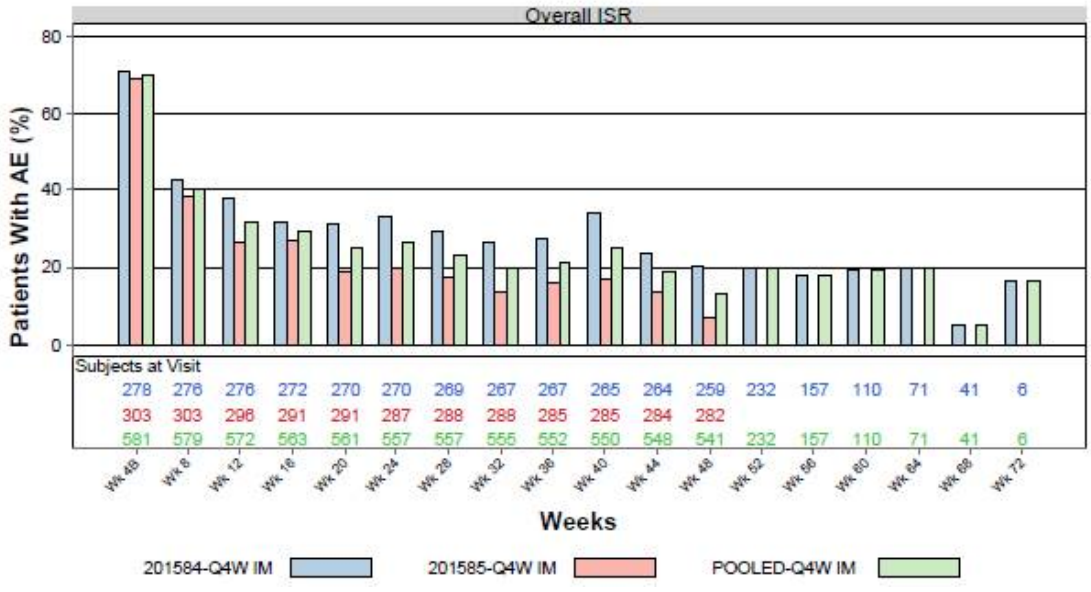
site hypersensitivity, injection site necrosis, and injection site warmth) leading to withdrawal (Table 35 and Data Source: GSK Doc. # 2019N406358_01 Table 3.22);

- 5 subjects in the Q4W group reported 3 ISRs (injection site pain, injection site swelling, and injection site nodule) leading to withdrawal;
    - All ISRs leading to withdrawal were reported by single subjects in 1 or both treatment groups except for injection site pain, which led to withdrawal in 1 subject (<1%) in the Q8W group and 4 subjects (<1%) in the Q4W group;
- 1 subject in the Q8W group and 4 subjects in the Q4W group withdrew due to intolerability of injections (Data Source: GSK Doc. # 2019N406358_01 Table 1.4);
    - Therefore, the overall rate for discontinuations due to injection tolerability was 6/522 (1%) in the Q8W group and 9/523 (2%) in the Q4W group.

ISRs Over Time

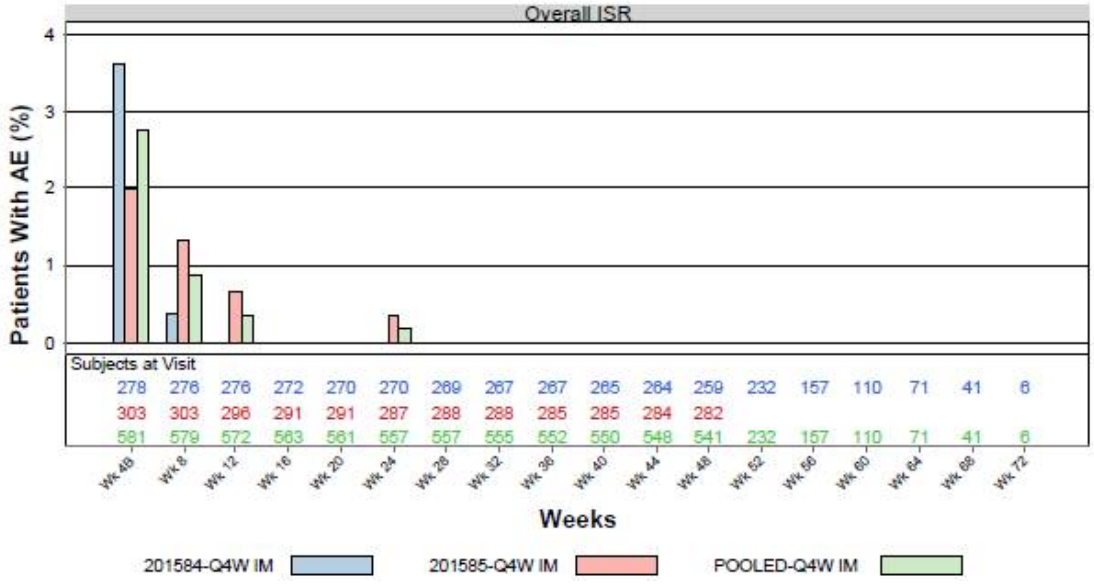
In Studies 201584 and 201585 at Week 4b, the initial loading injection of 3 mL was administered. Over time and with subsequent injections, the incidence and severity of ISRs decreased over the course of each study (Data Source: ISS/ISE Table 3.116) (Figure 3 and Figure 4).

Figure 3 Incidence of Overall ISR AEs for Studies 201584, 201585, and 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: ISS/ISE Figure 3.19.
Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Figure 4 Incidence of Grade 3 ISR AEs for Studies 201584, 201585, and 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)

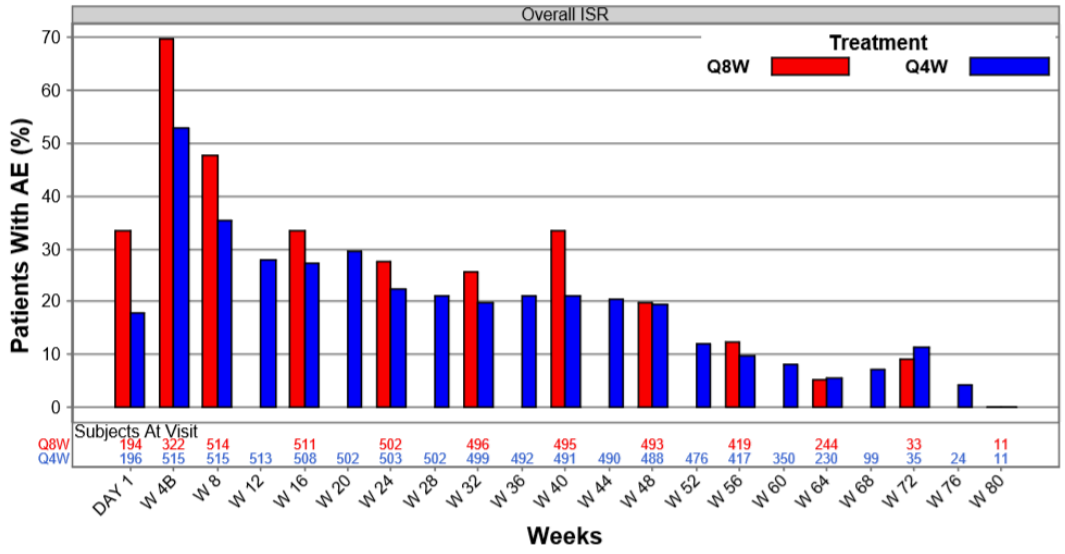


Data Source: ISS/ISE Figure 3.20.
Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: No Grade 4 or 5 AEs occurred.

Some subjects in Study 207966 were previously in Study 201585 and had received monthly injections for almost a year, at minimum, while some subjects entered de novo.

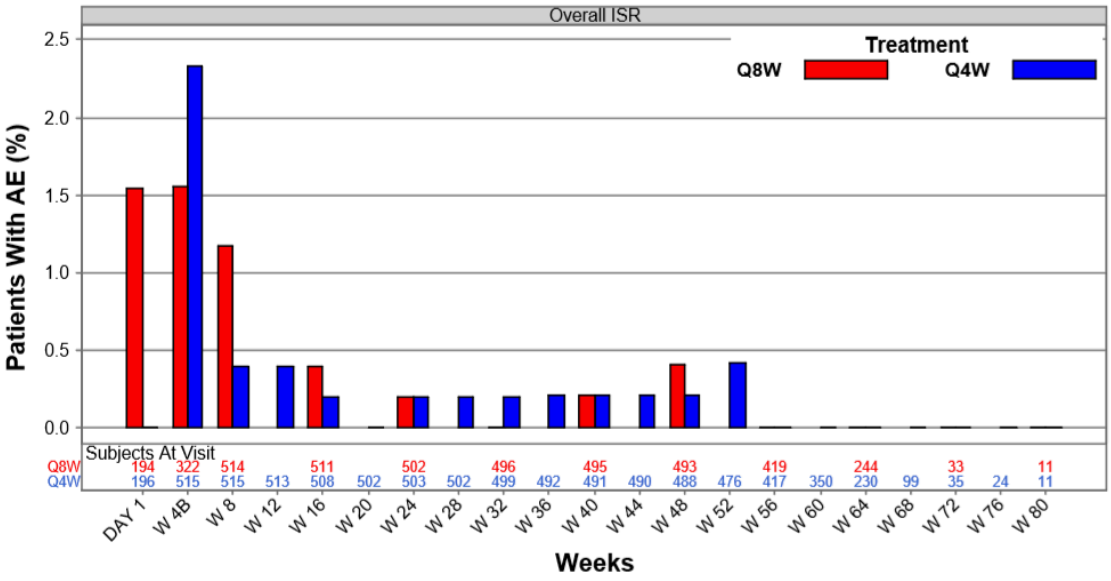
The incidence and intensity of reported ISRs in Study 207966 tended to decrease over time in both dosing groups (Figure 5 and Figure 6), similar to the results observed in Studies 201584 and 201585.

Figure 5 Incidence of Overall ISR AEs in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 3.6.
Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.

Figure 6 Incidence of Grade 3 ISR AEs in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)



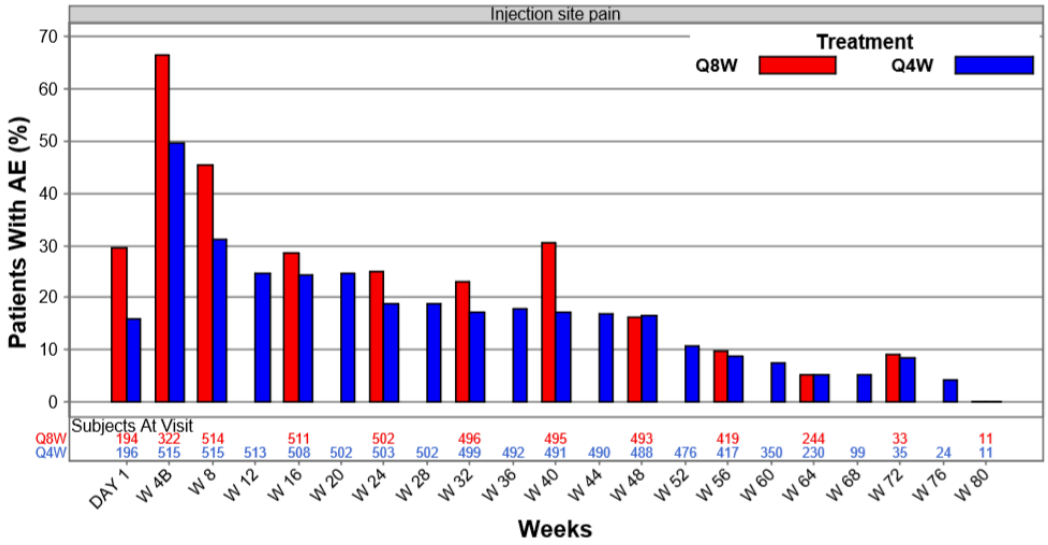
Data Source: GSK Doc. # 2019N406358_01 Figure 3.9.
Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.
Note: No Grade 4 or 5 ISR AEs occurred.

Types of ISRs

In pooled Studies 201584 and 201585, most of the subjects in the CAB + RPV Q4W group experienced ISRs related to pain (77%), and fewer experienced ISRs of nodule (14%), induration (12%), swelling (8%), erythema (4%), or pruritus (4%) (Data Source: ISS/ISE Table 3.50). Other ISRs occurred less commonly (affecting ≤3% of subjects).

In Study 207966, injection site pain was also the most frequently reported ISR, reported by 72% of subjects in the Q8W group and 70% of subjects in the Q4W group (Data Source: GSK Doc. # 2019N406358_01 Table 3.29 and Figure 8). The incidence of reported injection site pain was highest following the first set of injections received (Day 1 for 201585 rollover subjects and Week 4b for all other subjects) in both groups and decreased thereafter in both groups (Figure 7). Furthermore, as presented in Overview of ISRs, ISR tolerability, as evidenced by the proportion of Grade 1 and 2 events and the rate of ISR discontinuation was similar between the Q8W and Q4W groups. The median duration of events was 3 days in each group (Event-level Data).

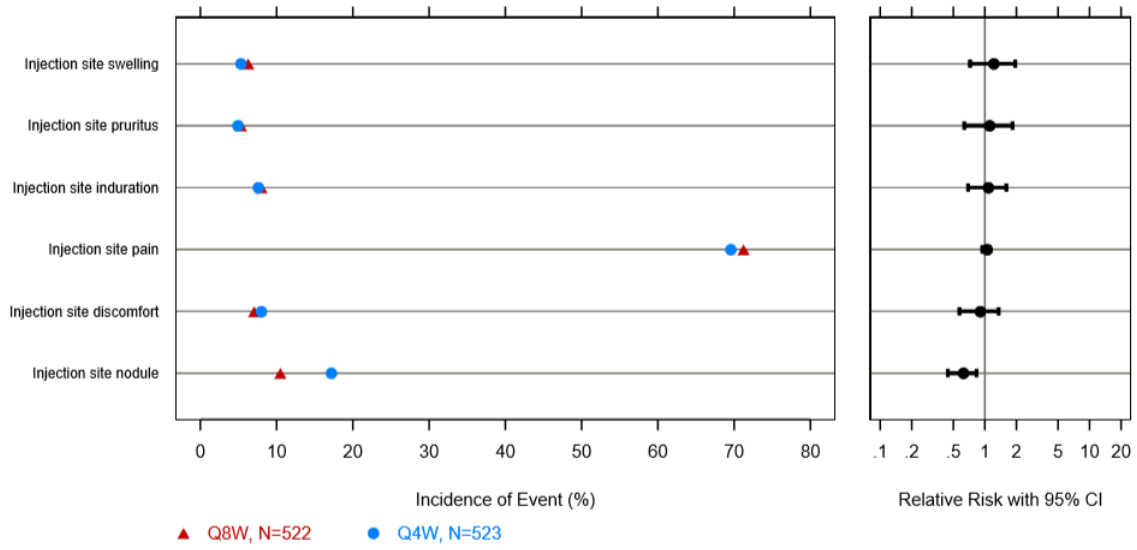
Figure 7 Incidence of Injection Site Pain in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 3.6.
Note: Bars represent incidence of onset ISR AEs relative to the most recent IM injection visit.

In addition to injection site pain, other common (≥5% of subjects in either group) ISRs are shown in Figure 8. Injection site nodules were reported less frequently in the Q8W group (10% of subjects) compared with the Q4W group (17% of subjects) (Data Source: GSK Doc. # 2019N406358_01 Table 3.5). Otherwise, the proportions of subjects reporting other types of ISRs (pain, induration, discomfort, etc) were similar between treatment groups. Only injection site pain and injection site nodule were reported by ≥10% of subjects in either treatment group.

Figure 8 Plot of Common (At Least 5% of Subjects in Either Treatment Group) Study Drug ISR AEs and Relative Risk in Study 207966 - Q8W vs. Q4W - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 3.2.

ISR by Study Drug

In Studies 201584 and 201585, no significant differences in ISRs between CAB and RPV were observed when analyzed by each injection drug (Data Source: ISS/ISE Table 3.112).

Association Between Needle Length/Gauge and ISR

A summary of needle length and gauge used in Studies 201584 and 201585 is presented in the CSRs (Data Source: GSK Doc. # 2017N345267_00 Table 14; GSK Doc. # 2018N370336_00 Table 12).

In pooled Studies 201584 and 201585, no trends were observed for an association between needle length and incidence, type, or severity of ISRs for either CAB or RPV (Table 37). Of note, the use of needles >2 inches was limited compared with those ≤2 inches.

Table 37 ISR AEs in Pooled Studies 201584 and 201585 by Needle Length and Injection Drug – Week 48 Analysis - Maintenance Phase (Safety Population)

	Pooled Studies 201584 and 201585 (CAB + RPV Q4W)			
	Needle Length			
	<2 in		≥2 in	
	CAB (N=7042)	RPV (N=7044)	CAB (N=297)	RPV (N=299)
Injection Site Pain	1352	1626	51	58
Injection Site Induration	79	58	0	0
Injection Site Nodule	72	62	2	3
Injection Site Swelling	44	37	3	2
Injection Site Erythema	32	26	1	1
Injection Site Warmth	21	23	1	2
Injection Site Bruising	12	11	1	0
Injection Site Pruritus	11	21	2	3
Injection Site Hematoma	7	5	0	0
Injection Site Reaction, Unspecified	3	1	0	0
Injection Site Abscess	2	3	0	0
Injection Site Anesthesia	2	1	0	0
Injection Site Discoloration	2	0	1	3
Injection Site Hemorrhage	2	1	0	0
Injection Site Cyst	1	1	0	0
Injection Site Discomfort	1	2	0	0
Injection Site Granuloma	1	0	0	0
Injection Site Necrosis	1	0	0	0
Injection Site Scar	1	1	0	0
Injection Site Cellulitis	0	2	0	0

Data Source: ISS/ISE Table 3.111; GSK Doc. # 2018N370336_00 Table 3.107, Table 3.108; GSK Doc. # 2017N345267_00 Table 3.117, Table 3.118.
N=Number of injections.
Note: An ISR reported more than once by the same subject was counted more than once.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, no trends were observed for an association between needle length and incidence, type, or severity of ISRs for either CAB or RPV (Data Source: GSK Doc. # 2019N406358_01 Table 3.34 and Table 3.38); however, because the use of needles >1.5 inches long was limited (≤11% of subjects in either treatment group) compared with needles ≤1.5 inches long, no definitive conclusions may be drawn from these data.

Event-level Data

In pooled Studies 201584 and 201585, most (94%) ISRs resolved within 14 days with a median duration of 3 days, and 5% lasted more than 14 days (Data Source: ISS/ISE Table 3.110).

In Study 207966, there was a higher frequency of overall ISR AE reporting at each injection visit in the Q8W group compared with the Q4W group (Table 38). The higher frequency of overall ISRs per injection in the Q8W group was driven largely by the higher frequency of injection site pain in this group. Compared with injection site pain, there were far fewer reports of other common ISRs, and ISRs per injection were similar between the Q8W and Q4W groups for induration, nodule, discomfort, pruritus, and swelling.

Table 38 Summary of Event-level Characteristics of Common (At Least 5% of Subjects in Either Group) Study Drug ISRs in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	CAB + RPV Q8W (N=522)	CAB + RPV Q4W (N=522)
Number of Subjects with Injection, n	516	517
Number of Injections, n	8470	15711
Overall ISR		
Number of ISRs, n	2507	3152
Number of ISRs/Number of Injections	0.3	0.2
Injection site pain		
Number of ISRs, n	2014	2567
Number of ISRs/Number of Injections	0.24	0.16
Injection site induration		
Number of ISRs, n	86	96
Number of ISRs/Number of Injections	0.01	0.01
Injection site nodule		
Number of ISRs, n	113	204
Number of ISRs/Number of Injections	0.01	0.01
Injection site discomfort		
Number of ISRs, n	92	110
Number of ISRs/Number of Injections	0.01	0.01
Injection site pruritus		
Number of ISRs, n	63	55
Number of ISRs/Number of Injections	0.01	0.00
Injection site swelling		
Number of ISRs, n	70	45
Number of ISRs/Number of Injections	0.01	0.00

Data Source: GSK Doc. # 2019N406358_01 Table 3.28.
Note: An ISR reported more than once by the same subject was counted more than once.

In Study 207966, for ISRs overall, the mean (SD) duration was similar between the treatment groups (Q8W: 6.4 [18.66] days; Q4W: 6.2 [15.92] days), and the median duration was 3 days in both groups (Data Source: GSK Doc. # 2019N406358_01 Table 3.28).

Association Between Injection Site and ISR

During the CAB + RPV development program with trials involving CAB LA and RPV LA, gluteal injection sites have been used successfully. Location of injection was not recorded in the clinical studies, so analysis by gluteal location is not available.

Consistent with guidance in the Phase III/IIIB studies, the ventrogluteal approach is preferred as it avoids proximity to the neurovascular bundle in the gluteal region. This injection site will be recommended in the IFU for CAB LA and RPV LA.

However, depending on local practices and guidelines, the dorsogluteal approach is also considered acceptable. This is reflected in the IFU.

Patient-Reported Outcomes: Injection Acceptance

The PIN instrument contains 21 items in total that generate 4 dimensions and 5 individually scored items. No total score is derived for the PIN instrument. The 4 PIN dimensions measure acceptability and tolerability of ISRs, as well as their impact on sleep and leg movement. The 5 items measure pain at injection site, anxiety before and after injection, and willingness to pursue injectable treatment outside of a clinical study. The Acceptance of ISRs dimension consists of 2 items: acceptance of local reactions and acceptance of pain. Statistical testing was pre-planned only for the Acceptance of ISRs dimension to avoid multiplicity issues.

In pooled Studies 201584 and 201585, at the first assessment (Week 5), the median Acceptance of ISRs domain score was 2.00 (very acceptable) (post hoc analysis; Table 39). At Weeks 41 and 48, the median was 1.50; ie, between 2.00 (very acceptable) and 1.00 (totally acceptable). The median Acceptance of ISRs domain score of the PIN showed a statistically significant improvement, both from Week 5 to Week 41 and from Week 5 to Week 48. Results from individual studies were similar (GSK Doc. # 2017N345267_00 Section 12.3.1 and GSK Doc. # 2018N370336_00 Section 12.1.3.1).

Table 39 Summary of Acceptance Dimension PIN Scores for Pooled Studies 201584 and 201585 – Week 48 Analysis - Maintenance Phase (LOCF) (CAB + RPV Q4W Group; ITT-E Population)

Actual Relative Time	(N=591) n	Mean	SD	Median	Q1	Q3	Min.	Max.	P Value[a,b]
Week 5	567	2.10	1.037	2.00	1.00	3.00	1.0	5.0	
Week 41	577	1.67	0.862	1.50	1.00	2.00	1.0	5.0	<0.001
Week 48	582	1.62	0.805	1.50	1.00	2.00	1.0	5.0	<0.001

Data Source: ISS/ISE Table 2.17.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
a. Week 41/48 was compared with the 1st visit (Week 5) based on Wilcoxon signed-rank test, respectively.
b. Post hoc analysis. alpha=0.0071. In the post hoc analysis, p-values were derived for 'Acceptance' only and a Bonferroni procedure adjusted for multiple testing.

Consistent results were reported for remaining dimensions and individual items of the PIN, although statistical analysis was not performed.

In Study 207966, at the first assessment (Week 8), the median Acceptance of ISRs domain score was 2.00 (very acceptable) in both treatment groups (Table 40). At Weeks 24 and 48, the median in both treatment groups was 1.50; ie, between 2.00 (very acceptable) and 1.00 (totally acceptable). The median Acceptance of ISRs domain score

of the PIN showed a statistically significant improvement in both treatment groups, both from Week 8 to Week 24 and from Week 8 to Week 48.

Table 40 Summary of Acceptance Domain PIN Scores in Study 207966 – Week 48 Analysis - Maintenance Phase (LOCF) (ITT-E Population)

Actual Relative Time	n	Mean	SD	Median	Q1	Q3	Min.	Max.	P Value[a]
CAB + RPV Q8W (N=522)									
Week 8	514	1.91	0.919	2.00	1.00	2.50	1.0	5.0	
Week 24	515	1.78	0.789	1.50	1.00	2.00	1.0	5.0	0.004
Week 48	515	1.73	0.868	1.50	1.00	2.00	1.0	5.0	<0.001
CAB + RPV Q4W (N=523)									
Week 8	515	1.88	0.891	2.00	1.00	2.50	1.0	5.0	
Week 24	515	1.76	0.828	1.50	1,00	2.00	1.0	5.0	0.002
Week 48	515	1.75	0.868	1.50	1.00	2.00	1.0	5.0	<0.001

Data Source: GSK Doc. # 2019N406358_01 Table 6.3.
Note: Acceptance of ISRs minimum score: 5 (not at all acceptable); maximum score 1 (totally acceptable).
a. Week 24/48 was compared with the first visit (Week 8) based on Wilcoxon signed-rank test, respectively. P-values were derived for 'Acceptance' only and not adjusted for multiple testing.

For results of additional health outcomes endpoints, see m2.7.3.

Longer-term Phase III Results

At the end of the MP in Study 201584, at least 1 ISR was reported by most subjects receiving CAB + RPV Q4W and were mostly Grade 1 or 2 in intensity (Table 41). An additional 6 subjects reported at least 1 ISR since the Week 48 analysis (Table 35). None were serious. One additional subject discontinued due to an ISR since the Week 48 analysis (ie, 2 subjects at Week 48 and 3 subjects at end of MP; Table 35 and Table 41).

Table 41 Summary of Subject-Level Characteristics of ISRs (Overall and Common) in Study 201584 at Week 100 – Maintenance Phase (Safety Population)

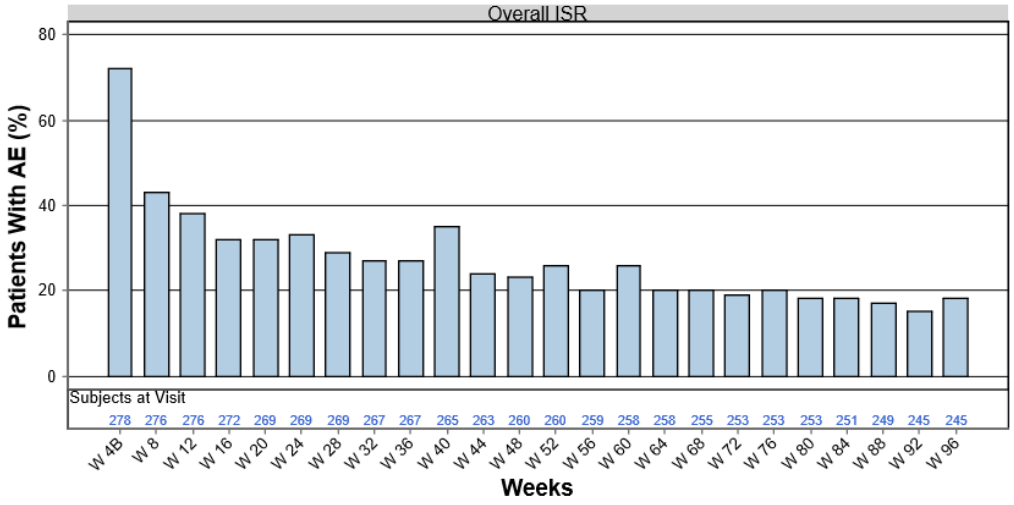
	CAB + RPV Q4W (N=283) n (%)
Number of subjects with injection	278 (98)
No. of subjects with ISRs	245 (88)
Any Grade[a]	
Grade 1 events	231 (83)
Grade 2 events	106 (38)
Grade 3 events	13 (5)
Maximum grade or intensity	
Mild or Grade 1	137 (49)
Moderate or Grade 2	95 (34)
Severe or Grade 3	13 (5)
Maximum duration (days)	
1-7	128 (46)
8-14	48 (17)
>14	67 (24)
Event characteristics	
Serious	0
Events leading to withdrawal/study drug withdrawn	3 (1)
Number of events	
n	278
Median (min, max)	6.0 (0, 109)
Rate of ISR events per injection visit[b]	
n	278
Median (min, max)	0.29 (0.0, 4.5)

Data Source: GSK Doc. # 2019N421511_00 Table 3.43.
Note: All percentages based on the number of subjects with at least 1 injection. For Any Grade, and Event Characteristics, the sum in a column may be greater than number of subjects because each event is assessed independently, so a subject can be counted in more than 1 category.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM.
a. No Grade 4 or 5 ISRs were reported.
b. Calculated for each subject as the number of events experienced by the subject divided by the number of injection visits attended by the subject.

In Study 201584, the median duration of ISRs was 3 days (Data Source: GSK Doc. # 2019N421511_00 Table 3.40), consistent with results from the Week 48 analysis (Event-level Data).

The incidence of ISRs over time was ≤20% after Week 64, not increasing over time in Study 201584 (Figure 9).

Figure 9 Plot of Incidence of ISR AEs Overall in Study 201584 at Week 100 - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N421511_00 Figure 3.14
Note: Bars represent incidence of onset of ISR AE relative to the most recent IM injection visit.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

In Study 201585, the frequency of ISR AEs in both treatment groups during the Extension Phase was consistent with results from the Maintenance Phase (Table 42). Only 1 additional subject in the CAB + RPV Q4W group reported ISRs during the Extension Phase compared with those who reported during the MP. Overall, injection site pain was the most commonly reported ISR during the Extension Phase.

ISRs that were reported in the CAB + RPV Q4W group during the Extension Phase in Study 201585 were all Grade 1 or Grade 2 in intensity (Data Source: GSK Doc. # 2019N399072_00 Table 13.26). None of the ISR AEs during the Extension Phase were considered to be serious, and none led to withdrawal from study drug.

ISRs that were reported in the Extension Switch to CAB + RPV Q4W group in Study 201585 were primarily Grade 1 or Grade 2, with the exception of 3 subjects who had single Grade 3 AEs (Data Source: GSK Doc. # 2019N399072_00 Table 13.27). None of these AEs were considered serious. No ISRs of Grade 4 or 5 intensity were reported. One subject in the Extension Switch to CAB + RPV Q4W group had 2 reports of injection site pain (1 for each study drug injection; both Grade 2) that led to withdrawal from study drug (Data Source: GSK Doc. # 2019N399072_00 Listing 108).

Table 42 Summary of Subject-level Characteristics of ISR AEs for Maintenance (up to Week 52) + Extension (Post-Week 52) Phases – Overall and Common (At Least 5%) in Study 201585 at Week 96 (Safety and Extension Switch Populations)

ISR	CAB + RPV Q4W Day 1 to Week 52 N=308 n (%)	CAR Day 1 to Week 52 N=308 n (%)	CAB + RPV Q4W Day 1 to Week 96 N=308 n (%)	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 N=174 n (%)
Overall ISRs	250 (83)	0	251 (83)	82 (49)
Injection site pain	231 (76)	0	231 (76)	78 (46)
Injection site nodule	37 (12)	0	38 (13)	2 (1)
Injection site induration	30 (10)	0	32 (11)	8 (5)
Injection site swelling	23 (8)	0	23 (8)	1 (<1)

Data Source: GSK Doc. # 2019N399072_00 in-text Table 15.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.
Note: All percentages based on the number of subjects with at least 1 injection. For any Grade, Event Characteristics, and Outcome, the sum in a column may be greater than number of subjects because each event is assessed independently so a subject can be counted in more than 1 category.

Event-level results for ISR AEs in the CAB + RPV Q4W and Extension Switch to CAB + RPV Q4W groups are presented in Table 43.

Table 43 Summary of ISR AEs (Event-level Summary) for Maintenance (up to Week 52) + Extension (Post-Week 52) Phases in Study 201585 at Week 96 (Safety and Extension Switch Populations)

Injection Site Reaction	CAB + RPV Q4W Day 1 to Week 52 N=308	CAR Day 1 to Week 52 N=308	CAB + RPV Q4W Day 1 to Week 96 N=308	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 N=174
Total number of injections (CAB or RPV), n	6978	0	8341	1264
Injection site pain, n	1208	0	1328	207
Injection site induration, n	54	0	62	14
Injection site nodule, n	54	0	61	3
Injection site swelling, n	48	0	50	4
Injection site erythema, n	38	0	40	0
Injection site pruritus, n	12	0	26	3
Injection site bruising, n	14	0	14	1
Injection site warmth, n	9	0	9	5
Hematoma, n	8	0	9	1
Other injection site reactions[a], n	15	0	15	0

Data Source: GSK Doc. # 2019N399072_00 in-text Table 16.
n=number of ISR events.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.
a. Other injection site reactions include unspecified reaction, abscess, cellulitis, anesthesia, discoloration, discomfort.

Phase IIB Results

ISR results in Studies 201584, 201585, and 207966 were consistent with those observed in Phase IIB Study 200056 (Data Source: GSK Doc. # 2017N337118_00 Section 7.5). In addition, Study 200056 provides longer term data through Week 160, continuing to highlight the low discontinuation rate over time and a stable rate of ISR AE event reporting.

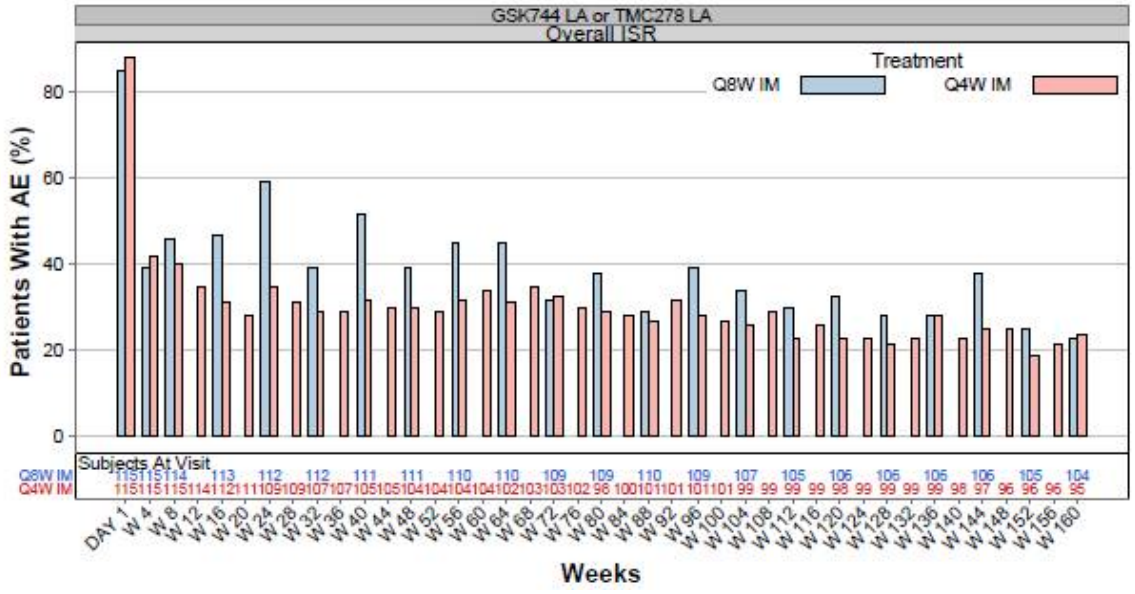
Overall, ISRs were more frequently reported at Day 1. The frequency of ISRs declined following Day 1, and with the exception of a slight increase at Week 24 appeared to remain steady or gradually decrease over time. Incidence rates were generally higher for the Q8W group compared with the Q4W group at visits with IM dosing for both arms (Figure 10). Injection site pain was the most common ISR reported. Incidence of other ISRs occurred in <20% of subjects at any visit. Furthermore, not every subject experienced an ISR at each administration.

Week 160 data from Study 200056 showed that ISR characteristics were similar but occurred at higher incidence overall (98% of subjects with ISR events; Data Source: GSK

Doc. # 2018N380094_00 Table 8.1035) and with higher incidence of individual ISR events (Data Source: GSK Doc. # 2018N380094_00 Table 8.1001).

Week 160 data from Study 200056 showed low injection site reaction discontinuation rates (3 subjects, 1%, Data Source: GSK Doc. # 2018N380094_00 Listing 8.1007) from ISRs over 3 years and a continuing trend towards decreased ISR reporting with time (Data Source: GSK Doc. # 2018N380094_00 Figure 8.1002).

Figure 10 Incidence of Overall ISRs for CAB + RPV Q4W and Q8W for Maintenance and Extension Phases in Study 200056 at Week 160 (Safety Maintenance Population)



Data Source: GSK Doc. # 2018N380094_00 Figure 8.1002.

A total of 14,562 injections have been administered in Study 200056 (Data Source: GSK Doc. # 2018N380094_00 in-text Table 37). A total of 6361 ISR events were reported, of which nearly all were classified as either mild (Grade 1: 85%) or moderate (Grade 2: 14%), with <1% of reactions classified as severe; a similar distribution of graded events was reported in each IM arm. The median duration of overall ISR events was 3 days in each treatment arm, with duration for specific ISR events ranging from 1 day to 713 days across both arms. Two subjects (Q8W) had ISRs leading to withdrawal (Data Source: GSK Doc. # 2018N380094_00 in-text Table 39).

Conclusion

ISR results across the CAB + RPV program are consistent among studies. ISRs are commonly reported (≥75% of subjects/group in pooled Studies 201584 and 201585 and in Study 207966). The most frequently reported ISR AEs were injection site pain, and much less commonly, injection site nodule. ISRs were mostly mild to moderate in intensity (no Grade 4 or 5 ISRs have been reported) and usually resolved after short durations; median duration was 3 days in each group in the Phase III/IIIB and IIB studies.

ISR SAE (injection site abscess) has been reported; the subject recovered following treatment including incision and drainage.

Throughout the CAB + RPV program, injections were generally well tolerated. The rates for discontinuations due to injection tolerability were low (1% in pooled Studies 201584 and 20158, 1% in the Study 207966 Q8W group and 2% in the Study 207966 Q4W group). Incidence and intensity of ISRs tend to decrease over time, while subjects' acceptance of injections increases over time.

ISRs were analyzed by drug, and results indicate that the characteristics of ISRs were similar for the CAB and RPV injections.

In Study 207966, there were no discernible differences between the overall ISR profiles of Q8W and Q4W with the exceptions of the incidences of injection site nodules (lower incidence in Q8W group compared with Q4W group; subject-level data) and ISRs per injection (higher frequency in Q8W group compared with the Q4W group; event-level data).

2.1.6.2. Hepatotoxicity

Elevated transaminases have been observed with INSTIs, including DTG and RAL. Elevated ALT values have been observed with exposure to CAB + RPV during the development program. These elevations were primarily attributed to the occurrence of acute viral hepatitis. A few subjects receiving oral CAB had transaminase elevations attributed to suspected drug-related hepatotoxicity. Aminotransaminase elevations in these subjects have been transient and reversible on discontinuation. Liver chemistry laboratory data are presented in Section 3.1.1.

Week 48 Phase III/IIIB Results

The primary method for detection of DILI was the evaluation of cases where subjects met protocol-defined LSC. The stopping criteria were based on a threshold for discontinuing drug treatment, regardless of the cause of liver chemistry changes. Once LSC were met, cases were further evaluated to determine the potential causes of the elevations in liver chemistries.

In the Phase III/IIIB studies, cases meeting LSC (CAB + RPV group only, as applicable) were evaluated by an independent hepatic adjudication committee operating under an Adjudication Committee Charter, as described in the respective protocols. The committee evaluated subjects who met LSC to determine if they could safely continue in the study. When an alternative (non-DILI) cause of transaminase elevations was identified and when liver chemistries stabilized, some subjects have been permitted to remain on/resume CAB + RPV or CAR. In addition, any case that did not meet LSC but was of potential interest was also reviewed by the Hepatic Adjudication Committee.

Monitoring of Liver Chemistry

No cases of DILI in subjects meeting LSC receiving CAB LA or RPV LA have been identified to date, as assessed by the independent Hepatic Adjudication Committee. In

Study 207966, there was 1 report of possible DILI that was considered to be related to oral CAB + RPV that occurred during the OLI part of the Maintenance Phase; additional information is provided in this section.

Of the 15 subjects with liver monitoring/stopping criteria in Studies 201584 and 201585, 11 subjects with LSC were in the CAB + RPV Q4W group and 3 subjects with LSC were in the CAR group (Data Source: ISS/ISE Table 3.136). One subject with liver monitoring criteria in the CAB + RPV Q4W group never reached LSC. All of the subjects who met LSC had acute viral hepatitis (Table 44), and there were more subjects in the CAB + RPV Q4W group who had acute viral hepatitis. In Study 207966, results were similar to those observed in Studies 201584 and 201585, and there were no clinically relevant differences between the Q8W and Q4W groups (Data Source: GSK Doc. # 2019N406358_01 Table 3.56).

Details of the 15 subjects with liver monitoring/stopping events in Studies 201584 and 201585 are presented in Table 44. It should be noted that more subjects receiving CAB + RPV Q4W (n=10) had acute viral hepatitis than those receiving CAR (n=3) during the MP (Week 48 analysis).

Table 44 Subjects with Liver Monitoring/Stopping Events in Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase

Study	Treatment Group	Study Phase	ALT	AST	Total Bilirubin	Resolved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201584	CAB + RPV Q4W	MP – oral (Week 4)	20.8xULN	12.5xULN	WNL	Y	Y	Acute hepatitis C
	CAB + RPV Q4W	MP – oral (Week 4)	8.8xULN	3.1xULN	1.5xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	MP – oral (Baseline)	43.7xULN	36.5xULN	1.3xULN	Y	Y	Illicit IV drug use, inorganic solvent abuse, chronic hepatitis C
	CAB + RPV Q4W	MP – LA (Week 20)	30.2xULN	17.9xULN	1.7xULN	N	Y	Acute hepatitis B
	CAB + RPV Q4W	MP – LA (Week 32)	98.1xULN	89.3xULN	6.9xULN	Y	N, Restarted Treatment	Acute hepatitis A
	CAB + RPV Q4W	MP – LA (Week 24)	7.4xULN	≥6.7xULN	1.7xULN	Y	N	Liver monitoring event. Never met LSC. Alcohol use 2 days before study visit; AE of direct bilirubin increased (known Gilbert's)
	CAB + RPV Q4W	MP – LA	155xULN	176.5xULN	7xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	MP – LA (Week 44)	8.1xULN	5.3xULN	1.5xULN	Y	Y	Acute hepatitis B
	CAR	MP (Week 36)	10.4xULN	6.0xULN	WNL	Y	Y	Acute hepatitis E
	CAR	MP (F/U 3 weeks after Week 8)	24.1xULN	18.5xULN	5.3xULN	Y	Y	Acute hepatitis A
201585	CAB + RPV Q4W	MP – LA (Week 12)	42.9xULN	29.2xULN	1.2xULN	Y	Y	Acute hepatitis B
	CAB + RPV Q4W	MP – LA (Week 36 to 40)	14.7xULN	6.7xULN	1.3xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	MP – LA (Week 16)	8.6xULN	4.8xULN	8xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	MP – LA (Week 24)	21.6xULN	8.4xULN	2.1xULN	N	Y	Acute hepatitis C
	CAR	MP (Week 8)	10.4xULN	4.5xULN	5.6xULN	Y	N, Restarted treatment	Acute hepatitis A

Data Source: ISS/ISE Listing 3; GSK Doc. # 2017N345267_00 Section 7.3.3.1.2 and Listing 64; GSK Doc. # 2019N399072_00 Section 7.3.3.1.2.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: Liver chemistry parameters represent peak values.
Note: Each row represents an individual subject.

In Study 207966, 1 subject had possible DILI in OLI:

- Subject was a 20- to 30-year-old female who was randomized to the Q4W group. The subject previously received SOC with lopinavir + ritonavir + abacavir + lamivudine. The subject had an asymptomatic increase in liver biochemistry (ALT 206 U/L; >4xULN and AST 137 U/L; >3xULN) with no elevation in bilirubin at Week 4a after receiving 28 days of oral CAB + RPV. Investigations were negative for viral hepatitis, syphilis, and an autoimmune screen. The OLI period was extended while the subject was investigated for alternative causes. During this time, ALT and AST remained elevated, and the subject was withdrawn from the study after receiving a total of 11 weeks of oral CAB + RPV. Total bilirubin was normal throughout this time. The subject commenced ABC/3TC/DTG, and ALT/AST returned to normal after 12 weeks. This subject did not meet LSC; however, a temporal association with ALT elevation and study drug was noted, and therefore the case was referred to the Hepatic Adjudication Committee as a case of potential interest. The Hepatic Adjudication Committee determined that this was a possible case of DILI related to CAB + RPV.

Overall, 5 subjects (2 on Q8W and 3 on Q4W) met LSC during the MP (Week 48 analysis) of Study 207966, and 3 additional subjects warranted monitoring based on liver chemistries (Table 45). Six of these 8 subjects had acute viral hepatitis. Of the 2 of 8 who did not, 1 was the subject with possible DILI considered related to oral CAB + RPV, and 1 was a subject whose liver biochemistry elevations resolved after discontinuation of a co-suspect concomitant medication (Melanotan II), which was presumed the most likely cause of the elevations. Three of the 8 subjects restarted study drug, and liver biochemistry elevations resolved for 7 of the 8 subjects; the 8th subject's liver biochemistry elevations normalized by Week 56. Brief summaries of these cases are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.2.

Table 45 Subjects with Liver Monitoring/Stopping Events in Study 207966 - Week 48 Analysis - Maintenance Phase

Placeholder ID/ Prior Exposure to CAB + RPV	Study Phase	ALT	AST	Total Bili	LSC Met	Re-solved?	Withdrew from study	Comments/ Restarted Study Drug? (Y/N)
Q8W CAB + RPV								
1 0 weeks prior exposure	MP-LA Week 16	22xULN	11xULN	10xULN (1 month after LSC)	Y	Y	Y	Acute hepatitis B/ N
2 >24 weeks prior exposure	MP-LA Week 8	9xULN	4xULN	WNL	Y	Y	N	Con med (Melanotan II)/ Y
Q4W CAB + RPV								
3 0 weeks prior exposure	MP-OLI Week 4a	6xULN	>4xULN	WNL	N	Y	Y	Possible DILI/ N
4 0 weeks prior exposure	MP-LA Week 36	47xULN	34xULN	3xULN	Y	Y	Y	Acute hepatitis B/ N
5 0 weeks prior exposure	MP-OLI Week 4b	3xULN	2xULN	WNL	N	N	N	Hepatitis E/ N
6 0 weeks prior exposure	MP-LA Week 40	9xULN	3xULN	WNL	Y	Y	N	Hepatitis E/ Y
7 >24 weeks prior exposure	MP-LA Week 32	22xULN	37xULN	13xULN (14 days later)	Y	Y	N	Hepatitis C/ Y
8 >24 weeks prior exposure	MP-LA Week 48	6xULN	3xULN	WNL	N	Y	N	Hepatitis C/ N

Data Source: GSK Doc. # 2019N406358_01 in-text Table 34.
Note: Each row represents an individual subject.

AEs

In Studies 201584 and 201585, 5 subjects each had 1 AE potentially associated with hepatotoxicity (CAB + RPV Q4W, 4 [<1%], CAR, 1 [<1%]) (Data Source: ISS/ISE Table 3.39). These events included hepatic cirrhosis (Grade 3; CAR group), hepatic steatosis (Grade 2; CAB + RPV Q4W group), hepatitis toxic (Grade 1; CAB + RPV Q4W group), hepatocellular injury (Grade 4; CAB + RPV Q4W group), and non-alcoholic steatohepatitis (Grade 1; CAB + RPV Q4W group) (Data Source: ISS/ISE

Table 3.20). No Grade 5 events occurred. Hepatocellular injury (CAB + RPV Q4W group), which occurred in a subject with acute hepatitis A, was considered serious and led to discontinuation of study drug (Data Source: ISS/ISE Table 3.33; Table 3.36; GSK Doc. # 2018N370336_00 Listing 30; full case narrative is available in GSK Doc. # 2018N370336_00 Section 15). Other AEs were not considered serious. None of the AEs were considered to be related to study treatment or to represent DILI (Data Source: ISS/ISE Table 3.25).

During Study 207966, 1 subject (<1%) in the Q8W group and no subjects in the Q4W group had an AE potentially associated with hepatotoxicity (Data Source: GSK Doc. # 2019N406358_01 Table 3.67). The AE, hepatic steatosis, was not serious (Data Source: GSK Doc. # 2019N406358_01 Table 3.16) and did not lead to withdrawal (Data Source: GSK Doc. # 2019N406358_01 Table 3.22). It was Grade 1 (Data Source: GSK Doc. # 2019N406358_01 Table 3.7) and not assessed as drug related by the investigator (Data Source: GSK Doc. # 2019N406358_01 Table 3.12).

Longer-term Phase III Results

No subjects have been identified as having DILI in Study 201584.

At the end of the MP in Study 201584, 9 subjects (3%) in the CAB + RPV Q4W group and 3 subjects (1%) in the CAR group met protocol-defined LSC (GSK Doc. # 2019N421511_00 Section 7.3.3.1.2). Since the Week 48 analysis, 2 subjects in the CAB + RPV Q4W group (hepatitis A and hepatitis C) and 1 subject in the CAR group (transaminitis) met LSC The 2 subjects in the CAB + RPV Q4W group were withdrawn from treatment due to meeting LSC. The subject in the CAR group had a concurrent event of acute cholecystitis (an SAE) and resumed treatment following normalization of LFTs and resolution of acute cholecystitis.

At the end of the MP in Study 201584, 1 additional subject in CAB + RPV Q4W group reported at least 1 AE potentially related to hepatotoxicity (hepatic steatosis) since the Week 48 analysis (Data Source: GSK Doc. # 2019N421511_00 Table 3.137). This AE was not serious and did not lead to withdrawal (Data Source: GSK Doc. # 2019N421511_00 Table 3.21 and Table 3.31).

In Study 201585, during the Extension Phase no subjects were identified as having DILI. Two subjects in the CAB + RPV Q4W group met LSC:

- The subject had high ALT (9.1/ULN) and high AST (8.5/ULN) at Week 72 that met LSC but were not considered an SAE. The abnormal liver enzyme levels had resolved at the subsequent visit and the subject continued on study drugs. This subject tested positive for acute hepatitis E (Data Source: GSK Doc. # 2019N399072_00 Listing 141, Listing 142, and Listing 147).
- The subject had high ALT (31.3/ULN), high AST (18.3/ULN), and high total bilirubin (0.9/ULN) at Week 80 that were considered an SAE (acute hepatitis B). The liver chemistry elevation was likely caused by acute hepatitis B. The high ALT and AST did not resolve by the data cut-off for the Week 96 report, and the subject was discontinued from study drug during the Extension Phase. This subject also had

creatinine renal clearance decreased, diverticulum intestinal, and polyuria (Data Source: GSK Doc. # 2019N399072_00 Listing 141, Listing 142, Listing 147).

No AEs suggestive of hepatotoxicity were reported in the Extension Switch to CAB + RPV Q4W group in Study 201585, and no subjects met LSC.

Phase I/II Results

Monitoring of Liver Chemistry

In the Phase IIB studies, subjects that had LSC were adjudicated by hepatic experts to determine whether DILI criteria were met (Table 46).

Table 46 Details of Liver Stopping Events in Studies LAI116482 (End of Study) and 200056 (Week 160)

Study	Treatment Group	ALT	AST	Total Bilirubin	Resolved	Withdrew from Study	Reason for Meeting LSC[a]
LAI116482	CAB oral 60 mg	12xULN	7xULN	WNL	Y	Y	Steatohepatitis; CMV; RPR; Possible DILI
	CAB oral 60 mg	10xULN	5xULN	WNL	Y	Y	Steatohepatitis; Possible DILI
	CAB oral 30 mg + RPV oral 25 mg	23xULN	25xULN	WNL	N	Y	Acute hepatitis C
	CAB oral 10 mg + RPV oral 25 mg	20xULN	10xULN	WNL	Y	Y	Syphilitic hepatitis/ hepatitis E/anabolic steroids/supplement use
	EFV/TDF/FTC	12xULN	15xULN	WNL	Y	Y	Acute hepatitis C
200056	CAB oral 30 mg	7xULN	11xULN	2xULN	N/A	Y	Probable DILI, subject with chronic active hepatitis C and Grade 3 or 4 fibrosis
	CAB oral 30 mg	10xULN	8xULN	WNL	N/A	Y	Acute hepatitis C
	CAB oral 30 mg	18xULN	11xULN	1xULN	N/A	Y	Acute hepatitis C
	CAB oral 30 mg	8xULN	5xULN	WNL	N/A	Y	Acute hepatitis C
	CAB oral 30 mg	9xULN	6.4xULN	WNL	N/A	Y	Steatohepatitis; Probable DILI
	CAB + RPV	7.8xULN	3xULN	WNL	N/A	N	Hepatitis/ syphilis
	CAB + RPV	11xULN	6xULN	0.6xULN	N/A	N	Acute hepatitis C
	CAB + RPV	9.4xULN	9.9xULN	1.8xULN	Y	N	Acute hepatitis C, Restarted treatment
	CAB + RPV	10xULN	5.9xULN	WNL	N/A	Y	Acute hepatitis C, restarted treatment
	CAB + RPV	13.2 xULN	8.9xULN	0.8xULN	Y	N	Acute hepatitis C, restarted treatment
	CAB + RPV, Q8W	25.3 xULN	13.5xULN	0.7xULN	Y	N	Acute hepatitis C/ Syphilis reinfection, restarted treatment
	CAB + RPV, Q8W	13.4x ULN	11.5xULN	1.2xULN	Y	N	Acute hepatitis C, restarted treatment
	CAB + RPV, Q8W	8.3xULN	2.7xULN	WNL	Y	N	Acute hepatitis C, restarted treatment

Data Source: GSK Doc. # 2018N380094_00 Table 49; GSK Doc. # 2014N216014_00 Section 7.7.2.1; GSK Doc. # 2019N404586_00 Listing 8.6, Listing 8.10, Listing 8.12.
Note: Liver chemistry parameters represent peak values.
Note: Each row represents an individual subject.
a. As adjudicated by the hepatic expert committee.

No cases of drug-related hepatoxicity in subjects meeting LSC receiving CAB LA + RPV LA were identified in Phase II studies. Subjects that had LSC were

adjudicated by hepatic experts to determine whether DILI criteria were met. Of the subjects who met LSC in Phase II, 4 subjects receiving oral CAB met LSC for which no alternative etiology has been identified (Table 47). One additional subject from a clinical pharmacology study (Study 205712) also met LSC for which no alternative etiology has been identified. These 5 subjects receiving oral CAB were adjudicated by hepatic experts to have suspected DILI or hepatotoxicity. Although mild to moderate hepatotoxicity has been identified in these subjects, severe hepatotoxicity with significant liver dysfunction or liver failure [Aithal, 2011] has not been observed. The degree of ALT elevation in these subjects was either Grade 3 or Grade 4 in severity according to the grading scale for AEs and laboratory values developed and maintained by DAIDS. Aminotransferase elevations in these subjects have been transient and reversible.

In summary, 5 male subjects receiving oral CAB from Phase IIb (200056, LAI116482; n=4) and from a DDI study with rifabutin (205712, n=1) met LSC, and alternative etiologies for aminotransferase elevations were not identified. These subjects were suspected to have had DILI as adjudicated by hepatology experts. Three of the 5 subjects were on oral CAB 30 mg once daily and the remaining 2 were on oral CAB 60 mg.

Table 47 Cases of Suspected DILI in the Phase I/IIA CAB Development Program

Study: Subject Details	Treatment	Time to Onset (Weeks from first dose of CAB)	Peak ALT ULN, BILI ULN, Pattern of Injury, R (ALT/ULN to ALK P/ULN Ratio)	Severity [a]	Comments
200056: 50- to 60-year-old HIV-infected male	CAB 30 mg QD + ABC/3TC QD	5	7 2.4 Hepatocellular 7	Moderate	Total bilirubin elevation: 2.4xULN, 36% conjugated bilirubin. The subject had a prior history of chronic active hepatitis C with Grade 3/4 fibrosis. Whilst this is suspected to be a case of DILI, a hepatitis C flare in the setting of significant underlying liver disease is a possible alternative cause of the abnormal liver chemistry; however, since the hepatitis C viral load did not change significantly, DILI could not be excluded. This case triggered the previously described INDSR on 23 July 2014 (IND [redacted], [redacted], Serial No. [redacted]).
200056: 20- to 30-year-old HIV-infected male	CAB 30 mg QD + ABC/3TC QD	44	9 WNL Hepatocellular 7	Mild	Subject experienced mild asthenia from the beginning of the study. Peak ALT 9xULN, total bilirubin was within normal limits. Possible inadvertent rechallenge LSC occurred 44 days from restart. A hepatic ultrasound revealed infiltration of fat, consistent with hepatic steatosis.
LAI116482: 30- to 40-year-old HIV-infected male	CAB 60 mg QD + ABC/3TC QD	8	10.1 WNL Hepatocellular 12.6	Mild	Actin IgG – positive - 75 Units. Fatty infiltration on hepatic ultrasound; steatosis (30-% of parenchyma) and patch lobular inflammation on liver biopsy 2.5 months later.
LAI116482: 40- to 50-year-old HIV-infected male	CAB 60 mg QD + ABC/3TC QD	4	12 WNL Hepatocellular 15	Mild	Subject experienced a low-grade fever 4 weeks after the first dose of CAB. Peak ALT 12xULN, total bilirubin was within normal limits. CT scan of abdomen approximately 1.5 years before event showed mild fatty infiltration. Ultrasound imaging of the liver at the time of the event showed increased echogenicity of the liver consistent with fatty change.
205712 (Clinical pharmacology study): 50- to 60-year-old healthy, obese male	CAB 30 mg QD + RBT 300 mg QD	7	8.34 WNL Mixed hepatocellular and cholestatic 7	Mild	Subject developed a mixed hepatocellular and cholestatic picture of hepatitis 3 weeks after administration of CAB and rifabutin ended (Period 2) during the follow up phase. Peak ALT elevation was 8.3xULN with total bilirubin within normal limits. (ALT/ULN to ALK P/ULN Ratio) = 7 indicating a predominant hepatocellular pattern. Liver workup was unremarkable except for a fatty liver on liver ultrasound and the subject was asymptomatic without a history of recreational drug or alcohol exposure. The transaminitis fully resolved.

a. Aithal, 2011.

Conclusion

Hepatotoxicity has been observed with INSTIs, including CAB.

No cases of DILI in subjects meeting LSC receiving CAB LA or RPV LA have been identified to date. Six cases of possible/probable DILI in subjects receiving oral CAB have been identified; 5 in Phase I/II studies and 1 in Phase IIIB Study 207966.

In Studies 201584 and 201585, more subjects receiving CAB + RPV Q4W (n=10) had acute viral hepatitis than those receiving CAR (n=3) at the Week 48 analysis. In Study 207966 at the Week 48 analysis, 4 of the 5 subjects who met LSC had acute viral hepatitis infections.

Elevated aminotransferases have been observed with exposure to CAB + RPV.

2.1.6.3. Hypersensitivity Reactions

Week 48 Phase III/IIIB Results

No cases of HSR have been observed following exposure to CAB during the CAB + RPV development program. No subjects were excluded from treatment with CAB LA and RPV LA because of suspected HSR during the OLI.

In Studies 201584 and 201585, 13 subjects in the pooled analysis (7 in the CAB + RPV Q4W treatment group and 6 in the CAR treatment group) reported AEs potentially associated with symptoms that may occur during a delayed-type hypersensitivity response (Table 48). The following AEs were considered to be related to study drug: lip swelling (1 subject in the CAB + RPV Q4W group) and eosinophilia (1 subject in the CAB + RPV Q4W group; 2 subjects in the CAR group) (Data Source: ISS/ISE Table 3.25). All AEs were Grade 1 or 2 in severity; no Grade 3 or 4 AEs were reported. No SAEs of HSR were reported. None of the events resulted in withdrawal of study treatment or withdrawal from the study (Data Source: ISS/ISE Table 3.36).

Table 48 AEs Potentially Associated with Hypersensitivity in Studies 201584, 201585 and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
AE PT	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)
Eosinophilia	3 (1)	2 (<1)	0	1 (<1)	3 (<1)	3 (<1)
Hypersensitivity	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Drug hypersensitivity	0	0	1 (<1)	0	1 (<1)	0
Eyelid edema	0	0	0	2 (<1)	0	2 (<1)
Eye swelling	0	0	1 (<1)	0	1 (<1)	0
Lip swelling	0	0	1 (<1)	0	1 (<1)	0

Data Source: ISS/ISE Table 3.40.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, 5 subjects (<1%) in the Q8W group and 6 subjects (1%) in the Q4W group reported at least 1 AE potentially associated with hypersensitivity (Data Source: GSK Doc. # 2019N406358_01 Table 3.68). A list of PTs (with VT) by subject for AEs potentially associated with hypersensitivity is provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.3.

An AE of injection site hypersensitivity in the Q8W group (see next paragraph) and 1 report of hypersensitivity in the Q4W group (summarized in Section 2.1.7) were considered related to study drug (Data Source: GSK Doc. # 2019N406358_01 Table 3.12). With 1 exception (summarized in Section 2.1.7), all AEs potentially associated with hypersensitivity were ≤Grade 2 (Data Source: GSK Doc. # 2019N406358_01 Table 3.6).

A nonserious AE of injection site hypersensitivity led to withdrawal of 1 subject (<1%) in the Q8W group; otherwise, with the exception of the case described in Section 2.1.7, there were no SAEs potentially associated with hypersensitivity (Data Source: GSK Doc. # 2019N406358_01 Table 3.16) or AEs potentially associated with hypersensitivity that led to withdrawal (Data Source: GSK Doc. # 2019N406358_01 Table 3.22).

The injection site hypersensitivity that led to withdrawal was nonserious, Grade 2, and considered to be related to study drug (GSK Doc. # 2019N406358_01 Section 7.1.5.3.3). The subject reported swelling and erythema overlying both injection sites that commenced 1 to 2 hours after the Week 48 injections. The subject also experienced a raised temperature and felt unwell for 24 to 48 hours. The subject did not seek medical advice at the time and reported these symptoms when reviewed at Week 56. The subject also reported mild symptoms (swelling, erythema, and fever) following the Week 40 injection. Based upon these reports, the investigator considered the constellation of symptoms possibly allergic in nature. This subject had a history of atopy and pollen and nut allergies and had previously taken oral RPV without any reported problems.

Longer-term Phase III Results

At the end of the MP in Study 201584, no additional subjects reported AEs potentially related to hypersensitivity since the Week 48 analysis (Table 48 and Data Source: GSK Doc. # 2019N421511_00 Table 3.140).

In Study 201585, 2 AEs suggestive of possible hypersensitivity reactions were reported during the Extension Phase in subjects in the CAB + RPV Q4W arm. One AE of drug hypersensitivity (allergic drug rash; Grade 1) and 1 AE of hypersensitivity vasculitis (leukozytoclastic vasculitis of the skin due to amoxicillin; Grade 1) were reported (Data Source: GSK Doc. # 2019N399072_00 Listing 109). Neither event was considered serious, related to study drug, or led to withdrawal from the study.

No AEs related to hypersensitivity reactions were reported in the Extension Switch to CAB + RPV Q4W group in Study 201585.

Conclusion

Hypersensitivity reactions have been reported as uncommon occurrences with other INSTIs than CAB, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure.

No cases of HSR have been observed following exposure to CAB during the CAB + RPV development program. No subjects were excluded from treatment with CAB LA and RPV LA because of suspected HSR during the OLI. Delayed-type HSR has not been reported with CAB + RPV to date.

2.1.6.4. Rash

For rash AESIs monitored as part of the CAB + RPV development program, any events related to a rash were identified by searching for PTs containing the words "rash," "eruption," "photosensitivity," or "urticaria," such as rash erythematous, rash generalized, rash papular, rash pruritic, toxic skin eruption, photosensitivity, and urticarial where these terms were classified as Grade 3 or 4 in severity.

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, there were no Grade 3 or 4 rashes observed; therefore, an analysis of rash AESIs for these studies was not produced (Data Source: ISS/ISE Table 3.41). At the Week 48 analysis in these studies, rash AESIs (i.e., identified using key words as described above) were reported in 23 subjects in the CAB + RPV Q4W group and 14 subjects in the CAR group (Data Source: GSK Doc. # 2017N345267_00 Section 7.3.3.1.4; GSK Doc. # 2018N370336_00 Section 7.3.3.1.4). There were no serious reports in the database for severe rash with terms that included Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme.

No rash AESIs were considered serious, 10 rash AESI reports were considered to be drug-related (9 CAB + RPV Q4W, 1 CAR), and none led to withdrawal of study drug.

AEs potentially of interest for "rash" are included in the Skin and subcutaneous tissue disorders System Organ Class. A higher proportion of subjects' AEs were reported in the CAB + RPV Q4W treatment group (CAB + RPV Q4W, n=83 [14%]; CAR, n=54 [9%]) for this System Organ Class (Data Source: ISS/ISE Table 3.12). Except for the PT of "rash," which was reported at 3% in the CAB + RPV Q4W group, all other AE PTs for this System Organ Class in both treatment groups were reported at ≤2%. All AEs in both treatment groups were Grade 1 or Grade 2, with the exception of one Grade 3 AE of night sweats in the CAB + RPV Q4W group (Data Source: ISS/ISE Table 3.20).

Drug-related AEs reported in the Skin and subcutaneous tissue disorders System Organ Class were experienced by 11% of subjects in the CAB + RPV Q4W group and by 10% of subjects in the CAR group (Data Source: ISS/ISE Table 3.25). All drug-related AEs (acne, eczema, neurodermatitis, rash) were Grade 1; no Grade 2 to 4 drug-related AEs were reported.

In Study 207966, there were no Grade 3, 4, or 5 AEs potentially associated with rash (Data Source: GSK Doc. # 2019N406358_01 Table 3.84). A total of 11 subjects (2%) in the Q8W group and 21 subjects (4%) in the Q4W group reported at least 1 'rash' AE (Data Source: GSK Doc. # 2019N406358_01 Table 3.69). None were serious although 1 subject in the Q8W group was withdrawn due to rash maculo-papular (Data Source: GSK Doc. # 2019N406358_01 Table 3.84 and Table 3.22). Additional details are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.4.

Longer-term Phase III Results

At the end of the MP in Study 201584, an AE potentially related to rash occurred in 14 (5%) subjects in the CAB + RPV Q4W group and 16 (6%) subjects in the CAR group (GSK Doc. # 2019N421511_00 Section 7.3.3.1.4). Since the Week 48 analysis, 2 subjects in the CAB + RPV Q4W group and 6 subjects in the CAR group had a rash event (all Grade 1 or 2). No rash events led to withdrawal/permanent discontinuation of study drug or were SAEs.

In Study 201585, one Grade 1 rash was reported in the CAB + RPV Q4W group during the Extension Phase (Data Source: GSK Doc. # 2019N399072_00 Table 13.22; Listing 109). It did not resolve by the time of data cut off for the Week 96 report. The rash AE was not considered to be related to study treatment and did not lead to discontinuation.

Two Grade 1 rashes were reported in the Extension Switch to CAB + RPV Q4W group in Study 201585 (Data Source: GSK Doc. # 2019N399072_00 Table 13.23; Listing 109). One was considered to be related to study treatment and it resolved after 4 days; the second rash was not considered to be related to study treatment and resolved after 4 days; neither AE led to withdrawal from the study drug.

Conclusion

Grade 1 and 2 rash has been reported with treatment with CAB +RPV. In Studies 201584 and 201585, the incidence of rash with CAB + RPV Q4W was comparable to CAR. Most events did not lead to withdrawal. No rash event was considered serious. Rash is an ADR for oral RPV.

2.1.6.5. QT Prolongation

The effects of each drug individually and together on QT prolongation were evaluated as part of the CAB + RPV development program. During the CAB + RPV development program, subjects using medications that are associated with TdP were excluded.

Results from ECG analyses are presented in Section 4.3.

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, 5 AEs potentially related to QT prolongation (4 in the CAB + RPV Q4W group, 1 in the CAR group) were reported (Data Source: ISS/ISE Table 3.42). These reported AEs were 'electrocardiogram QT prolonged'

(3 subjects in CAB + RPV Q4W group, 1 subject in the CAR group) and 'electrocardiogram repolarization abnormality' (1 subject in CAB + RPV Q4W group).

Study 201584 (Data Source: GSK Doc. # 2017N345267_00 Table 3.8, Listing 62, and Listing 63):

- One subject in the CAR group had an AE of "electrocardiogram QT prolonged (QTc elevation)." The AE was Grade 1 and was not considered by the investigator to be study drug related. QTcF interval was <500 msec at Maintenance Baseline (Day 1) and Week 48.
- One subject in the CAB + RPV Q4W group had an AE of "electrocardiogram repolarization abnormality (syndrome proleptic repolarization of ventricle)." The event was Grade 1 and was not considered by the investigator to be study drug related. Corrected QTcF was <500 msec at Maintenance Baseline (Day 1) and at Week 48.

Study 201585 (Data Source: GSK Doc. # 2018N370336_00 Table 3.8, Listing 57, Listing 58):

- One subject in the CAB + RPV Q4W group had a Grade 1 AE of "electrocardiogram QT prolonged" that was not considered to be related to study drug. QTcF interval was <500 msec.
- One subject in the CAB + RPV Q4W group had a Grade 1 AE of "electrocardiogram QT prolonged" that was considered to be study drug related. QTcF interval was <500 msec.
- One subject in the CAB + RPV Q4W group had a Grade 2 AE of "electrocardiogram QT prolonged" that was considered to be study drug related. QTcF interval was <500 msec; the subject had a mixture of QTcF and QTc unspecified.

Additionally, some subjects had AEs of syncope or loss of consciousness. None were serious or led to withdrawal and all had either QTcF or QTc unspecified <500 msec.

- In Study 201584, 5 subjects had AEs of syncope (Data Source: GSK Doc. # 2017N345267_00 Listing 62 and Listing 63). All AEs of syncope were Grade 1 or 2 in severity.
    - 3 subjects receiving CAB + RPV Q4W had AEs of syncope. 1 event was considered drug related and 2 events were considered not drug related. One subject with syncope that was not drug related had 3 episodes.
    - 2 subjects receiving CAR had AEs of syncope. All of these AEs occurred during the Induction Period and were considered not drug related.
- In Study 201585, 3 subjects had AEs of syncope and 1 subject had AE of loss of consciousness (Data Source: GSK Doc. # 2018N370336_00 Listing 57 and Listing 58). All were Grade 1 or 2 in severity.
    - 3 subjects had AEs of syncope. Two subjects were receiving CAB + RPV Q4W, and 1 subject was receiving CAR. All of the AEs of syncope were not drug related.

- 1 subject had an AE of loss of consciousness and was receiving CAB + RPV Q4W; the AE was not drug related.

None of these AEs indicate any clinically relevant effect of CAB + RPV on the QT interval.

In Study 207966, no AEs potentially related to QT prolongation have been reported (Data Source: GSK Doc. # 2019N406358_01 Table 3.70). Results from a broader search for AEs potentially related to TdP/QT prolongation included cardio-respiratory arrest in 1 subject in the Q8W group and syncope in 3 subjects in the Q4W group (Data Source: GSK Doc. # 2019N406358_01 Listing 57). The subject in the Q8W group died due to sepsis, a complication of acute pancreatitis (Section 2.1.2); there were no ECG values of potential clinical importance for this subject (Data Source: GSK Doc. # 2019N406358_01 Listing 23). AEs related to syncope are briefly summarized in Section 2.1.6.7 with additional details provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.7. None of these AEs were serious or led to withdrawal. Of the 3 subjects with syncope, none had any ECG values of potential clinical importance (Data Source: GSK Doc. # 2019N406358_01 Listing 23).

In Study 207966, isolated instances of QTcF intervals >500 msec or changes from Baseline >60 msec were observed in single subjects; no patterns were observed. Results from ECG analyses are presented in Section 4.3.

Longer-term Phase III Results

At the end of the MP in Study 201584, no additional subjects reported AEs potentially related to QT prolongation since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.5).

In Study 201585, no AEs of QT prolonged were reported during the Extension Phase (Data Source: GSK Doc. # 2019N399072_00 Listing 145).

Thorough QTc Study with Oral CAB

In a TQTc study (Study LAI117009; GSK Doc. # 2014N208600_00) evaluating a supratherapeutic dose of oral CAB 150 mg (30 mg x 5 tablets) every 12 hours x 3 doses, CAB had no significant effect on cardiac repolarization in healthy subjects. Administration of CAB 150 mg every 12 hours x 3 doses yielded a geometric mean plasma CAB Cmax of 22.5 µg/mL, which is approximately 3-fold the Cmax following oral CAB 30 mg once daily and 5-fold the Cmax following CAB LA 400 mg IM once monthly. The CAB plasma concentrations from CAB LA + RPV LA every 4 weeks are consistent with those observed with oral CAB 10 mg once daily (see Section 5.5.1 for details).

Conclusion

Treatment with CAB + RPV did not have clinically relevant effects on the QT interval.

2.1.6.6. Neuropsychiatric Adverse Events

Neuropsychiatric AESIs for CAB + RPV comprised suicidal ideation/behavior, depression, anxiety, mood disorders, bipolar disorder, psychosis, and sleep disorders.

DTG (an INSTI compound related to CAB) has been associated with reports of depression and suicidal ideation and/or behavior in HIV-infected patients. Depression is an ADR for RPV. Therefore, depression and suicidal ideation are AESIs in the CAB + RPV development program.

Mood and sleep disorders are common in the HIV-infected population. These include irritability, insomnia, and abnormal dreams. DTG (an INSTI closely related to CAB) is associated with reports of mood (anxiety) and sleep disorders (abnormal dreams and insomnia).

Week 48 Phase III/IIIB Results

Past History of Depression, Anxiety, and Suicidal Ideation/Behavior

Some of the subjects had a past history of psychiatric illness and specifically for the categories of depression, anxiety, and suicidal ideation, those with histories of the disorders had a higher incidence reported during the studies, suggesting that, in some cases, the reported events may have represented recurrence of a former condition (Table 49).

In Study 207966, of subjects with a prior history of anxiety, a larger proportion of subjects in the Q8W group (17%) had an AE related to anxiety compared with subjects in the Q4W group (4%); however, randomization was not stratified by past history of psychiatric illness. In addition, it should be noted that there was a small number of subjects with a prior history of anxiety, and as such, these results should be interpreted with caution. Furthermore, in pooled Studies 201584 and 201585, 12% of subjects in the CAB + RPV Q4W group with a prior history of anxiety had a treatment-emergent AE related to anxiety. In contrast, in the Q4W group in Study 207966, 4% of subjects with a prior history of anxiety had a treatment-emergent AE related to anxiety. These results suggest that there may be a high level of variability of recurrence of anxiety AEs among studies.

Of the 36 subjects with anxiety-related AEs in Study 207966, none were serious, all were Grade 1 or Grade 2, none led to discontinuation of study drug, and 4 subjects (all Q8W) had AEs considered to be related to study drug (Data Source: GSK Doc. # 2019N406358_01 Table 3.84). When AEs possibly related to anxiety are analyzed regardless of past history, the incidence is similar between treatment groups (Q8W: 4%; Q4W: 3%; Table 50).

Table 49 Summary of Post-Baseline Depression, Anxiety, or Suicidal Ideation by Prior History of Depression, Anxiety, or Suicidal Ideation in Studies 201584+201585 Pooled and 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

	Pooled Studies 201584 and 201585				Study 207966			
	With Prior History		With No Prior History		With Prior History		With No Prior History	
Past History of:	CAB + RPV Q4W N=591 n/N (%)	CAR N=591 n/N (%)	CAB + RPV Q4W N=591 n/N (%)	CAR N=591 n/N (%)	CAB + RPV Q8W N=522 n/N (%)	CAB + RPV Q4W N=523 n/N (%)	CAB + RPV Q8W N=522 n/N (%)	CAB + RPV Q4W N=523 n/N (%)
Depression[a]	3/86 (3%)	5/82 (6%)	13/505 (3%)	9/509 (2%)	5/83 (6)	7/108 (6)	7/439 (2)	7/415 (2)
Anxiety[b]	8/66 (12%)	7/88 (8%)	19/525 (4%)	13/503 (3%)	13/77 (17)	4/92 (4)	9/445 (2)	10/431 (2)
Suicidal Ideation[c]	2/23 (9%)	0/26	2/568 (<1%)	5/565 (<1%)	0/18	0/19	1/504 (<1)	0/504

Data Source: ISS/ISE Table 3.151; GSK Doc. # 2019N406358_01 Table 3.66 and m5.3.5.3, Table 3.98.

Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

a. Includes Depression, Depressed mood, Adjustment disorder with depressed mood, Major depression.

b. Includes Anxiety, Anxiety disorder, Panic attack, Acute stress disorder, Nervousness, Stress, Tension.

c. Includes Suicidal ideation, Intentional self-injury, Suicide attempt, Suicidal behavior, Depression suicidal.

All Neuropsychiatric AESIs

Neuropsychiatric AESIs occurring in >1% of subjects in all treatment groups in Studies 201584, 201585, and 207966 were those potentially related to depression, anxiety, or sleep disorders (Table 50). All other neuropsychiatric AESIs occurred in ≤1% of subjects in all treatment groups.

Table 50 Summary of Neuropsychiatric AESIs in Studies 201584+201585 Pooled and 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

	Pooled Studies 201584 and 201585		Study 207966	
Neuropsychiatric AESI	CAB + RPV Q4W N=591 N (%)	CAR N=591 N (%)	CAB + RPV Q8W N=522 N (%)	CAB + RPV Q4W N=523 N (%)
Suicidal Ideation and Behavior	4 (<1)	5 (<1)	1 (<1)	0
Depression	16 (3)	14 (2)	12 (2)	14 (3)
Anxiety	27 (5)	20 (3)	22 (4)	14 (3)
Mood Disorders	7 (1)	1 (<1)	4 (<1)	2 (<1)
Bipolar Disorder	0	0	1 (<1)	0
Psychosis	1 (<1)	0	1 (<1)	0
Sleep Disorders	38 (6)	21 (4)	22 (4)	36 (7)

Data Source: ISS/ISE Table 3.43, Table 3.44, Table 3.45, Table 3.46, Table 3.47, Table 3.48, and Table 3.49; GSK Doc. # 2019N406358_01 Table 3.71, Table 3.72, Table 3.73, Table 3.74, Table 3.75, Table 3.76, and Table 3.77.

For pooled Studies 201584 and 201585 (Week 48 results), neuropsychiatric AESIs are summarized below by category.

For Study 207966, neuropsychiatric AESIs are presented in GSK Doc. # 2019N406358_01 Section 7.1.5.3.6; SAEs and AEs leading to withdrawal are summarized below by category. For any that met SAE criteria, full case narratives are provided in GSK Doc. # 2019N406358_01 Section 13.

Suicidal Ideation

Week 48 Phase III/IIIB Results

No completed suicides occurred during Studies 201584, 201585, and 207966.

In Studies 201584 and 2015854, <1% subjects in each treatment group had at least 1 AE potentially related to suicidal ideation or behavior (Table 50). Most of the AEs were Grade 1 (2 CAB +RPV; 1 CAR) or Grade 2 (2 CAB + RPV Q4W; 2 CAR) intensity. 1 subject in the CAB + RPV Q4W group had an AE of suicidal depression that was considered to be related to study drug and was subsequently discontinued from the study. 2 AEs in the CAR group were Grade 3; these 2 subjects had no prior history of suicidal ideation (Data Source: ISS/ISE Table 3.151). One of the Grade 3 AEs of suicidal

ideation was considered to be an SAE and related to study drug. This subject also experienced Grade 3 AEs of anxiety and depression (Data Source: ISS/ISE Table 3.25); see Study 201585 CSR for details.

2 subjects in the CAR group had SAEs of suicidal ideation (n=1) and suicide attempt (n=1) (Data Source: ISS/ISE Table 3.33). 3 subjects withdrew from study drug due to AEs of suicidal ideation (n=1, CAR group), suicide attempt (n=1, CAR group), and depression suicidal (n=1, CAB + RPV Q4W group) (Data Source: ISS/ISE Table 3.36).

An analysis of treatment effect on suicidal ideation indicated that there was no significant difference between treatment groups (Data Source: ISS/ISE Table 3.156). Onset, duration, and severity of suicidal ideation AEs in pooled Studies 201584 and 201585 are presented in Data Source: ISS/ISE Figure 3.22.

In pooled Studies 201584 and 201585, based on analyses of the eC-SSRS, a low proportion of subjects (CAB +RPV: 5%; CAR: 6%) in each treatment group reported any suicidal ideation or behavior and 9 subjects (3 CAB +RPV; 6 CAR) had positive PSRAEs; a summary of potential treatment-emergent suicidality using the eC-SSRS is presented in Section 4.4.

In Study 207966, there were no SAEs or AEs leading to withdrawal that were potentially related to suicidal ideation or behavior in either treatment group. Based on analyses of the eC-SSRS, a low proportion of subjects (Q8W: 2%; Q4W: 4%) in each treatment group reported any suicidal ideation or behavior and 2 subjects (1 Q8W; 1 Q4W) had positive PSRAEs; a summary of potential treatment-emergent suicidality using the eC-SSRS is presented in Section 4.4.

Longer-term Phase III Results

At the end of the MP in Study 201584, there were no additional subjects who reported AEs potentially related to suicidal ideation or behavior since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6).

In Study 201585, there were no additional subjects who reported AEs potentially related to suicidal ideation or behavior in either the Safety or Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.22 and Table 13.23).

Conclusion

Suicidality assessments were collected prospectively during Phase III studies (Section 4.4). Validated true positive alerts for suicidality assessments occurred at lower incidence in the CAB+RPV group compared with the CAR group during Phase 3 studies. Serious events potentially related to suicidal ideation or behavior were reported at low incidence with treatment with CAB + RPV. The incidence was comparable to CAR during Studies 201584 and 201585. Suicidal ideation and behavior is not considered attributable to treatment with CAB+RPV. The onset of these events appeared to be early in treatment with CAB + RPV Q4W during Studies 201584 and 201585. In most cases treatment with CAB + RPV was continued without interruption. In a few cases treatment with CAB + RPV was interrupted or withdrawn.

Depression

Week 48 Phase III/IIIB Results

During Studies 201584 and 201585, a similar proportion of subjects in both treatment groups reported at least 1 AE potentially related to depression (Table 50).

5 subjects in the CAB + RPV Q4W group had depression AEs that were considered study drug-related (Data Source: ISS/ISE Table 3.62). Most of the AEs of depression were Grade 1 (8 subjects in the CAB + RPV Q4W group; 6 subjects in the CAR group) or Grade 2 (8 CAB + RPV Q4W; 7 CAR). Additionally, 1 subject in the CAR group with no prior history of depression had a Grade 3 AE of depression that was considered to be related to study drug and led to discontinuation from the study (Data Source: ISS/ISE Table 3.151; ISS/ISE Table 3.36). None of the depression AEs were considered serious (Data Source: ISS/ISE Table 3.62).

An analysis of treatment effect on depression indicated that there was no significant difference between treatment groups (Data Source: ISS/ISE Table 3.156). Onset, duration, and severity of depression AEs in pooled Studies 201584 and 201585 are presented in Data Source: ISS/ISE Figure 3.22.

In Study 207966, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to depression (Table 50). There was 1 subject in the Q8W group who had an SAE of major depression (considered not related to study drug) that did not lead to withdrawal (GSK Doc. # 2019N406358_01 Section 7.1.5.3.6). The same subject had a concurrent SAE of substance-induced psychotic disorder. Also, 1 subject in the Q4W group had an AE of depression considered related to study drug that led to withdrawal.

Longer-term Phase III Results

At the end of the MP in Study 201584, since the Week 48 analysis, there were 2 new AEs of depression, both considered related to study drug, which resulted in withdrawal from the study (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6). Neither was serious (Data Source: GSK Doc. # 2019N421511_00 Table 3.21).

In Study 201585, there were additional reports of depression and/or depressed mood AEs in both the Safety and Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.22 and Table 13.23). None were SAEs or led to withdrawal (Data Source: GSK Doc. # 2019N399072_00 Table 13.10, Table 13.11, Table 13.15, and Table 13.16).

Conclusion

Events of depression were reported with treatment with CAB + RPV with a low incidence. The incidence of events was comparable to CAR during Studies 201584 and 201585. There was 1 CAB + RPV subject with an SAE of depression. Most events did not lead to withdrawal. Depression is an ADR for treatment with CAB+RPV.

Anxiety

Week 48 Phase III/IIIB Results

During Studies 201584 and 201585, a similar proportion of subjects in both treatment groups reported at least 1 AE potentially related to anxiety (Table 50). Most of these were reported as anxiety; other anxiety-related terms included stress, acute stress disorder, panic attack, anxiety disorder, nervousness, panic disorder, and tension (each <1%) (Data Source: ISS/ISE Table 3.48).

Most AEs reported were Grade 1 (18 subjects in the CAB + RPV Q4W group; 13 subjects in the CAR group) or Grade 2 (8 subjects in the CAB + RPV Q4W group; 5 subjects in the CAR group) (Data Source: ISS/ISE Table 3.66 and Table 3.151). 2 AEs of Grade 3 anxiety occurred in the CAR group in subjects with a previous history of anxiety; one of these Grade 3 events was considered to be related to study drug and resulted in withdrawal from the study (see Study 201585 CSR for details). AEs of anxiety were considered to be related to study drug in 10 other subjects (8 CAB + RPV Q4W; 2 CAR) (Data Source: ISS/ISE Table 3.66). No Grade 4 or Grade 5 events of anxiety occurred in Studies 201584 and 201585.

There were no SAEs of anxiety reported in Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.66). 1 subject in the CAB + RPV Q4W group and 1 subject in the CAR group withdrew from study due to AEs of anxiety or anxiety disorder (Data Source: ISS/ISE Table 3.36 and Table 3.66).

An analysis of treatment effect on anxiety indicated that there was no significant difference between treatment groups in Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.156). Onset, duration, and severity of anxiety AEs in pooled Studies 201584 and 201585 are presented in Data Source: ISS/ISE Figure 3.22.

In Study 207966, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to anxiety (Table 50). There were no SAEs or AEs leading to withdrawal that were potentially related to anxiety in either treatment group (GSK Doc. # 2019N406358_01 Section 7.1.5.3.6).

Longer-term Phase III Results

At the end of the MP in Study 201584, there were no additional subjects who reported AEs potentially related to anxiety since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6).

In Study 201585, there were additional reports of AEs potentially related to anxiety in the Safety Population but not in the Extension Switch Population (Data Source: GSK Doc. # 2019N399072_00 Table 13.22 and Table 13.23). There were no SAEs that were potentially related to anxiety in either the Safety or Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.10 and Table 13.11). In the Safety Population, 1 subject had an AE of fear (considered related to study drug) that led to withdrawal (Data Source: GSK Doc. # 2019N399072_00 Table 13.15, Listing 108).

No subjects in the Extension Switch Population had an AE potentially related to anxiety that led to withdrawal (Data Source: GSK Doc. # 2019N399072_00 Table 13.16).

Conclusion

Anxiety has been reported at a low incidence with treatment with CAB + RPV. In Studies 201584 and 201585, the incidence of anxiety with CAB + RPV Q4W was comparable to CAR. Most events did not lead to withdrawal. Anxiety is an ADR for CAB+RPV.

Mood Disorders

Week 48 Phase III/IIIB Results

During Studies 201584 and 201585, a similar proportion of subjects in both treatment groups reported at least 1 AE potentially related to mood disorder (Table 50). These AEs included affect lability (n=2), affective disorder (n=1), irritability (n=1), mood altered (n=1), and mood swings (n=1) in the CAB + RPV Q4W group; and lethargy (n=2; 1 CAB + RPV Q4W, 1 CAR) (Data Source: ISS/ISE Table 3.47).

All mood disorder AEs were either Grade 1 or Grade 2 in intensity (Data Source: ISS/ISE Table 3.27). AEs of mood disorder were considered to be related to study drug in 3 subjects in the CAB + RPV Q4W group and 1 subject in the CAR group (Data Source: ISS/ISE Table 3.25).

No SAEs and no withdrawals due to AEs of mood disorder were reported in Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.33 and Table 3.36). Onset, duration, and severity of mood disorders AEs in pooled Studies 201584 and 201585 are presented in Data Source: ISS/ISE Figure 3.22.

In Study 207966, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to mood disorders (Table 50). There were no SAEs or AEs leading to withdrawal potentially related to mood disorders reported in either treatment group (GSK Doc. # 2019N406358_01 Section 7.1.5.3.6).

Longer-term Phase III Results

At the end of the MP in Study 201584, there were no additional subjects who reported AEs potentially related to mood disorders since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6).

In Study 201585, there was an additional report of an AE potentially related to mood disorders (irritability) in the Extension Switch Population but none in the Safety Population (Data Source: GSK Doc. # 2019N399072_00 Table 13.23 and Table 13.22). There were no SAEs or AEs leading to withdrawal that were potentially related to mood disorders in either the Safety or Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.10, Table 13.11, Table 13.15, and Table 13.16).

Conclusion

Events of mood disorders were reported at a low incidence with treatment with CAB + RPV. The incidence was higher compared with that of the CAR group during Studies 201584 and 201585 although the incidence of drug-related events was comparable. There were no serious events of mood disorders with CAB + RPV during Phase III/IIIB studies. Severity was generally Grade 1 or Grade 2. Mood disorder events did not lead to withdrawal. Mood disorders are not considered attributable to treatment with CAB+RPV.

Bipolar Disorder

Week 48 Phase III/IIIB Studies

During Studies 201584 and 201585, no subjects reported an AE potentially related to bipolar disorder (Table 50).

In Study 207966, 1 subject in the Q8W group had an SAE of bipolar disorder (considered not related to study drug) that did not lead to withdrawal (GSK Doc. # 2019N406358_01 Section 7.1.5.3.6). No AEs potentially related to bipolar disorder were reported in the Q4W group.

Longer-term Phase III Results

At the end of the MP in Study 201584, there were no additional subjects who reported AEs potentially related to bipolar disorder since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6).

In Study 201585, there were no additional subjects who reported AEs that were potentially related to bipolar disorder in either the Safety or Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.22, Table 13.23).

Conclusion

One SAE associated with bipolar disorder was reported; it was not considered related to study drug. Bipolar disorders are not considered attributable to treatment with CAB + RPV.

Psychosis

Week 48 Phase III/IIIB Results

During Studies 201584 and 201585, 1 subject reported at least 1 AE potentially related to psychosis (Table 50). This was a subject in the CAB + RPV Q4W group who had an AE of paranoia (Grade 1), which was considered related to study drug (Data Source: ISS/ISE Table 3.25, Table 3.27, and Table 3.46). This case was not an SAE and did not lead to discontinuation (Data Source: ISS/ISE Table 3.33 and Table 3.36). See Study 201584 CSR for more details.

In Study 207966, 1 subject in the Q8W group had an SAE of substance-induced psychotic disorder (considered not related to study drug) that did not lead to withdrawal (GSK Doc. # 2019N406358_01 Section 7.1.5.3.6). The same subject had a concurrent SAE of major depression. No AEs potentially related to psychosis were reported in the Q4W group.

Longer-term Phase III Results

At the end of the MP in Study 201584, there were no additional subjects who reported AEs potentially related to psychosis since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6).

In Study 201585, there were no additional subjects who reported AEs that were potentially related to psychosis in either the Safety or Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.22, Table 13.23).

Conclusion

Two events potentially related to psychosis, 1 assessed as related to study drug, were reported with treatment with CAB + RPV; neither led to withdrawal. Psychosis is not considered attributable to treatment with CAB+RPV.

Sleep Disorders

Week 48 Phase III/IIIB Results

During Studies 201584 and 201585, a similar proportion of subjects in both treatment groups reported at least 1 AE potentially related to sleep disorder (Table 50). Most of these AEs were insomnia, which was reported in 22 (4%) subjects in the CAB + RPV Q4W group and 8 (1%) subjects in the CAR group (Data Source: ISS/ISE Table 3.49). Other events (each ≤1%) included abnormal dreams, sleep disorder, nightmare, somnolence, poor quality sleep, and sleep apnea syndrome. All but 1 subject had a sleep disorder AE with a maximum intensity of Grade 1 or Grade 2; 1 subject in the CAB + RPV Q4W group had a sleep disorder AE that was Grade 3 (Data Source: ISS/ISE Table 3.67). In 18 subjects in the CAB + RPV Q4W group and 5 subjects in the CAR group, AEs of sleep disorder were considered to be related to study drug. No SAEs and no withdrawals due to AEs of sleep disorders were reported in Studies 201584 and 201585. Onset, duration, and severity of sleep disorder AEs in pooled Studies 201584 and 201585 are presented in Data Source: ISS/ISE Figure 3.22.

In Study 207966, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to sleep disorders (Table 50). A total of 1 subject in the Q4W group had an SAE of sleep apnea (considered not related to study drug) that did not lead to withdrawal, and 2 subjects in the Q4W group withdrew due to sleep disorders that were considered related to study drug (GSK Doc. # 2019N406358_01 Section 7.1.5.3.6):

- 1 due to abnormal dreams and sleep disorder (as well 9 other AEs that led to withdrawal) (Data Source: GSK Doc. # 2019N406358_01 Listing 17).

- 1 due to abnormal dreams and insomnia (as well 5 other AEs that led to withdrawal) (Data Source: GSK Doc. # 2019N406358_01 Listing 17).

Longer-term Phase III Results

At the end of the MP in Study 201584, there were no additional subjects who reported AEs potentially related to sleep disorders since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.6).

In Study 201585, there were additional reports of AEs potentially related to sleep disorder in both the Safety and Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.22 and Table 13.23). There were no SAEs or AEs leading to withdrawal that were potentially related to sleep disorders in either the Safety or Extension Switch Populations (Data Source: GSK Doc. # 2019N399072_00 Table 13.10, Table 13.11, Table 13.15, and Table 13.16).

Conclusion

Events of sleep disorders were reported with treatment with CAB + RPV. The incidence of events (including drug-related events), particularly insomnia, was higher in the CAB + RPV Q4W group compared with CAR during Studies 201584 and 201585. There was 1 SAE potentially related to sleep disorders with CAB + RPV that was not considered related to study drug and did not lead to withdrawal. Severity was generally Grade 1 or Grade 2. Insomnia and abnormal dreams are ADRs for treatment with CAB + RPV.

2.1.6.7. Seizures and Seizure-like Events

There is no convincing evidence from the CAB + RPV development program that CAB exposure is associated with seizure or with reduction of seizure threshold.

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, 6 (1%) subjects in the CAB + RPV Q4W group and 2 (<1%) subjects in the CAR group had AEs potentially associated with seizure (Data Source: ISS/ISE Table 3.38). The events of syncope and loss of consciousness are further described under QT prolongation (Section 2.1.6.5). None of these events were considered to be seizures, were not serious, and did not lead to withdrawal. Most were Grade 1 or 2 (one Grade 3 event of seizure occurred in the CAR group in Study 201585 and is described below; no Grade 4 or 5 events occurred) and all were considered not related to study treatment with CAB + RPV Q4W with 1 exception of an event of syncope with a verbatim term of 'vasovagal syncope-not cardiac' (Data Source: ISS/ISE Table 3.25, Table 3.20).

One subject in Study 201584 who had withdrawn from the study due to ISR had a seizure approximately 2 months after the last dose of CAB + RPV Q4W, which was not considered to be related to study drug. The event was considered to be caused by influenza meningoencephalitis and a case narrative is available (Data Source: GSK Doc. # 2017N345267_00 Section 17). Additionally, in Study 201585, 1 non-serious AE of

seizure (Grade 3) occurred in a subject in the CAR group during MP. It was not considered to be study drug related and did not lead to discontinuation (GSK Doc. # 2018N370336_00 Section 7.3.3.1.7).

In Study 207966, 1 subject (<1%) in the Q8W group and 3 subjects (<1%) in the Q4W group had an AE potentially related to seizure (Data Source: GSK Doc. # 2019N406358_01 Table 3.78). The subject in the Q8W group had a Grade 3 SAE of epilepsy and the case is described in Table 51. All 3 subjects in the Q4W group had AEs of syncope, none of which were serious or lead to withdrawal (Data Source: GSK Doc. # 2019N406358_01 Table 3.16 and Table 3.22); these subjects are also discussed in Section 2.1.6.5. Additional details regarding subjects with an AE potentially related to seizure are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.7.

Overall CAB Development Program for HIV-1 Treatment

Throughout the CAB development program for HIV-1 treatment to 30 July 2019, 6 seizure-type events (events of seizure or that could potentially be associated with seizure) have been reported for subjects administered CAB (Table 51). Overall, when evaluating the total body of evidence, including a review of preclinical and secondary pharmacology data, individual case details, and expected rates of seizures in the overall HIV positive and negative population, there is insufficient evidence to establish a likely or probable causal association between CAB and seizures.

Table 51 Seizures and Potential Seizure-related Events Reported in CAB Development Program for HIV-1 Treatment

Study: Subject Details	Study Product Exposure[a]	Time to Onset[b]	Risk Factors/Confounders	Drug Related[c]	Comments
LAI116815: 20 – 30-year-old healthy male	30 mg oral CAB for ~4 weeks followed by single dose of 400 mg IM CAB	42 weeks 5 days	History of seizure activity at 1[redacted] years of age Large amounts of alcohol consumption CAB levels undetectable 6 months prior to seizure event	No	The subject received a single dose of 400 mg IM CAB, which was preceded by an oral lead in with CAB. The subject had experienced a generalized tonic-clonic seizure (Grade 2) 42 weeks and 5 days after the first dose of CAB with some myoclonus prior to the event. EEG and neurology consultation were consistent with an underlying diagnosis of juvenile myoclonic epilepsy. He had a medical history of seizure activity at 1[redacted] years of age. He had consumed large amounts of alcohol ([redacted]) the night before the seizure. GSK1265744 levels were below the limit of quantification (<0.01 μg/mL) 6 months prior to the seizure event. The subjects pre-existing condition and the lack of drug exposure during the event make this event unlikely related to investigational product, as determined by the study investigator and sponsor.
201584: 50 – 60-year-old HIV-infected male	30 mg oral CAB and 25 mg oral RPV for ~5 weeks followed by single loading dose 600 mg CAB LA and 900 mg RPV LA then monthly (Q4W) 400 mg CAB LA and 600 mg RPV LA	26 weeks and 2 days	Influenza meningoencephalitis Recent oseltamivir use Subsequent discovery of subdural hematomas	No	Subject had withdrawn from the study due to injection site reaction. 26 weeks and 2 days after first dose of CAB and approximately 2 months after his last CAB + RPV injections, he was found collapsed by his [redacted] He had a witnessed episode of a generalized seizure while in the ambulance and was noted to be confused while in the A&E. A lumbar puncture (all infectious work-up results in CSF negative to date) and CT scan of the head (see below) were carried out and a throat swab confirmed Influenza A infection. This presentation was preceded by a viral prodrome with cough, coryza, and myalgia. The subject was treated with a course of oseltamivir. It is unknown currently when oseltamivir was initiated in relation to hospitalization. While in the hospital, subject received a course of teicoplanin, gentamicin, acyclovir IV for 5 days (until CSF HSV PCR neg) and received IV pabrinex (thiamine, riboflavin, pyridoxine, nicotinamide, and ascorbic acid) in view of a history of regular alcohol consumption. A diagnosis of influenza meningoencephalitis is considered likely and was not considered by the investigator or sponsor to be reasonably likely related to investigational product. Approximately 3 months after the seizure, the subject presented with feeling unsteady and dizzy for the past 12 days. MRI scan identified bilateral chronic subdural hematomas that required evacuation.

Study: Subject Details	Study Product Exposure[a]	Time to Onset[b]	Risk Factors/Confounders	Drug Related[c]	Comments
207966: 60 – 70-year-old HIV-infected male	30 mg oral CAB and 25 mg oral RPV for 4 weeks followed by single loading dose 600 mg IM CAB LA and 900 mg RPV LA then monthly (Q4W) 400 mg CAB LA and 600 mg RPV LA	23 weeks and 5 days	Right fronto-temporal tumor with mass effect	No	Prior to his presentation the subject had been generally well and reported no neurological symptoms until 4 days before his presentation. He reported frequent severe headaches and some visual symptoms from 4 days prior to his presentation onwards; however, he did not report this to anyone or seek medical advice. He collapsed at home 23 weeks and 4 days after his first dose of CAB and experienced a grand-mal seizure witnessed by his [redacted] and was taken by emergency services to his local hospital. On arrival he was given IV dexamethasone and oral levetiracetam and his seizure stopped shortly afterwards and since admission he has not experienced any further seizures. An MRI brain scan undertaken the next day demonstrated a large right fronto-temporal tumor, with mass effect, which may be suggestive of a glial tumor or metastasis. He was transferred to another hospital the following day under the care of the neurosurgical team and underwent incomplete excision of his tumor 3 days later. Histology is pending. The diagnosis is considered primary or secondary cerebral malignancy presenting as a grand mal seizure and was not considered by the investigator or sponsor to be reasonably likely related to investigational product.
200056: 30 - 40-year-old HIV infected male	30 mg oral CAB plus ABC/3TC for 20 weeks, then 25 mg oral RPV added for 4 weeks, then single loading dose 800 mg IM CAB LA, followed by monthly (Q4W) 400 mg CAB LA and 600 mg RPV LA	49 weeks and 6 days	Papaverine detected in urine and serum Recent history of recreational drug use Long latency period	No	49 weeks and 6 days following treatment with CAB, the subject developed acute onset status epilepticus lasting for approximately 6 hours without medical attention, leading to anoxic brain injury and death. The subject was found unconscious and unresponsive and having generalized tonic-clonic seizures [redacted] MRI showed diffuse cerebral edema without evidence of a focal lesion. Papaverine was detected on urine and serum spectroscopy, and social history indicated a recent history of recreational drug use. No other illicit drugs were detected at the time despite extensive screening. An autopsy was not conducted at the family's request. As a result of the strong circumstantial evidence of recreational drug use provided by the site PIs and discussions with the subjects close contact corroborated by the detection of papaverine, the long latency period from the initiation of investigational product, and a review of background rates of seizures in HIV-infected individuals, the event was not considered by the investigator or sponsor to be reasonably likely related to investigational product.

Study: Subject Details	Study Product Exposure[a]	Time to Onset[b]	Risk Factors/Confounders	Drug Related[c]	Comments
LAI116482: 30 – 40-year-old HIV-infected male	60 mg oral CAB plus ABC/3TC for 24 weeks then CAB 30 mg oral and RPV 25 mg oral	191 weeks and 1 day	Prior history of substance abuse ([redacted]) Atypical presentation of suspected seizure Long latency period	Yes	Subject had been generally virologically suppressed on CAB for 3.7 years at the time of this event reported a possible seizure-like event that was witnessed by a [redacted] He was witnessed by a [redacted] on one occasion to be flailing around in his sleep and making noises. He had saliva from his mouth and nasal discharge and was difficult to rouse at the time. The patient did not have any recollection of the event and reported that he felt dizzy at work the next day. The subject had a prior history of gamma hydroxybutyrate and crystal meth use and had used some left over "[redacted]" on the day of the event. He could not recall the type of [redacted] taken. This event was disclosed to the investigator 2 days later during discussion of the informed consent including seizure data during the CAB program. However, it is not clear that the event represented an actual seizure and alternative diagnoses such as a night terror cannot be excluded. The subject had over 3 years of exposure to CAB. The subject reported active illicit drug use at the time of the event, and some of these are known to be associated with neurological events and seizures. On the basis of the information currently available, the event was considered by the investigator to be reasonably likely related to investigational product. The sponsor did not consider the event to be drug related.

Study: Subject Details	Study Product Exposure[a]	Time to Onset[b]	Risk Factors/Confounders	Drug Related[c]	Comments
207966: 40 - 50-year-old HIV-infected male	30 mg oral CAB and 25 mg oral RPV for 4 weeks followed by single loading dose 600 mg IM CAB LA and 900 mg RPV LA then monthly (Q4W) 400 mg CAB LA and 600 mg RPV LA (201585) then 2-monthly 600 mg IM CAB LA and 900 mg RPV LA (207966)	74 weeks 3 days	Cardiorespiratory arrest with posterior reversible encephalopathy syndrome and bilateral cerebral infarcts secondary to complications following acute severe pancreatitis Carbapenem use Long latency period	No	Subject had a past medical history of hyperlipidemia and pancreatitis (5 months and 10 years prior to entry into Study 207966) following an ERCP for gallstones with no prior history of seizures and no neurological symptoms. He had never smoked, denied ever taking recreational drugs, and prior to his presentation he had been generally well. He was randomized to the Q8W arm of Study 207966. He was previously enrolled in Study 201585. This subject presented with severe abdominal pain after dinner and on investigation was confirmed to have acute severe pancreatitis; 488 days after the first dose of CAB + RPV. He was admitted to ICU on Day 124 of study participation. He experienced a cardiopulmonary arrest (Day 125) and was resuscitated following which he continued to have an impaired consciousness level; (Glasgow Coma Scale =4). Imaging by MRI/MRA and CT scan at the time were consistent with posterior reversible encephalopathy syndrome and bilateral cerebral infarcts. An EEG undertaken on Day 143 of study participation showed slow waves and low brain activity. CSF examination was normal. Following the severe pancreatitis, this subject experienced several complications including pancreatic pseudocysts, pyothorax (Day 170)) and a right deep vein thrombosis and pulmonary embolism (Day 190). On Day 194, the subject experienced a focal seizure of his upper limbs and tensing of his jaw lasting a few minutes. He was treated with levetiracetam and diazepam and this resolved. A further short-lived episode occurred on Day 201, lasting a few seconds. He continued to receive levetiracetam. Blood tests did not highlight a biochemical cause of the seizures. He was receiving the following medication at the time of onset of the seizures; vancomycin, caspofungin, heparin, fentanyl, ranitidine, frusemide, and total parenteral nutrition. Meropenem was commenced on 6 days before the onset of seizures. Seizures have infrequently been reported during treatment with carbapenems. This subject subsequently died following complications (sepsis) of the pancreatitis, cardiorespiratory arrest, and ICU stay (Section 2.1.2). The seizure was not considered by the investigator or Sponsor to be reasonably likely related to study drug. However, the investigator considered the pancreatitis to be related to study drug.

Data Source: GSK Doc. # 2014N208332_00 Section 5.3.2 and Section 10; GSK Doc. # 2017N345267 Section 7.3.3.1.7 and Section 16; GSK Doc. # 2018N380094_00 Section 7.3.2 and Section 12; GSK Doc. # 2019N406358_01 Section 7.1.5.3.7 and Section 13; GSK Doc. # 2019N404586_00 Section 7.5.3 and Section 12.

a. Exposure prior to event.
b. Time since first dose of CAB/study drug.
c. Drug-related is based on investigator assessment.

Conclusion

Review of cases of seizures identified confounders, risk factors, and alternative etiologies. Events of seizure were not associated with treatment with CAB + RPV.

2.1.6.8. Weight Gain

Results from analyses of body weight are presented in Section 4.2.

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, 2 (<1%) subjects in the CAB + RPV Q4W group and no subjects in the CAR group reported at least 1 AE possibly indicative of weight gain (Data Source: ISS/ISE Table 3.51). The event was 'weight increased,' which was reported in 1 subject each in Study 201584 and Study 201585. One subject who received CAB + RPV Q4W in Study 201584 had a Grade 1 AE of weight increased that was not considered study drug related (GSK Doc. # 2017N345267_00 Section 7.3.3.1.8.). One subject who received CAB + RPV Q4W in Study 201585 had a Grade 1 AE of weight increased that was considered study drug related (GSK Doc. # 2018N370336_00 Section 7.3.3.1.8.). No SAEs and no withdrawals due to AEs of weight gain were reported in Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.33 and Table 3.36).

In Study 207966, 9 subjects (2%) in the Q8W group and 4 subjects (<1%) in the Q4W group reported at least 1 AE possibly indicative of weight gain (Data Source: GSK Doc. # 2019N406358_01 Table 3.79). None were SAEs (Data Source: GSK Doc. # 2019N406358_01 Table 3.16) or led to withdrawal (Data Source: GSK Doc. # 2019N406358_01 Table 3.22). Additional details regarding AEs possibly indicative of weight gain are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.8.

Longer-term Phase III Results

At the end of the MP in Study 201584, 9 (3%) subjects in the CAB + RPV Q4W group and 3 (1%) subjects in the CAR group had an AE potentially related to weight gain (PTs include weight increased, abnormal weight gain, and obesity) (GSK Doc. # 2019N421511_00 Section 7.3.3.1.8). All events were Grade 1 or 2, and none were considered drug related. Since the Week 48 analysis, 8 subjects in the CAB + RPV Q4W group and 3 subjects in the CAR group had an AE potentially related to weight gain. None of these AEs were serious and none lead to withdrawal (Data Source: GSK Doc. # 2019N421511_00 Table 3.21 and Table 3.31).

In Study 201585, 1 AE (Grade 1) of weight increase was reported in the CAB + RPV Q4W group during the Extension Phase (Data Source: GSK Doc. # 2019N399072_00 Table 13.5). In the Extension Switch to CAB + RPV Q4W group, 2 AEs of weight decrease (one Grade 1; one Grade 2) were reported (Data Source: GSK Doc. # 2019N399072_00 Table 13.6). These 3 weight-related AEs were not considered serious and did not lead to withdrawal from study drugs (Data Source: GSK Doc. # 2019N399072_00 Listing 109). Only the Grade 1 AE of weight decrease in the

Extension Switch group was considered possibly related to study drugs; the other 2 weight-related AEs were considered not related to study drugs.

Conclusion

AEs possibly indicative of weight gain were reported with treatment with CAB + RPV. The incidence of events was higher with CAB + RPV Q4W compared with that for CAR during Studies 201584 and 201585. There were no serious events possibly indicative of weight gain with CAB + RPV. Severity was generally Grade 1 or Grade 2. Events possibly indicative of weight gain in these study populations did not lead to withdrawal.

2.1.6.9. Rhabdomyolysis

Transient, asymptomatic elevations of CK levels have been observed in subjects participating in the CAB + RPV development program, although the elevations are not associated with myoglobinuria, acute kidney injury, or other serious adverse events. An analysis of laboratory parameter abnormalities for creatine kinase is presented in Section 3.1.6.

Week 48 Phase III/IIIB Results

Regarding Studies 201584 and 201585, rhabdomyolysis was not observed in Study 201584. 1 case in the CAR group was reported in Study 201585. The case in Study 201585 was Grade 3 in severity, was not serious, was not considered study drug related, and did not lead to withdrawal (Data Source: GSK Doc. # 2018N370336_00 Listing 30).

In Studies 201584 and 201585, 25 (4%) subjects in the CAB + RPV Q4W group and 9 (2%) subjects in the CAR group had at least 1 AE potentially associated with rhabdomyolysis (Data Source: ISS/ISE Table 3.52). None of these AEs were serious (Data Source: ISS/ISE Table 3.33). 11 events (44%) in the CAB + RPV Q4W group and 1 event (11%) in the CAR group were considered drug related. There were no AEs that were Grade 3 or 4 in severity in the CAB + RPV Q4W group and 1 AE in the CAR group was Grade 3 in severity (rhabdomyolysis – not considered drug related and described above) (Data Source: ISS/ISE Table 3.70). More subjects in the CAB + RPV Q4W group had AEs of myalgia compared with those in the CAR group (24 [4%] subjects vs. 8 [1%] subjects, respectively). 1 AE of myalgia (CAB + RPV Q4W group) led to study drug discontinuation (Data Source: ISS/ISE Table 3.36). 1 subject in the CAB + RPV Q4W group had a Grade 2 AE of myositis associated with Grade 4 CK elevation and the myositis was considered related to treatment (Data Source: GSK Doc. # 2018N370336_00 Table 3.20, Listing 30).

In Study 207966, 11 subjects (2%) in the Q8W group and 15 subjects (3%) in the Q4W group reported at least 1 AE potentially associated with rhabdomyolysis (Data Source: GSK Doc. # 2019N406358_01 Table 3.80). Of these 26 subjects, 25 (Q8W: 10 subjects; Q4W: 15 subjects) reported AEs of myalgia (myalgia is not in the SMQ for rhabdomyolysis but is a PT that was added to the search). Rhabdomyolysis was reported for 1 subject in the Q8W group; the VT indicated it was secondary to exercise.

It was Grade 2, not considered drug related, not serious, and did not result in withdrawal of the subject from the study (Data Source: GSK Doc. # 2019N406358_01 Table 3.7, Table 3.14, Table 3.16, Table 3.22, and Listing 19).

None of the reports of myalgia in Study 207966 were SAEs (Data Source: GSK Doc. # 2019N406358_01 Table 3.16). One subject in the Q4W group withdrew due to myalgia (Data Source: GSK Doc. # 2019N406358_01 Table 3.22), assessed as Grade 2 and related to study drug; myalgia was 1 of 11 AEs leading to withdrawal for this subject (Data Source: GSK Doc. # 2019N406358_01 Listing 17).

Additional details regarding AEs potentially related to rhabdomyolysis or increased blood CPK are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.9.

Longer-term Phase III Results

No AEs of rhabdomyolysis have been reported in Study 201584 (GSK Doc. # 2019N421511_00 Section 7.3.3.1.9). At the end of the MP in Study 201584, at least 1 AE of blood creatine phosphokinase increased was reported for 11 (4%) subjects in the CAB + RPV Q4W group and 8 (3%) subjects in the CAR group. None of these AEs were serious or lead to withdrawal (Data Source: GSK Doc. # 2019N421511_00 Table 3.21 and Table 3.31).

In addition, at the end of the MP in Study 201584, 18 subjects (6%) in the CAB + RPV Q4W group and 7 subjects in the CAR group reported at least 1 AE potentially related to rhabdomyolysis (myalgia) (Data Source: GSK Doc. # 2019N421511_00 Table 3.164). That total includes 4 additional CAB + RPV Q4W subjects and 2 additional CAR subjects since the Week 48 analysis (Data Source: ISS/ISE Table 3.52). None of the AEs of myalgia were serious or lead to withdrawal (Data Source: GSK Doc. # 2019N421511_00 Table 3.21 and Table 3.31).

In Study 201585, there were no AEs of blood creatine phosphokinase increase reported during the Extension Phase in either treatment group (Data Source: GSK Doc. # 2019N399072_00 Table 13.5, Table 13.6). No AEs of rhabdomyolysis were reported for either treatment group during the Extension Phase.

Conclusion

Events of rhabdomyolysis were not associated with treatment with CAB + RPV. During the first 48 weeks of Studies 201584 and 201585, more AEs of myalgia and more Grade 3 and 4 CK elevations (Section 3.1.6) occurred in the CAB + RPV Q4W group compared with the CAR group. However, these were not serious or treatment limiting and did not result in rhabdomyolysis. CK elevations were considered to be due to strenuous exercise.

2.1.6.10. Pancreatitis

HIV infection has been associated with asymptomatic elevation of lipase [Argiris, 1999].

Results for analyses of lipase are presented in Section 3.1.7.

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, 3 (<1%) subjects in the CAB + RPV Q4W group (n=4 events) and no subjects in the CAR group had AEs potentially associated with pancreatitis (Data Source: ISS/ISE Table 3.53). One subject in Study 201584 had 2 episodes of pancreatitis that were non-serious, not considered drug related, and the second episode was Grade 2 in severity (grade of first episode not available); no lipase elevations were reported and no interruptions to study drug occurred (Data Source: GSK Doc. # 2017N345267_00 Listing 32). One subject in Study 201585 reported a non-serious AE of pancreatitis that was not considered drug-related and was Grade 2 in severity. 1 SAE of acute pancreatitis was reported in the CAB + RPV Q4W group in Study 201585; the event was not considered study drug related and it resolved within 5 days. The event was considered to be caused by gallstones. (Data Source: ISS/ISE Table 3.33; GSK Doc. # 2018N370336_00 Section 7.3.3.1.10). None of the AEs led to study drug discontinuation (Data Source: ISS/ISE Table 3.36).

In Study 207966, 2 subjects (<1%) in the Q8W group and no subjects in the Q4W group had an AE potentially associated with pancreatitis (Data Source: GSK Doc. # 2019N406358_01 Table 3.81). A subject in the Q8W group had a Grade 4 SAE of acute pancreatitis considered to be drug related that resulted in withdrawal, as well as a Grade 3 SAE of pancreatic pseudocyst that was not assessed as drug related (Data Source: GSK Doc. # 2019N406358_01 Table 3.19 and Listing 16). This subject had a complicated and protracted hospital course and ultimately died due to sepsis (Section 2.1.2). A case narrative is provided in GSK Doc. # 2019N406358_01 Section 13. One other subject in the Q8W group had a Grade 1 AE of pancreatitis (Data Source: GSK Doc. # 2019N406358_01 Table 3.7) that was nonserious (Data Source: GSK Doc. # 2019N406358_01 Table 3.16), and not treatment limiting (Data Source: GSK Doc. # 2019N406358_01 Table 3.22). Additional details regarding these subjects are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.10.

Longer-term Phase III Results

At the end of the MP in Study 201584, no additional subjects reported AEs potentially related to pancreatitis since the Week 48 analysis (GSK Doc. # 2019N421511_00 Section 7.3.3.1.10).

In Study 201585, there were no AEs of pancreatitis reported for the CAB + RPV Q4W group during the Extension Phase. One Grade 3 AE of pancreatitis was reported in the Extension Switch to CAB + RPV Q4W group; this AE was nonserious, not related to study drug, and did not lead to withdrawal from study drug (Data Source: GSK Doc. # 2019N399072_00 Table 13.6, Table 13.11, and Table 13.16).

Conclusion

There is no convincing evidence to date of a causal association between AEs potentially related to pancreatitis and CAB + RPV. One subject in Study 207966 had a SAE of acute pancreatitis that was considered by the investigator to be drug related as it was not possible to exclude a causative association. However, the Sponsor does not believe the evidence supports the study medication being causative in this instance.

2.1.6.11. Impact on Creatinine

Results for analyses of creatinine laboratory assessments are presented in Section 3.1.2.

Week 48 Phase III/IIIB Results

Few subjects in Phase III/IIIB studies had at least 1 AE potentially associated with impact on creatinine (Table 52).

Table 52 Summary of Impact of Creatinine AESIs in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Preferred Term	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
ANY EVENT	**0**	**2 (<1)**	**2 (<1)**	**1 (<1)**	**2 (<1)**	**3 (<1)**	**2 (<1)**	**0**
Renal failure	0	2 (<1)	0	0	0	2 (<1)	0	0
Renal impairment	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Chronic kidney disease	0	0	1 (<1)	0	1 (<1)	0	0	0
Acute kidney injury	0	0	0	0	0	0	1 (<1)	0

Data Source: ISS/ISE Table 3.54; GSK Doc. # 2019N406358_01 Table 3.82.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 201584, 2 subjects on CAR (DTG/ABC/3TC) had non-serious AEs of renal failure ('renal insufficiency'). Both events were considered related to treatment with CAR and were Grade 2 in severity. One event led to withdrawal and the other one did not (Data Source: GSK Doc. # 2017N345267_00 Table 3.107, Table 3.108, Listing 32).

In Study 201585, 1 subject on CAB + RPV Q4W had renal impairment ('deteriorating renal function'), which was Grade 1 in severity, nonserious, not considered drug related, and did not lead to withdrawal. 1 subject on CAB + RPV Q4W had chronic kidney disease ('chronic renal failure'), which was Grade 3 in severity, nonserious, not considered drug related, and did not lead to withdrawal. In the CAR group of Study 201585, 1 subject had renal impairment, which was Grade 2 in severity, not serious, and not considered drug related but led to withdrawal (Data Source: GSK Doc. # 2018N370336_00 Listing 30).

No SAEs related to creatinine abnormalities were reported during Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.33). 2 AEs (renal failure, renal impairment) in the CAR group led to study drug discontinuation as described above (Data Source: ISS/ISE Table 3.36).

In Study 207966, 1 subject had an AE of renal impairment (considered related to study drug) and the other subject had an SAE of acute kidney injury (considered not related to

study drug) (GSK Doc. # 2019N406358_01 Section 7.1.5.3.11 and Data Source: GSK Doc. # 2019N406358_01 Table 3.16); this subject had additional complications and died due to sepsis (Section 2.1.2). Neither AE led to withdrawal (Data Source: GSK Doc. # 2019N406358_01 Table 3.22). Additional details regarding AEs potentially related to impact on creatinine are provided in GSK Doc. # 2019N406358_01 Section 7.1.5.3.11.

Longer-term Phase III Results

At the end of the MP in Study 201584, 1 additional subject in the CAB + RPV Q4W group had an AE of renal impairment since the Week 48 analysis (Table 52 and Data Source: GSK Doc. # 2019N421511_00 Table 3.170). This AE was not serious and did not lead to withdrawal (Data Source: GSK Doc. # 2019N421511_00 Table 3.21 and Table 3.31).

In Study 201585, there were no AEs of blood creatinine increase during the Extension Phase in either treatment group (Data Source: GSK Doc. # 2019N399072_00 Table 13.5, Table 13.6).

No AEs of creatinine renal clearance decreased were reported for the CAB + RPV Q4W group during the Extension Phase in Study 201585. Two subjects reported AEs (Grade 1; Grade 2) of creatinine renal clearance decreased for the Extension Switch to CAB + RPV Q4W group (Data Source: GSK Doc. # 2019N399072_00 Table 13.5, Table 13.6). Both AEs were considered to be related to study drug; the study drug dose was not changed or discontinued.

Conclusion

An SAE associated with a potential impact on creatinine has been reported, but it was not associated with treatment with CAB + RPV.

2.1.6.12. Safety in Pregnancy

Adverse events potentially related to safety in pregnancy are presented here. A detailed summary of pregnancy data and outcomes is presented in Section 5.4.1.

Week 48 Phase III/IIIB Results

In pooled Studies 201584 and 201585, 1 subject (<1%) in each treatment group had at least 1 AE potentially related to safety in pregnancy (Data Source: ISS/ISE Table 3.55). The AEs related to safety in pregnancy were abortion missed (nonviable pregnancy was terminated) (n=1, CAB + RPV Q4W group) and abortion spontaneous (n=1, CAR group). Both were SAEs and not considered drug related (Data Source: ISS/ISE Table 3.33).

In Study 207966, no subjects in the Q8W group and 1 subject (<1%) in the Q4W group reported at least 1 AE potentially related to safety in pregnancy (Data Source: GSK Doc. # 2019N406358_01 Table 3.83). The subject had a spontaneous abortion, which was an SAE (Data Source: GSK Doc. # 2019N406358_01 Table 3.16) that was not assessed as drug related (Data Source: GSK Doc. # 2019N406358_01 Table 3.19). A case narrative is provided in GSK Doc. # 2019N406358_01 Section 13.

Longer-term Phase III Results

There were no findings related to safety in pregnancy in Study 201584 at the end of the MP (Data Source: GSK Doc. # 2019N421511_00 Table 3.173).

There were no pregnancies reported during the Extension Phase in Study 201585 (Data Source: GSK Doc. # 2019N399072_00 Listing 111, Listing 112).

2.1.7. Post-injection Reactions

An acute exposure to higher than normal systemic drug levels could happen if an injection were accidentally administered into a vein rather than muscle as recommended, leading to possibly increased systemic peak drug levels shortly thereafter. Transient high levels could theoretically lead to a safety risk from overexposure to drug and could also lead to a risk of virologic failure as systemic concentrations would fall more quickly than from an IM injection.

Ad hoc analysis of PK levels of CAB and RPV measured at 2 hours post-dose at specified routine visits during the Phase IIb/III Studies 200056, 201584, and 201585 as well during the Phase III Study 207966 at approximately 2 hours post-dose in response to AEs indicate that inadvertent (partial) IV injections (defined by plasma concentration levels unlikely to have resulted from pure IM injection) occurred infrequently during the CAB + RPV development program (m2.7.2 Section 3.1.7). Unexpectedly high PK for CAB at 2 hours post-dose, defined as concentrations >22.5 μg/mL, occurred in 17 of the 2501 (0.7%) samples measured. Unexpectedly high PK for RPV at 2 hours post-dose, defined as concentrations >800 ng/mL, occurred in 21 of the 2495 (0.8%) samples measured.

In the majority of cases, these unexpectedly high post-injection PK levels were not associated with AEs or impact on virologic suppression. No specific AEs have been identified with CAB subjects with unexpectedly high PK.

Two-hour post dose RPV PK levels >800 ng/mL resulted in 1 subject with CVF in Study 200056: 1 subject (Q8W) with presumed partial IV administration of RPV at the Week 4b visit (2-hour post-dose RPV PK level 2390 ng/mL) had PK levels around the quantification limit of RPV at the subsequent 1-week visit (3 ng/mL) and undetectable RPV PK at Week 8, leading to CVF without the emergent of resistance at Week 8. There were no symptoms or safety findings. See also m2.7.2 Section 2.1.4.4 and m2.7.3 Section 5.2 (first subject).

Two-hour post-dose RPV PK levels >800 ng/mL very infrequently resulted in AEs. A few subjects (<1%) developed post-injections reactions that were serious although these reactions resolved a few minutes after the injection. Including data received up to 31 January 2020, inclusive, 4 subjects were reported to have post-injection reactions; 3 with apparent IV injection of RPV (based on PK). The fourth case was not confirmed because a suitably timed post-dose PK sample was not collected.

In Study 200056, 1 subject experienced a post-injection reaction:

- Grade 2 abdominal pain, chest pain, and flushing; Grade 1 dyspnea, Q4W group
  The subject was noted to be active, leading a healthy lifestyle, and was not on any concomitant medications. The subject was noted to have a history of sinus bradycardia on ECG. On Week 256 (relative to first IM doses of CAB + RPV; oral doses given prior) at approximately 1 minute after IM administration of RPV LA, the subject reported feeling abdominal cramps, chest pain, and shortness of breath. Facial and body flushing were observed. Vital signs were respiration rate of 20 breaths/minute and blood pressure of 145/91 mmHg. The subject was monitored closely during the event and remained alert and oriented. No treatment was administered. Symptoms gradually improved and subsided around 20 minutes after onset, prior to administration of CAB LA IM. The investigator considered the event to be due to RPV LA injection. Peak RPV level was 1340 ng/mL at 23 minutes post-dose, which is suggestive of (partial) IV administration. Symptoms did not recur after the initial incident although the subject reported feeling tired for the rest of the day. Upon review, the subject had had an episode of facial flushing after injection at Week 104 and a 5-minute episode of facial flushing, chest tightness, and stomach cramps at Week 236. These episodes subsided on their own. The subject attributed these episodes to RPV LA as well; however, they occurred after both RPV and CAB IM, so causality would be unable to be determined with certainty. An SAE of abdominal pain was reported, and study medication was discontinued.

Of the 3 subjects in Study 207966 who experienced post-injection reactions, the first 2 cases (presyncope and hypersensitivity) were reported prior to the data cutoff date (Week 48 analysis) for Study 207966, and case narratives are provided in GSK Doc. # 2019N406358_01 Section 13. The third case (drug hypersensitivity) was reported following the data cutoff date for Study 207966. Brief summaries are provided for all 3 cases.

- <u>Grade 3 presyncope, Q8W group</u>
  At Week 40 in Study 207966, the subject developed a severe reaction immediately after receiving both the IM RPV LA and CAB LA injections. The subject had previously participated in Study 201585, randomized to the Q4W group, and had had no prior similar reactions. The subject was very distressed and agitated, felt faint and unable to breathe, and experienced numbness of the face, severe heavy chest pain, and abdominal cramping that radiated to the left back. The heart rate dropped from 71 bpm to 65 bpm, and blood pressure dropped from 123/79 mmHg to 68/22 mmHg, which was associated with dizziness. No alteration in consciousness was observed, and the subject did not experience injection site pain, nausea, sweating, rashes, wheezing, or cyanosis. The subject received oxygen and an IV infusion with normal saline. Within 10 minutes after onset of the symptoms, the subject had recovered. Laboratory investigations, including troponin T, were normal. The RPV plasma concentration prior to study drug administration was 112 ng/mL, which was consistent with expected Week 40 exposures. The RPV plasma concentration measured 47 minutes after study drug administration was 1400 ng/mL (preliminary result was recorded as 1570 ng/mL [over the LOQ] and sample was reanalyzed), which was 12.5-fold higher than expected when compared

with the pre-dose concentration. The presyncope was considered by the investigator as possibly related to CAB LA and RPV LA and to the suspected inadvertent partial IV administration of RPV LA, leading to high RPV levels immediately after injection. The subject was withdrawn from the study.

- Grade 3 hypersensitivity, Q4W group
  At Week 12, the subject developed a severe reaction immediately following the IM administration of RPV LA while the needle was still in situ. CAB LA was not administered due to the onset of the event. The subject had received prior CAB + RPV injections and oral dosing without issue and had previously participated in Study 201585, randomized to the CAR group. The subject had no history of atopy. The subject developed tingling in the throat, shortness of breath, and nausea along with tingling in the tongue and lips. There was no rash, urticaria, wheezing, or reduction in consciousness level. The subject was noted to be transiently cyanosed (centrally and peripherally). The subject was treated with adrenaline, steroids, antihistamines, and IV fluids in case this was an allergic type reaction, but per report of the investigator, the subject was already improving clinically prior to these treatments being administered. The reaction resolved completely within 1 hour, and the subject was hemodynamically stable with no impairment in consciousness level throughout. Laboratory investigations and ECGs were normal. The subject's RPV plasma concentration prior to study drug administration was 56.6 ng/mL, which was consistent with expected Week 12 exposures. The RPV plasma concentration measured 3 hours after study drug administration was 1450 ng/mL, which was 26-fold higher than expected when compared with the pre-dose concentration, consistent with partial IV administration. The investigator considered the event related to RPV LA and considered a Type I allergic reaction unlikely. The subject was withdrawn from the study.

- Grade 3 drug hypersensitivity, Q4W group
  At Week 88, the subject developed a severe reaction 10 minutes after the CAB injection and 7 minutes after the RPV injection. The subject had received prior CAB + RPV injections and oral dosing without issue. Within 1 minute of getting up from the abdominal position after receiving the injections, the subject developed a rash (Grade 3), urticaria of the face (Grade 3), and bronchospasm lasting a few minutes (Grade 2). The subject turned dark red in the face, started to cough, and reported chest pressure. These symptoms improved but were followed by urticaria on the face with itching and then wheals. At 8 minutes following the onset of the reaction, BP was 130/95 mmHg and HR was 74 bpm; 50 minutes later, BP was 125/85 mmHg. The subject remained fully responsive, and an ECG at 14 minutes following the onset of the reaction was normal. The subject was treated with prednisolone 100 mg IV and clemastine 2 mg at 8 minutes following the onset of the reaction, and drug hypersensitivity resolved the same day. The subject reported being able to breathe again and did not require oxygen; oxygen saturations were not obtained. The subject did not have mouth edema. The subject stayed on site for an additional 2 hours for observations. No PK or laboratory tests (including serum tryptase) were obtained immediately following the event. The subject had not experienced any issues with past injections apart from developing pain or swelling presenting as injection site reactions. There was no history of allergy, atopy, or food allergies. The investigator considered that there was a reasonable possibility that the

drug allergy may have been caused by CAB + RPV. The subject was withdrawn from the study. Pre-dose PK samples at Week 88 for CAB and RPV were 3560 ng/mL and 103 ng/mL, respectively. Post-dose PK samples taken 6 days later were 4590 ng/mL and 270 ng/mL, respectively. The Sponsor notes that the rapid onset of symptoms and resolution were similar to other post-injection reactions reported with RPV. While the concentrations for CAB and RPV 6 days post-dose were within the normal expected ranges, it is not possible to exclude a partial IV administration of either drug in this case. Another possibility is drug allergy to either CAB or RPV, although the rapid resolution of symptoms would be atypical of an immediate allergic response.

Conclusion

Four subjects were reported to have post-injection reactions that were SAEs; 3 with apparent IV injection of RPV (based on PK). The fourth case was not confirmed because a suitably timed post-dose PK sample was not collected. In Study 200056, 1 case was reported. In Study 207966, 3 cases were reported. No specific AEs have been identified with CAB subjects with unexpectedly high PK. The SAEs of post injection reactions were transient in nature and did not result in clinically significant sequelae.

2.1.8. Once Daily Oral CAB 30 mg

2.1.8.1. Phase III/IIIB Studies (Oral Lead-in)

An OLI of CAB + RPV was included in Studies 201584, 201585, and 207966 to evaluate the potential in each subject for AEs that would preclude IM dosing with CAB LA + RPV LA. The duration of OLI varied by subject, with 4 to 5 weeks being the minimum duration; see Section 1.2.2 for extent of exposure.

The AE data for the combined OLI CAB + RPV periods in Studies 201584 and 201585 and the OLI in Study 207966 did not identify any new AE trends. There was 1 subject in Study 207966 who had possible DILI during OLI.

During the OLI for Studies 201584 and 201585, 590 subjects received OLI (Data Source: ISS/ISE Table 3.01) and 187 (32%) subjects in the CAB + RPV group had at least 1 AE (Data Source: ISS/ISE Table 3.13). The most frequently reported (≥10 subjects) AEs during OLI were nasopharyngitis (n=16 [3%]), headache (n=17 [3%]), vitamin D deficiency (n=16 [3%], and diarrhea (n=12 [2%]). Most AEs that occurred during the OLI were mild to moderate in severity (GSK Doc. # 2017N345267_00 Section 7.4 and GSK Doc. # 2018N370336_00 Section 7.4). A total of 4 subjects in the CAB + RPV group had SAEs during the OLI period, none of which were considered drug related: see Section 2.1.3.1 for details. A total of 6 subjects had 7 AEs that led to discontinuation of study drug during the OLI period; see Section 2.1.5.1 for details.

No AEs of DILI or HSR were reported during the OLI for Studies 201584 and 201585. There were no withdrawals due to AEs that could have represented DILI or HSR during this period. See Section 2.1.6.2 for more details about AEs potentially related to hepatotoxicity and Section 2.1.6.3 for more details about AEs potentially related to hypersensitivity.

In Study 207966, 655 subjects received OLI (Data Source: GSK Doc. # 2019N406358_01 Table 1.12). At least 1 AE was reported by 28% of subjects (91 of 328) randomized to receive CAB + RPV Q8W and 36% of subjects (118 of 327) randomized to receive CAB + RPV Q4W (Data Source: GSK Doc. # 2019N406358_01 Table 3.9), for an overall total of 32% in OLI (209 of 655 subjects). At least 1 SAE was reported by 1 subject (<1%) randomized to receive CAB + RPV Q8W and 4 subjects (1%) randomized to receive CAB + RPV Q4W (Data Source: GSK Doc. # 2019N406358_01 Table 3.18), for an overall total of 1% in OLI (5 of 655 subjects); see Section 2.1.3.1 for details. At least 1 AE leading to withdrawal was reported by 2 subjects (<1%) randomized to each treatment group (Data Source: GSK Doc. # 2019N406358_01 Table 3.23) for an overall total of <1% in OLI (4 of 655 subjects); see Section 2.1.5.1 for details. Overall, 2 subjects withdrew due to similar AEs (asthenia and fatigue); otherwise, there were no discernible patterns of SAEs or of AEs leading to withdrawal by PT as each event was reported in a single subject.

Of the 655 subjects receiving OLI on Study 207966 (Data Source: GSK Doc. # 2019N406358_01 Table 1.12), 1 subject meeting criteria for enhanced monitoring of liver chemistries had a possible DILI (Section 2.1.6.2), and the subject was withdrawn. No subjects had AEs consistent with hypersensitivity that led to withdrawal (Data Source: GSK Doc. # 2019N406358_01 Table 3.23).

2.1.8.2. Phase IIB Studies

In Studies LAI116482 and 200056, there was no OLI period. In Study 200056, subjects were virologically suppressed with CAB 30 mg and ABC/3TC (600 mg/300 mg) once daily during the 20-week Induction Period. Oral RPV 25 mg once daily was added to the regimen for the last 4 weeks of Induction, prior to transitioning to the Maintenance Period.

Specific to the safety of daily oral CAB 30 mg within the CAB + RPV program, Study LAI116482 evaluated the safety and efficacy of a CAB 30 mg dosing arm (n=60), in combination with NRTIs through Week 24 and with oral RPV through Week 144. On the CAB 30 mg arm, 4 subjects had AEs that led to withdrawal through EOS (panic attack [CAB + NRTIs]; Burkitt's lymphoma, acute hepatitis C, depression, and suicidal ideation (CAB + RPV) (Data Source: GSK Doc. # 2019N404586_00 Table 8.15 and Listing 8.6). CAB 30 mg + NRTIs was also evaluated in Study 200056 for 20 weeks (n=309) with 6 withdrawals due to AEs (2%), 3 considered possibly related (nausea, affective disorder, DILI) (GSK Doc. # 2015N246053_00 Section 7.1.5). One additional case of possible DILI was observed on CAB 30 mg + NRTIs through Week 96 (GSK Doc. # 2017N337118_00 Section 7.8.3). Information about AEs potentially related to hepatoxicity is presented in Section 2.1.6.2.

Overall, the frequency and categories of drug-related AEs reported with daily oral CAB 30 mg have been similar to those reported with CAB LA and are infrequently treatment limiting.

2.1.9. AEs During Long-term Follow-up (Phase III/IIIB Studies)

Only SAEs are reported for this population. It should be noted that AEs starting after the last dose of study drug and before the start of LTFU Phase HAART would be considered in both the MP and LTFU Phase; see Section 1.1.6.5.

At the Week 96/100 data cutoff in Study 201584, 20 subjects were ongoing in the LTFU Phase, and 15 subjects had completed the LTFU Phase (1 subject was lost to follow-up) (GSK Doc. # 2019N421511_00 Section 7.4). During the LTFU Phase, 5 subjects had a total of 7 SAEs (CAB + RPV Q4W group: 2 subjects had hepatitis A, 1 subject had subdural hematoma and epilepsy, 1 subject had abortion missed; CAR-switch group: 1 subject had cellulitis and herpes simplex). None of these SAEs were considered related to prior exposure to CAB + RPV. Case narratives for these events are provided in GSK Doc. # 2019N421511_00 Section 15.

At the Week 96 data cutoff in Study 201585, 28 subjects had entered LTFU and 7 were ongoing (Data Source: GSK Doc. # 2019N399072_00 Table 11.3). A total of 3 subjects in the CAB + RPV Q4W group were reported to have SAEs (hepatitis A, shigella infection, hepatocellular injury, hyperbilirubinemia, and hypertension); no subjects in the Extension Switch to CAB + RPV Q4W group had SAEs (Data Source: GSK Doc. # 2019N399072_00 Table 13.12). All SAEs except for shigella infection were reported within 3 weeks of the subject's last injection of CAB + RPV. The shigella infection was reported on the 31st day after the last injection and after the subject had started new ARTs (EVG/cobi+TAF+FTC) (Data Source: GSK Doc. # 2019N399072_00 Listing 110 and Listing 129). A narrative for the subject with an SAE of hypertension is provided in GSK Doc. # 2019N399072_00. Narratives for the other 2 subjects were provided in the Week 48 CSR (GSK Doc. # 2018N370336_00).

At the Week 48 data cutoff (Section 1.1.4.1), 46 subjects (Q8W: n=22; Q4W: n=24) had entered LTFU in Study 207966 and 37 were ongoing (Data Source: GSK Doc. # 2019N406358_01 Table 1.12). One subject (5%) in the Q8W group and 2 subjects (8%) in the Q4W group reported at least 1 SAE (Data Source: GSK Doc. # 2019N406358_01 Table 3.17). In the Q8W group, the subject had injection site abscess (see summary in Section 2.1.6.1). In the Q4W group, the reported SAEs were glioblastoma in 1 subject (summarized in GSK Doc. # 2019N406358_01 Section 7.1.5.3.7) and pulmonary embolism as well as deep vein thrombosis in 1 subject; none were assessed as related to study drug (Data Source: GSK Doc. # 2019N406358_01 Table 3.19). Case narratives for SAEs are provided in GSK Doc. # 2019N406358_01 Section 13.

2.2. Narratives

Case narratives for fatal SAEs, other SAEs, and pregnancies reported through the data cut-off date for the most recent analyses are included in the corresponding CSRs as follows:

- Study 201584
  - Week 48: GSK Doc. # 2017N345267_00 Section 16

  - Week 96/100: GSK Doc. # 2019N421511_00 Section 15
- Study 201585
  - Week 48: GSK Doc. # 2018N370336_00 Section 15
  - Week 96: GSK Doc. # 2019N399072_00
- Study 207966: GSK Doc. # 2019N406358_01 Section 13
- Study LAI116482: GSK Doc. # 2019N404586_00 Section 12
- Study 200056: GSK Doc. # 2018N380094_00 Section 12

3. CLINICAL LABORATORY EVALUATIONS

3.1. Clinical Chemistry

Week 48 Phase III/IIIB Results

Results of the clinical laboratory findings demonstrated that there were no laboratory signals of concern in subjects in Studies 201584 and 201585 switching from CAR to receiving CAB + RPV Q4W treatment. The majority (389/521 [74.7%%] in the CAB + RPV Q4W group and 413/515 [80.2%] in the CAR group) of the post-Baseline emergent clinical chemistry abnormalities were Grade 1 or Grade 2 in intensity (Table 53). No clinically relevant differences were observed overall in subjects with at least 1 Grade 3 or Grade 4 post-Baseline emergent toxicity between the CAB + RPV Q4W and CAR groups. It should be noted that while the study protocols suggested for blood samples to be collected before administration of study drug injections, the actual sequence of each procedure for subjects was not recorded.

In Study 207966, there were no clinically relevant differences between treatment groups for overall clinical chemistry abnormalities (including liver chemistry) in either frequency or toxicity grade (Table 53 and GSK Doc. # 2019N406358_01 Section 7.2.1). Furthermore, based on analyses of clinical laboratory evaluations in Study 207966, no clinically significant new safety issues have been identified for CAB + RPV in subjects dosed Q8W compared with subjects dosed Q4W.

Table 53 Summary of Maximum Post-Baseline Intensity for All Chemistry Parameters During Studies 201584, 201585, 201584+201585 Pooled, and 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Grade(s)	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
1 to 4	**249 (88)**	**244 (86)**	**272 (88)**	**271 (88)**	**521 (88)**	**515 (87)**	**437 (84)**	**453 (87)**
2 to 4	168 (59)	157 (55)	190 (62)	197 (64)	358 (61)	354 (60)	252 (48)	297 (57)
3 to 4	69 (24)	45 (16)	63 (20)	57 (19)	132 (22)	102 (17)	60 (11)	71 (14)
1	81 (29)	87 (31)	82 (27)	74 (24)	163 (28)	161 (27)	185 (35)	156 (30)
2	99 (35)	112 (40)	127 (41)	140 (45)	226 (38)	252 (43)	192 (37)	226 (43)
3	51 (18)	30 (11)	37 (12)	43 (14)	88 (15)	73 (12)	46 (9)	44 (8)
4	18 (6)	15 (5)	26 (8)	14 (5)	44 (7)	29 (5)	14 (3)	27 (5)

Data Source: ISS/ISE Table 3.123; GSK Doc. # 2019N406358_01 Table 3.43.
Note: No Grade 5 chemistry toxicities were reported.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Longer-term Phase III Results

At the end of the MP in Study 201584, clinical chemistry toxicities were observed in 93% of subjects in both the CAB + RPV Q4W and CAR groups (GSK Doc. # 2019N421511_00 Section 7.5.1). Maximum Grade 3 or 4 toxicities occurred in 30% of subjects in the CAR + RPV group and 20% of subjects in the CAR group.

In Study 201585, overall, trends in Week 96 clinical laboratory parameters were consistent with those observed at Week 48. Few Grade 3 or Grade 4 clinical laboratory abnormalities were observed during the Extension Phase (Table 54). Results of the clinical laboratory findings demonstrated few changes in laboratory values over time or between treatment groups (Data Source: GSK Doc. # 2019N399072_00 Table 13.28 and Table 13.29).

Table 54 Summary of Maximum Post-Baseline Emergent Grade 3 or 4 Clinical Laboratory Values in Study 201585 at Week 96 (Safety and Extension Switch Populations)

	CAB + RPV Q4W Day 1 to Week 52 N=308 n (%)	CAR Day 1 to Week 52 N=308 n (%)	CAB + RPV Q4W Day 1 to Week 96 N=308 n (%)	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 N=174 n (%)
All Parameters	**63 (20)**	**57 (19)**	**69 (22)**	**10 (6)**
ALT	4 (1)	1 (<1)	6 (2)	0
AST	7 (2)	0	9 (3)	0
Bilirubin	1 (<1)	2 (<1)	2 (<1)	0
Cholesterol	0	1 (<1)	0	1 (<1)
Creatine Kinase	24 (8)	12 (4)	27 (9)	1 (<1)
Creatinine	1 (<1)	0	1 (<1)	0
Direct Bilirubin	6 (2)	8 (3)	8 (3)	0
GFR from creatine adjusted using CKD-EPI	8 (3)	8 (3)	9 (3)	1 (<1)
Glucose	2 (<1)	5 (2)	3 (<1)	1 (<1)
Hyperglycemia	1 (<1)	4 (1)	1 (<1)	1 (<1)
Hyperkalemia	2 (<1)	2 (<1)	3 (<1)	0
Hypoglycemia	1 (<1)	1 (<1)	2 (<1)	0
LDL Cholesterol	3 (<1)	3 (<1)	5 (2)	1 (<1)
Lipase	15 (5)	8 (3)	15 (5)	5 (3)
Phosphate	10 (3)	14 (5)	10 (3)	1 (<1)
Potassium	2 (<1)	2 (<1)	3 (<1)	0
Triglycerides	1 (<1)	0	1 (<1)	0

Data Source: GSK Doc. # 2019N399072_00 in-text Table 17.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.
Note: Fasting data are shown for lipids and glucose. Subjects with missing Baseline values were assumed to be normal.

Phase IIB Results

At EOS in Study LAI116482, of subjects who had a treatment-emergent laboratory abnormality, the largest proportion of subjects in both the CAB +RPV and EFV groups had a maximum toxicity of Grade 1 or Grade 2 (Table 55). Proportions of subjects with maximum toxicities of Grade 3 or 4 were similar between the CAB + RPV and EFV groups.

Table 55 Summary of Maximum Treatment-Emergent Laboratory Toxicities in Study LAI116482 at End of Study (Safety Population)

All Parameters	CAB 10 mg + RPV (N=60) N (%)	CAB 30 mg + RPV (N=60) N (%)	CAB 60 mg + RPV (N=61) N (%)	CAB + RPV Subtotal (N=181) N (%)	EFV 600 mg + 2 NRTIs (N=62) N (%)
Grade 1	14 (23)	8 (13)	7 (11)	29 (16)	14 (23)
Grade 2	18 (30)	30 (50)	21 (34)	69 (38)	16 (26)
Grade 3	14 (23)	8 (13)	18 (30)	40 (22)	14 (23)
Grade 4	11 (18)	9 (15)	13 (21)	33 (18)	9 (15)

Data Source: GSK Doc. # 2019N404586_00 Table 8.35.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

At Week 160 in Study 200056, of subjects who had a treatment-emergent laboratory abnormality, the largest proportion of subjects for both the Safety Maintenance and Extension Switch Populations had a maximum toxicity of Grade 1 or Grade 2 (Table 58).

Table 56 Summary of Maximum Maintenance and Extension Period Treatment-Emergent Clinical Chemistry Toxicities (Relative to Maintenance Baseline) and During Extension Period (Relative to Extension Baseline) in Study 200056 at Week 160 (Safety Maintenance and Extension Switch Populations)

All Parameters	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	IM Total N=230 n (%)	Optimized Q8W IM[c] N=34 n (%)	Optimized Q4W IM[d] N=10 n (%)	Optimized IM Total N=44 n (%)
Grade 1	31 (27)	32 (28)	63 (27)	9 (26)	4 (40)	13 (30)
Grade 2	49 (43)	41 (36)	90 (39)	13 (38)	4 (40)	17 (39)
Grade 3	15 (13)	28 (24)	43 (19)	3 (9)	0	3 (7)
Grade 4	13 (11)	10 (9)	23 (10)	0	1 (10)	1 (2)

Data Source: GSK Doc. # 2018N380094_00 Table 8.1061 and Table 8.1066.
a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 weeks.
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 weeks.
c. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension Period.
d. Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension Period.

3.1.1. Liver Chemistry

Details about AEs potentially related to hepatotoxicity and monitoring of liver chemistry (ie, LSC) in the CAB + RPV development program are presented in Section 2.1.6.2.

3.1.1.1. Week 48 Phase III/IIIB Results

Overall Hepatobiliary Abnormalities

Table 57 presents a summary of subjects with hepatobiliary abnormalities during the MP (Week 48 analysis) in Studies 201584 and 201585. 4 subjects (2 in the CAB + RPV Q4W group; 2 in the CAR group) had ALT >3xULN and total bilirubin >2xULN.

In Studies 201584 and 201585, 10 subjects had acute viral hepatitis in the CAB + RPV Q4W group (6 subjects in Study 201584 and 4 subjects in Study 201585) and 3 subjects had acute viral hepatitis in the CAR group (2 subjects in Study 201584 and 1 subject in Study 201585) (Table 44 and Section 5.1.2). Other cases of LSC were due to transaminitis related to illicit drug use and inorganic solvent abuse and known Gilbert's disease with reported alcohol use prior to the clinic visit. Refer to Section 2.1.6.2 for additional details of assessment of potential hepatotoxicity in these cases.

Table 57 Summary of Subjects Meeting Hepatobiliary Abnormality Criteria at Any Post-Baseline Visit for Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

Laboratory Criteria[a,b]	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=282) n (%)	CAR (N=281) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=307) n (%)	CAB + RPV Q4W (N=590) n (%)	CAR (N=588) n (%)
ALT ≥3xULN and BIL ≥2xULN[c,d]	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Hepatocellular injury[e]	12 (4)	5 (2)	4 (1)	0	16 (3)	5 (<1)
Hepatocellular injury[e] and BIL ≥2xULN[c,d]	1 (<1)	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
ALT ≥3xULN - <5xULN	4 (1)	2 (<1)	1 (<1)	0	5 (<1)	2 (<1)
ALT ≥5xULN - <10xULN	5 (2)	1 (<1)	1 (<1)	0	6 (1)	1 (<1)
ALT ≥10xULN - <20xULN	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)
ALT ≥20xULN	3 (1)	1 (<1)	2 (<1)	0	5 (<1)	1 (<1)
BIL ≥2xULN[c]	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Time from First Dose to First ALT Elevation ≥3xULN (days)						
n (%)	12 (4)	5 (2)	5 (2)	1 (<1)	17 (3)	6 (1)
Mean	159.3	222.8	195.0	56.0	169.8	195.0
SD	114.06	108.77	123.01		114.06	118.75
Median	175.5	252.0	148.0	56.0	175.0	196.0
Min, Max	6, 379	81, 335	70, 377	56, 56	6, 379	56, 335

Data Source: ISS/ISE Table 3.135.

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

a. Subjects may be counted in more than one category.
b. ALT: alanine aminotransferase; ALP: alkaline phosphatase; BIL: total bilirubin; INR: International Normalized Ratio; ULN: upper limit of normal.
c. If direct bilirubin is available (on the same date as total bilirubin), then direct bilirubin as a portion of total bilirubin must be ≥35% when total bilirubin is ≥2xULN, in order to satisfy the criteria.
d. Bilirubin value is on or up to 28 days after ALT value.
e. Hepatocellular injury is defined as ([ALT/ALT ULN)/(ALP/ALP ULN])≥5 and ALT≥3xULN. ALT and ALP values must occur on the same day.

In Study 207966, 18 subjects had ALT ≥3xULN (Table 58). Hepatocellular injury criteria were reported for <1% of subjects in the Q8W group and 2% of subjects in the Q4W group. All subjects with ALT ≥3xULN to <5xULN remained in the study with the exception of one subject in the Q4W group, who had nonserious AEs of headache, hyperhidrosis, nausea, and presyncope (3 months after ALT elevation) that led to withdrawal from the study. One subject with ALT ≥3xULN to <5xULN had acute hepatitis E; additional details on this case are presented in Section 2.1.6.2.

Table 58 Summary of Subjects Meeting Hepatobiliary Abnormality Criteria in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

Laboratory Criteria[a] n (%)	CAB + RPV Q8W (N=522)	CAB + RPV Q4W (N=523)
n	520	521
Hepatocellular injury[b]	4 (<1)	11 (2)
n	520	521
Hepatocellular injury[b] and BIL ≥2xULN[c, d]	1 (<1)	2 (<1)
n	520	521
ALT ≥3xULN	5 (<1)	13 (2)
ALT ≥5xULN	2 (<1)	5 (<1)
ALT ≥8xULN	2 (<1)	3 (<1)
ALT ≥10xULN	1 (<1)	2 (<1)
ALT ≥20xULN	1 (<1)	2 (<1)

Data Source: GSK Doc. # 2019N406358_01 Table 3.57.

a. Subjects may be counted in more than one category.
b. Hepatocellular injury is defined as ([ALT/ALT ULN)/(ALP/ALP ULN]) ≥5 and ALT ≥3xULN. ALT and ALP values must occur on the same day.
c. If direct bilirubin is available (on the same date as Total Bilirubin), then direct bilirubin as a portion of total bilirubin must be ≥35% when total bilirubin is ≥2xULN, in order to satisfy the criteria.
d. Bilirubin value is on or up to 28 days after ALT value.

ALT

The occurrences of liver enzyme abnormalities in Studies 201584, 201585, and 207966 were primarily associated with acute hepatitis infections (Table 59). A scatter plot of maximum vs. Baseline for ALT in Studies 201584 and 201585 is provided in Data Source: GSK Doc. # 2017N345267_00 Figure 3.2 and GSK Doc. # 2018N370336_00 Figure 3.2.

In Study 207966, there were no clinically relevant differences between treatment groups for maximum post-Baseline ALT in either frequency or toxicity grade (Table 59 and Figure 11). Apart from the 1 subject with possible DILI, the remainder of subjects with ALT abnormalities (ALT>5xULN) were explained either by acute viral hepatitis (hepatitis B, C, and E) or concomitant use of Melanotan II (Section 2.1.6.2). Additional information for liver chemistry abnormalities is provided in GSK Doc. # 2019N406358_01 Section 7.2.1.1.

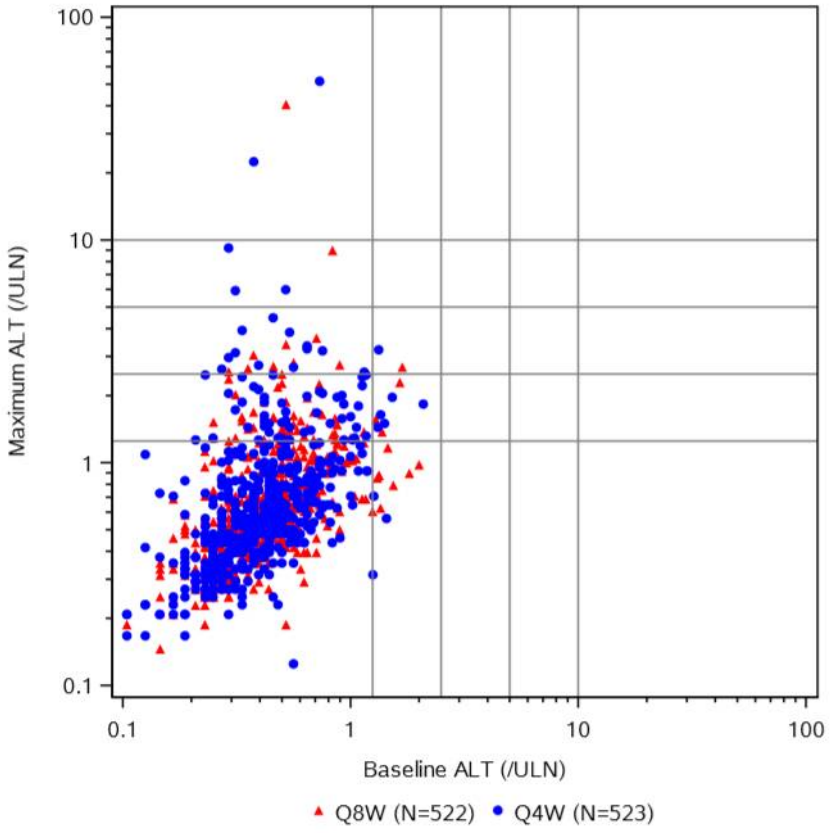
Table 59 Summary of Maximum Post-Baseline Intensity of ALT in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	201584		201585		Pooled Studies 201584 and 201585		Study 207966	
Grade (s)	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
1 to 4	**44 (16)**	**29 (10)**	**46 (15)**	**33 (11)**	**90 (15)**	**62 (10)**	**57 (11)**	**67 (13)**
1	28 (10)	22 (8)	38 (12)	28 (9)	66 (11)	50 (8)	45 (9)	49 (9)
2	9 (3)	4 (1)	4 (1)	4 (1)	13 (2)	8 (1)	10 (2)	13 (2)
3	4 (1)	1 (<1)	1 (<1)	0	5 (<1)	1 (<1)	1 (<1)	3 (<1)
4	3 (1)	2 (<1)	3 (<1)	1 (<1)	6 (1)	3 (<1%)	1 (<1)	2 (<1)

Data Source: ISS/ISE Table 3.123; GSK Doc. # 2019N406358_01 Table 3.43.
Note: No Grade 5 chemistry toxicities were reported.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

The 3 subjects who had elevations of ALT (upper left quadrant of Figure 11) in Study 207966 are the same 3 subjects who had elevations of both total bilirubin and ALT (upper right quadrant of Figure 14); these 3 subjects were identified as having acute viral hepatitis; see GSK Doc. # 2019N406358_01 Section 7.1.5.3.2 for details.

Figure 11 Scatter Plot of Maximum vs. Baseline for ALT in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 3.12.
Note: Axes are on a log10 scale.
Note: Reference lines at 1.25, 2.5, 5 and 10 represent DAIDS Grade 1 to 4 toxicity levels, respectively.
Note: The 3 outliers (upper left) had acute viral hepatitis; see GSK Doc. # 2019N406358_01 Section 7.1.5.3.2.

Post-Baseline Emergent Increases in ALT ≥3xULN in Studies 201584 and 201585

In Studies 201584 and 201585, there were 17 subjects in the CAB + RPV Q4W group and 6 subjects in the CAR group with elevations of ALT ≥3xULN (Table 60). Most of these subjects met LSC; however, 9 of the elevations were due to other causes.

Table 60 Summary of Subjects with Post-Baseline Emergent Increases in ALT At Least 3xULN in Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)

Study	Treatment Group	ALT	AST	Total Bilirubin	Resolved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201584	CAR	4.1xULN	16.6xULN	WNL	Y	N	NA
	CAR	3.7xULN	8xULN	WNL	Y	N	NA
	CAB + RPV Q4W	4xULN	10.9xULN	WNL	Y	N	NA
	CAB + RPV Q4W	4.4xULN	2.5xULN	WNL	Y	N	NA
	CAB + RPV Q4W	3.9xULN	2.7xULN	1.4xULN	Y	N	NA
	CAB + RPV Q4W	4.6xULN	2xULN	WNL	Y	N	NA
	CAR	5.1xULN	4.4xULN	WNL	Y	N	NA
	CAB + RPV Q4W	20.8xULN	12.5xULN	WNL	Y	Y	Acute hepatitis C
	CAB + RPV Q4W	8.8xULN	3.1xULN	1.5xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	43.7xULN	36.5xULN	1.3xULN	Y	Y	Illicit IV drug use, inorganic solvent abuse, chronic hepatitis C
	CAB + RPV Q4W	30.2xULN	17.9xULN	1.7xULN	N	Y	Acute hepatitis B
	CAB + RPV Q4W	98.1xULN	89.3xULN	6.9xULN	Y	N, Restarted Treatment	Acute hepatitis A
	CAB + RPV Q4W	7.4xULN	≥6.7xULN	1.7xULN	Y	N	Liver monitoring event. Never met LSC. Alcohol use 2 days before study visit; AE of direct bilirubin increased (known Gilbert's)
	CAB + RPV Q4W	155xULN	176.5xULN	7xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	8.1xULN	5.3xULN	1.5xULN	Y	Y	Acute hepatitis B
	CAR	10.4xULN	6.0xULN	WNL	Y	Y	Acute hepatitis E
	CAR	24.1xULN	18.5xULN	5.3xULN	Y	Y	Acute hepatitis A

Study	Treatment Group	ALT	AST	Total Bilirubin	Resolved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201585	CAB + RPV Q4W	4xULN	NA	2.9xULN	Y	N	NA
	CAB + RPV Q4W	42.9xULN	29.2xULN	1.2xULN	Y	Y	Acute hepatitis B
	CAB + RPV Q4W	14.7xULN	6.7xULN	1.3xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	8.6xULN	4.8xULN	8xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	21.6xULN	8.4xULN	2.1xULN	N	Y	Acute hepatitis C
	CAR	10.4xULN	4.5xULN	5.6xULN	Y	N, Re-started treatment	Acute hepatitis A

Data Source: ISS/ISE Table 3.135, Listing 3; GSK Doc. # 2017N345267_00 Section 7.3.3.1.2, Listing 61, Listing 64; GSK Doc. # 2018N370336_00 Section 7.3.3.1.2, Listing 56.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: Liver chemistry parameters represent peak values.
Each row represents an individual subject.

Post-Baseline Emergent Increases in ALT ≥3xULN but <5xULN in Studies 201584 and 201585

In Studies 201584 and 201585, 5 subjects treated with CAB + RPV Q4W and 2 subjects in the CAR group had post-Baseline emergent ALT values ≥3xULN but <5xULN at any post-Baseline visit (Table 61). None of these subjects met LSC.

Table 61 Summary of Subjects with Post-Baseline Emergent Increases in ALT At Least 3xULN But <5xULN in Studies 201584 and 201585 – Week 48 Analysis - Maintenance Phase (Safety Population)

Study	Treatment Group	ALT	AST	Total Bilirubin	Resolved	Withdrew from study
201584	CAR	4.1xULN	16.6xULN	WNL	Y	N
	CAR	3.7xULN	8xULN	WNL	Y	N
	CAB + RPV Q4W	4xULN	10.9xULN	WNL	Y	N
	CAB + RPV Q4W	4.4xULN	2.5xULN	WNL	Y	N
	CAB + RPV Q4W	3.9xULN	2.7xULN	1.4xULN	Y	N
	CAB + RPV Q4W	4.6xULN	2xULN	WNL	Y	N
201585	CAB + RPV Q4W	4xULN	NA	2.9xULN	Y	N

Data Source: ISS/ISE Table 3.135; GSK Doc. # 2017N345267_00 Section 7.3.3.1.2, Listing 61, Listing 64; GSK Doc. # 2018N370336_00 Section 7.7.1.1, Listing 56.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: Liver chemistry parameters represent peak values.
Each row represents an individual subject.

Post-Baseline Emergent Increases in ALT ≥5xULN but <10xULN in Studies 201584 and 201585

In Studies 201584 and 201585, 5 subjects treated with CAB + RPV Q4W and 1 subject in the CAR group had post-Baseline emergent ALT values ≥5xULN but <10xULN at any post-Baseline visit (Table 62).

Table 62 Subjects with Post-Baseline Emergent Increases in ALT At Least 5xULN but <10xULN in Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)

Study	Treatment Group	ALT	AST	Total Bilirubin	Re-solved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201584	CAB + RPV Q4W	8.8xULN	3.1xULN	1.5xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	7.4xULN	≥6.7xULN	1.7xULN	Y	N	Liver monitoring event. Never met LSC. Alcohol use 2 days before study visit; AE of direct bilirubin increased (known Gilbert's)
	CAB + RPV Q4W	8.1xULN	5.3xULN	1.5xULN	Y	Y	Acute hepatitis B
	CAB + RPV Q4W	6.5xULN	4.4xULN	WNL	Y	N	NA
	CAR	5.1xULN	4.4xULN	WNL	Y	N	NA
201585	CAB + RPV Q4W	8.6xULN	4.8xULN	8xULN	Y	Y	Acute hepatitis A

Data Source: ISS/ISE Listing 3; GSK Doc. # 2019N421511_00 Section 7.3.3.1.2, Listing 61, Listing 64; GSK Doc. # 2018N370336_00 Section 7.3.3.1.2, Listing 56.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: liver chemistry parameters represent peak values.
Each row represents an individual subject.

Post-Baseline Emergent Increases in ALT ≥10xULN in Studies 201584 and 201585

In Studies 201584 and 201585, 8 subjects treated with CAB + RPV Q4W and 3 subjects in the CAR group had post-Baseline emergent ALT values ≥10xULN at the Week 48 analysis (Table 63). All of these subjects met LSC and were subsequently identified as having acute viral hepatitis or inorganic solvent abuse.

Table 63 Summary of Subjects with Maximum Post-Baseline Emergent ALT At Least 10xULN in Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)

Study	Treatment Group	Study Phase	ALT	AST	Total Bilirubin	Re-solved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201584	CAB + RPV Q4W	MP – oral (Week 4)	20.8xULN	12.5xULN	WNL	Y	Y	Acute hepatitis C
	CAB + RPV Q4W	MP – oral (Baseline)	43.7xULN	36.5xULN	1.3xULN	Y	Y	Illicit IV drug use, inorganic solvent abuse, chronic hepatitis C
	CAB + RPV Q4W	MP – LA (Week 20)	30.2xULN	17.9xULN	1.7xULN	N	Y	Acute hepatitis B
	CAB + RPV Q4W	MP – LA (Week 32)	98.1xULN	89.3xULN	6.9xULN	Y	N, Restarted Treatment	Acute hepatitis A
	CAB + RPV Q4W	MP – LA	155xULN	176.5xULN	7xULN	Y	Y	Acute hepatitis A
	CAR	MP (Week 36)	10.4xULN	6.0xULN	WNL	Y	Y	Acute hepatitis E
	CAR	MP (F/U 3 weeks after Week 8)	24.1xULN	18.5xULN	5.3xULN	Y	Y	Acute hepatitis A
201585	CAB + RPV Q4W	MP – LA (Week 12)	42.9xULN	29.2xULN	1.2xULN	Y	Y	Acute hepatitis B
	CAB + RPV Q4W	MP – LA (Week 36 to 40)	14.7xULN	6.7xULN	1.3xULN	Y	Y	Acute hepatitis A
	CAB + RPV Q4W	MP – LA (Week 24)	21.6xULN	8.4xULN	2.1xULN	N	Y	Acute hepatitis C
	CAR	MP (Week 8)	10.4xULN	4.5xULN	5.6xULN	Y	N, Restarted treatment	Acute hepatitis A

Data Source: ISS/ISE Table 3.135, Listing 3; GSK Doc. # 2017N345267_00 Section 7.3.3.1.2, Listing 61, Listing 64; GSK Doc. # 2018N370336_00 Section 7.3.3.1.2, Listing 56.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: liver chemistry parameters represent peak values.
Each row represents an individual subject.

In Study 207966, 18 subjects had ALT ≥3xULN (Table 64).

Post-Baseline Emergent Increases in ALT in Study 207966

Table 64 Summary of Subjects with ALT Greater Than or Equal to 3xULN in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

Criteria[a]	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
ALT ≥3xULN to <5xULN	3 (<1)	8 (2)
ALT ≥5xULN to <10xULN	1 (<1)	3 (<1)
ALT ≥10xULN to <20xULN	0	0
ALT≥20xULN	1 (<1)	2 (<1)

Data Source: GSK Doc. # 2019N406358_01 Table 3.57.
a. Subjects may be counted in more than one category.

Maximum severity of Grade 3 or 4 treatment-emergent ALT abnormalities was observed in 2 (<1%) subjects in the Q8W group and 5 (<1%) subjects in the Q4W group (Table 59). These subjects met LSC or were monitored for hepatobiliary abnormalities during the MP (Week 48 analysis) (GSK Doc. # 2019N406358_01 in-text Table 41). Most subjects who met LSC met it due to acute viral hepatitis.

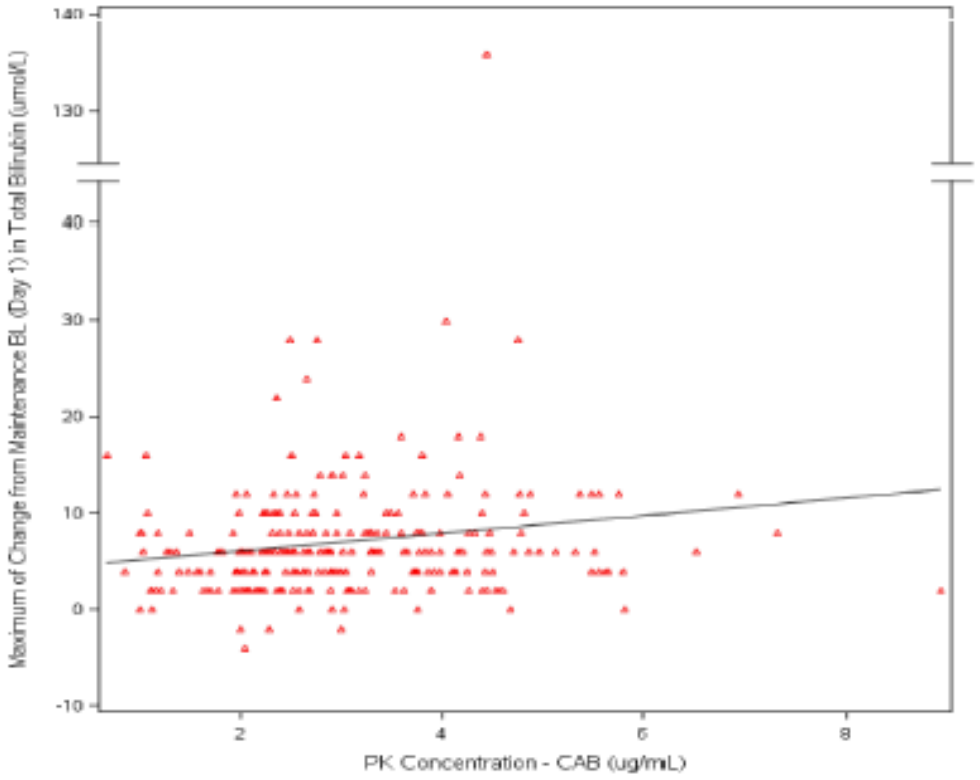
Bilirubin

During Studies 201584 and 201585, isolated, asymptomatic, non-progressive total bilirubin elevations have been observed without other liver chemistry abnormalities present (including transaminases). Total bilirubin elevations were mostly Grade 1 or 2 (57/59 CAB + RPV Q4W; 28/31 CAR) (Data Source: ISS/ISE Table 3.123). No Grade 3 bilirubin elevations occurred. Five Grade 4 elevations occurred (2 CAB + RPV Q4W; 3 CAR).

The relationship between last CAB trough concentration and maximum change in bilirubin in Study 201584 is shown in Figure 12. There was a positive correlation between increasing CAB concentrations and change in bilirubin. The bilirubin elevations could represent competition between CAB and unconjugated bilirubin for a common clearance pathway (UGT1A1). This is not considered to be clinically relevant and is likely to be reversible upon discontinuation of CAB.

Details of the PK/PD analysis are available in GSK Doc. # 2017N345267_00 Section 8.5 and in GSK Doc. # 2018N370336_00 Section 8.5.

Figure 12 Scatter Plot of Maximum Change from Maintenance Baseline (Day 1) in Total Bilirubin Versus Last Trough Concentration for CAB in Study 201584 - Week 48 Analysis - Maintenance Phase (PK Population)

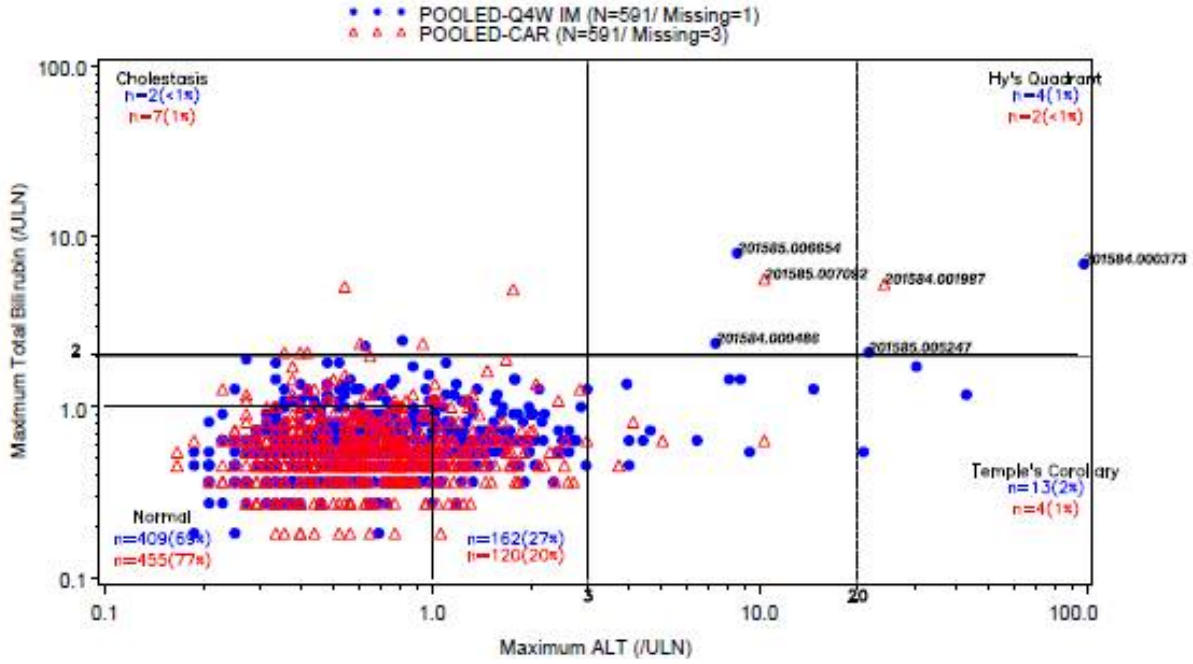


Data Source: GSK Doc. # 2017N345267_00 Figure 5.15.
Note: Line indicated linear regression between change from baseline in total bilirubin and PK concentration.

ALT and Bilirubin

An eDISH plot of maximum total bilirubin versus maximum ALT in pooled Studies 201584 and 201585 is provided in Figure 13. There were 15 subjects (6 CAB + RPV Q4W; 9 CAR) with bilirubin ≥2xULN, the majority of which occurred in subjects on concurrent treatment with ATV in the CAR group. An analysis of peak Baseline over Baseline ratio for total bilirubin vs. ALT was consistent (Data Source: ISS/ISE Figure 3.11).

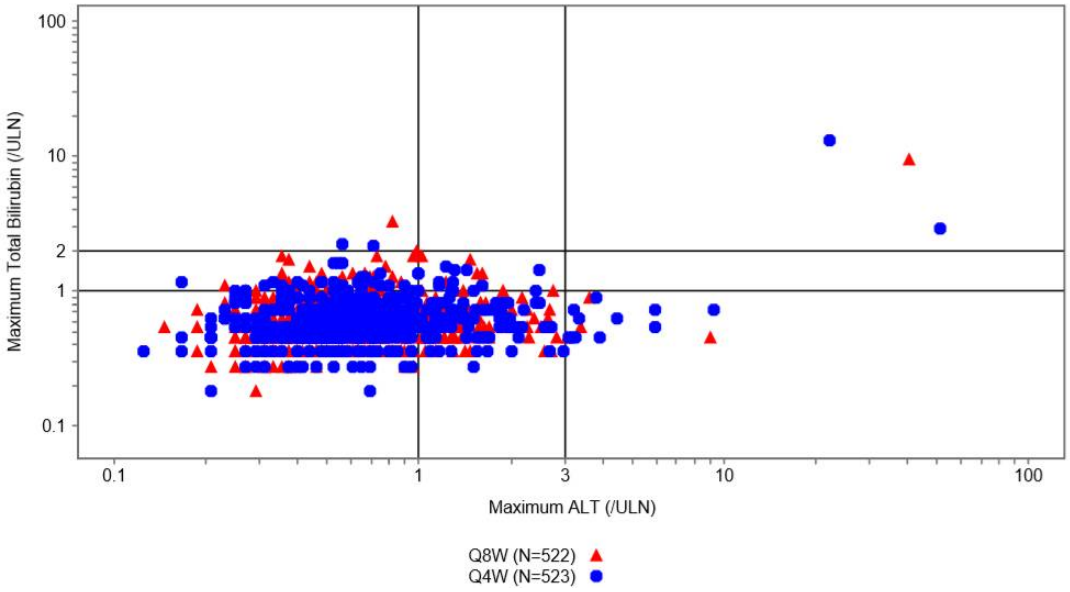
Figure 13 eDISH Plot of Maximum Total Bilirubin vs. Maximum ALT in Pooled Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: ISS/ISE Figure 3.10.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC
Note: Subject numbers are provided for subjects with maximum ALT >3xULN and maximum total bilirubin >2xULN.

In Study 207966, the 3 subjects who had elevations of both total bilirubin and ALT (upper right quadrant of Figure 14) were identified as having acute viral hepatitis; see GSK Doc. # 2019N406358_01 Section 7.1.5.3.2 for details.

Figure 14 Scatter Plot of Maximum Total Bilirubin vs. Maximum ALT in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: GSK Doc. # 2019N406358_01 Figure 3.13.
Note: Reference lines for Total Bilirubin represent 1xULN and 2xULN and for ALT 1xULN and 3xULN.
Note: The 3 outliers (upper right) had acute viral hepatitis; see GSK Doc. # 2019N406358_01 Section 7.1.5.3.2.

Post-Baseline Emergent Increases in ALT ≥3xULN and Total Bilirubin >2xULN and ALP <2xULN

In Studies 201584 and 201585, 2 subjects treated with CAB + RPV Q4W and 1 subject in the CAR group had a combination of ALT ≥3xULN with total bilirubin >2xULN and ALP <2xULN at any post-Baseline visit (Table 65). These 3 subjects had acute infectious hepatitis.

Table 65 Summary of Subjects with Post-Baseline Emergent Increases in ALT At Least 3xULN, Total Bilirubin >2xULN, and ALP <2xULN in Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)

Study	Treatment Group	ALT	AST	Total Bilirubin	Resolved	Withdrew from study	Reason for Meeting Liver Monitoring/ Stopping Criteria
201584	CAB + RPV Q4W	98.1xULN	89.3xULN	6.9xULN	Y	N, Restarted Treatment	Acute hepatitis A
	CAR	24.1xULN	18.5xULN	5.3xULN	Y	Y	Acute hepatitis A
201585	CAB + RPV Q4W	8.6xULN	4.8xULN	8xULN	Y	Y	Acute hepatitis A

Data Source: ISS/ISE Listing 3; GSK Doc. # 2017N345267_00 Section 7.3.3.1.2, Listing 61, Listing 64; GSK Doc. # 2018N370336_00 Section 7.3.3.1.2, Listing 56.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: Liver chemistry parameters represent peak values.
Each row represents an individual subject.

3.1.1.2. Longer-term Phase III Results

At the end of the MP in Study 201584, 6% of CAB + RPV Q4W subjects and 2% of CAR subjects had ALT ≥3xULN (Table 66).

Table 66 Summary of Subjects with ALT Greater Than or Equal to 3xULN in Study 201584 at Week 100 - Maintenance Phase (Safety Population)

	CAB+ RPV (N=283) n (%)	CAR (N=283) n (%)
n with laboratory test	**282**	**281**
ALT ≥3xULN	**17 (6)**	**6 (2)**
ALT ≥3xULN to <5xULN	7 (2)	2 (<1)
ALT ≥5xULN to <10xULN	6 (2)	1 (<1)
ALT ≥10xULN to <20xULN	0	2 (<1)
ALT≥20xULN	4 (1)	1 (<1)

Data Source: GSK Doc. # 2019N421511_00 Table 3.97
Note: Subjects were summarized based on the maximum post Baseline value.
Note: Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.

Grade 3 or 4 ALT toxicities for Study 201585, including in the Extension Phase, are presented in Table 54.

3.1.1.3. Phase IIB Results

At EOS in Study LAI116482, of subjects who had a treatment-emergent laboratory abnormality in liver chemistry parameters, most had an elevation in ALT and/or AST; few had elevations in ALP or total bilirubin (Table 67). The proportions of subjects with Grade 3 or 4 elevations in AST or ALT were similar between the CAB + RPV and EFV groups.

Table 67 Summary of Maximum Maintenance Treatment-Emergent Liver Chemistry Abnormalities in Study LAI116482 at End of Study (Safety Maintenance Population)

	CAB 10 mg + RPV (N=52) n (%)	CAB 30 mg + RPV (N=53) n (%)	CAB 60 mg + RPV (N=55) n (%)	CAB+ RPV Subtotal (N=160) n (%)	EFV 600 mg + 2 NRTIs (N=47) n (%)
Alanine Aminotransferase (IU/L)					
Grade 1	9 (17)	12 (23)	17 (31)	38 (24)	6 (13)
Grade 2	6 (12)	6 (11)	5 (9)	17 (11)	3 (6)
Grade 3	0	1 (2)	0	1 (<1)	0
Grade 4	1 (2)	1 (2)	0	2 (1)	1 (2)
Alkaline Phosphatase (IU/L)					
Grade 1	2 (3)	1 (2)	4 (7)	7 (4)	5 (8)
Grade 2	0	1 (2)	0	1 (<1)	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Aspartate Aminotransferase (IU/L)					
Grade 1	5 (10)	13 (25)	13 (24)	31 (19)	5 (11)
Grade 2	5 (10)	8 (15)	5 (9)	18 (11)	2 (4)
Grade 3	2 (4)	0	2 (4)	4 (3)	3 (6)
Grade 4	2 (4)	1 (2)	0	3 (2)	2 (4)
Total Bilirubin (μMOL/L)					
Grade 1	7 (13)	1 (2)	8 (15)	16 (10)	0
Grade 2	2 (4)	3 (6)	4 (7)	9 (6)	0
Grade 3	0	1 (2)	0	1 (<1)	0
Grade 4	0	0	0	0	0

Data Source: GSK Doc. # 2019N404586_00 Table 8.38.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes. .

At Week 160 in Study 200056, of subjects who had a treatment-emergent abnormality in liver chemistry, the largest proportion of subjects had a maximum toxicity of Grade 1 (Table 68).

Table 68 Summary of Maximum Maintenance and Extension Period Treatment-Emergent Liver Chemistry Toxicities in Study 200056 at Week 160 (Safety Maintenance Population)

Relative to Maintenance Baseline	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	IM Total N=230 n (%)
Alanine Aminotransferase (IU/L)			
Grade 1	19 (17)	10 (9)	29 (13)
Grade 2	1 (<1)	5 (4)	6 (3)
Grade 3	3 (3)	2 (2)	5 (2)
Grade 4	3 (3)	3 (3)	6 (3)
Alkaline Phosphatase (IU/L)			
Grade 1	3 (3)	1 (<1)	4 (2)
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Aspartate Aminotransferase (IU/L)			
Grade 1	13 (11)	15 (13)	28 (12)
Grade 2	11 (10)	6 (5)	17 (7)
Grade 3	2 (2)	5 (4)	7 (3)
Grade 4	2 (2)	2 (2)	4 (2)
Total Bilirubin (µmol/L)			
Grade 1	12 (10)	10 (9)	22 (10)
Grade 2	7 (6)	4 (3)	11 (5)
Grade 3	0	1 (<1)	1 (<1)
Grade 4	0	0	0

Data Source: GSK Doc. # 2018N380094_00 Table 8.1061.

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 weeks.

b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 weeks.

Few subjects in the Extension Period had a treatment-emergent abnormality in liver chemistry and all had a maximum toxicity of Grade 1 or 2 (Table 69).

Table 69 Summary of Maximum Extension Period Treatment-Emergent Liver Chemistry Toxicities in Study 200056 at Week 160 (Extension Switch Population)

Relative to Extension Baseline	Optimized Q8W IM[a] N=34 n (%)	Optimized Q4W IM[b] N=10 n (%)	Optimized IM Total N=44 n (%)
Alanine Aminotransferase (IU/L), n (%)			
Grade 1	1 (3)	0	1 (2)
Grade 2	1 (3)	0	1 (2)
Grade 3	0	0	0
Grade 4	0	0	0
Alkaline Phosphatase (IU/L), n (%)			
Grade 1	1 (3)	0	1 (2)
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Aspartate Aminotransferase (IU/L), n (%)			
Grade 1	4 (12)	0	4 (9)
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	0	0
Total Bilirubin (µmol/L), n (%)			
Grade 1	0	1 (10)	1 (2)
Grade 2	1 (3)	0	1 (2)
Grade 3	0	0	0
Grade 4	0	0	0

Data Source: GSK Doc. # 2018N380094_00 Table 8.1066.

a. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 weeks during the Extension Period.

b. Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 weeks during the Extension Period.

3.1.2. Creatinine

Results for AEs potentially related to impact on creatinine are presented in Section 2.1.6.11.

Week 48 Phase III/IIIB Results

Analysis of cystatin-c, assessed in Studies 201584 and 201585 only, did not suggest worsening of eGFR, glomerular disease, or proximal tubule dysfunction (Table 70). A median decrease in serum creatinine of 3.5 µmol/L at Week 48 (from Baseline) was observed for the CAB + RPV Q4W group in Studies 201584 and 201585. Retinol binding protein laboratory results are presented in Section 3.1.5.

In Studies 201584 and 201585, subjects in the CAB + RPV Q4W group had stable levels of serum creatinine through 48 weeks (ISS/ISE Table 3.118). The change from Baseline in CKD-EPI GFR from creatinine (mL/min/1.73 m^2) showed no significant difference between the CAB + RPV Q4W group and CAR group and little change from Baseline in either treatment group (Data Source: ISS/ISE Table 3.118). No clinically significant changes from Baseline over 48 weeks in eGFR using cystatin C were observed based on median values in either treatment group in Studies 201584 and 201585 (Data Source: GSK Doc. # 2017N345267_00 Table 3.55; GSK Doc. # 2018N370336_00 Table 3.56). Changes from Baseline in creatinine and cystatin C are presented in Table 70.

Table 70 Summary of Chemistry Changes from Baseline in Creatinine and Cystatin C During Maintenance Phase for Pooled Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)

Treatment	N	Actual Relative Time	n	Mean	SD	Median	Q1	Q3	Min.	Max.
Creatinine (umol/L)										
CAB + RPV Q4W	591	Baseline	591	83.8	16.961	83.1	71.6	95.5	43	149
		Week 48	512	-3.5	11.790	-3.5	-11.5	3.6	-42	83
CAR	591	Baseline	591	81.6	16.575	81.3	69.0	91.1	39	151
		Week 48	554	2.8	59.075	0.9	-5.3	5.3	-50	1376
Cystatin C (mg/L)										
CAB + RPV Q4W	591	Baseline	589	0.7	0.144	0.8	0.7	0.8	0	1
		Week 48	542	0	0.113	0	-0.1	0	0	0
CAR	591	Baseline	585	0.7	0.148	0.7	0.7	0.8	0	1
		Week 48	552	0	0.118	0	-0.1	0.1	0	0

Data Source: ISS/ISE Table 3.118.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

During Studies 201584 and 201585 through 48 weeks of treatment, 10 subjects in the CAB + RPV Q4W group and 18 subjects in the CAR group had maximum post-Baseline Grade 1 or 2 elevations in creatinine laboratory values (Table 71). 1 subject in the CAB + RPV Q4W group had a Grade 3 elevation, and 1 subject in the CAR group developed a Grade 4 elevation. However, there was no clinically significant difference in incidence of Grades 1 to 4 creatinine elevations between the CAB + RPV Q4W group and the CAR group.

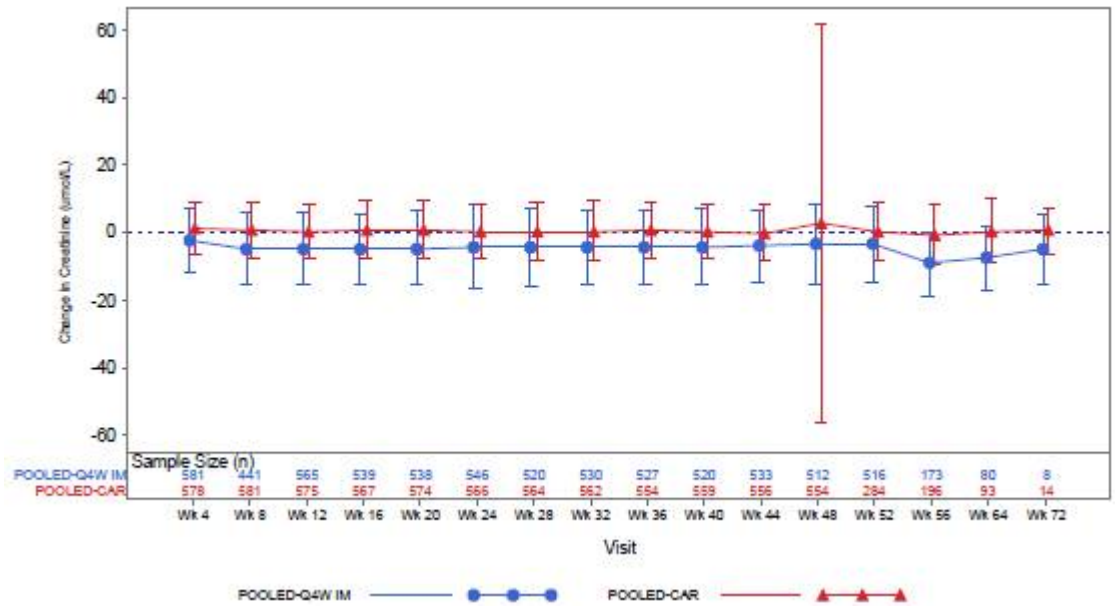
Table 71 Summary of Maximum Post-Baseline Intensity of Creatinine (mg/dL) Elevations in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) N (%)	CAR (N=283) N (%)	CAB + RPV Q4W (N=308) N (%)	CAR (N=308) N (%)	CAB + RPV Q4W (N=591) N (%)	CAR (N=591) N (%)
Grade 1	4 (1)	9 (3)	5 (2)	6 (2)	9 (2)	15 (3)
Grade 2	1 (<1)	2 (<1)	0	1 (<1)	1 (<1)	3 (<1)
Grade 3	0	0	1 (<1)	0	1 (<1)	0
Grade 4	0	1 (<1)	0	0	0	1 (<1)

Data Source: ISS/ISE Table 3.123.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

During Studies 201584 and 201585, for CAB + RPV Q4W through 48 weeks of treatment, there was a median 3.5 μmol/L decrease in serum creatinine from Baseline, which was not considered clinically significant (Figure 15 and ISS/ISE Table 3.118). This decrease may represent a switch from DTG to CAB, which does not impact the OCT2 transporter and thus does not produce a factitious elevation in creatinine. No clinically significant changes were observed in the CAR group (median increase of 0.9 μmol/L).

Figure 15 Mean (±SD) Creatinine Change from Baseline Over Time in Pooled Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)



Data Source: ISS/ISE Figure 3.14.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, there were no clinically relevant differences between treatment groups for creatinine results (GSK Doc. # 2019N406358_01 Section 7.2.1.2).

Longer-term Phase III Results

At the end of the MP in Study 201584, toxicities for creatinine occurred in 3% of subjects in the CAB + RPV Q4W group and 5% of subjects in the CAR group (GSK Doc. # 2019N421511_00 Section 7.5.1.2). Creatinine toxicities for CAB +RPV subjects were Grade 1 or 2.

Grade 3 or 4 creatinine toxicities for Study 201585, including in the Extension Phase, were observed in 1 CAB + RPV Q4W subject (<1%) as presented in Table 54.

Phase IIB Results

At EOS in Study LAI116482, of subjects who had a treatment-emergent abnormality in creatinine, all had a maximum toxicity of Grade 1 or 2 in both the CAB +RPV and EFV groups (Data Source: GSK Doc.# 2019N404586_00 Table 8.38).

At Week 160 in Study 200056, of subjects who had a treatment-emergent laboratory abnormality in creatinine, 1 subject (<1%) had a maximum toxicity of Grade 3 (Safety Maintenance Population), and all subjects in the Extension Switch Population had a maximum toxicity of Grade 1 (Data Source: GSK Doc.# 2018N380094_00 Table 8.1061 and Table 8.1066).

Conclusion

During Studies 201584 and 201585, for CAB + RPV Q4W there was a median 3.5 µmol/L decrease in serum creatinine from Baseline at Week 48, which was not considered clinically significant, confirming that CAB + RPV does not cause an increase in serum creatinine. There were few subjects who had a Grade 3 or 4 serum creatinine toxicity in studies with longer-term data.

Creatinine elevation has been associated with DTG, another drug in the INSTI class. This elevation does not lead to worsening renal function and is due to the inhibitory effect of DTG on OCT2. CAB has no inhibitory effect on OCT2. Small mean increases in serum creatinine have been observed with RPV therapy.

3.1.3. GFR

Week 48 Phase III/IIIB Results

Changes from Baseline in GFR measured by serum creatinine were mostly Grade 2 through 48 weeks in Studies 201584 and 201585 (Table 72). Also refer to results for eGFR based on cystatin C in the study reports (GSK Doc. # 2017N345267_00 Section 7.6.1.3 and GSK Doc. # 2018N370336_00 Section 7.7.1.3).

Table 72 Summary of Maximum Post-Baseline Intensity of GFR From Creatinine in Studies 201584, 201585, 201584+201585 Pooled – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) N (%)	CAR (N=283) N (%)	CAB + RPV Q4W (N=308) N (%)	CAR (N=308) N (%)	CAB + RPV Q4W (N=591) N (%)	CAR (N=591) N (%)
Grade 1	0	0	0	0	0	0
Grade 2	36 (13)	61 (22)	84 (27)	82 (27)	120 (20)	143 (24)
Grade 3	2 (<1)	12 (4)	7 (2)	8 (3)	9 (2)	20 (3)
Grade 4	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)

Data Source: ISS/ISE Table 3.123.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, there were no clinically relevant differences between treatment groups for eGFR results (GSK Doc. # 2019N406358_01 Section 7.2.1.3).

Longer-term Phase III Results

At the end of the MP in Study 201584, the majority of emergent eGFR toxicity values estimated using creatinine and adjusted for BSA were assessed as maximum Grade 2 (GSK Doc. # 2019N421511_00 Section 7.5.1.3). eGFR values assessed as maximum Grade 3 were observed in 2 (<1%) subjects in the CAB + RPV Q4W group and 15 (5%) subjects in the CAR group. In addition, one maximum Grade 4 event was observed in a subject in the CAR group.

Grade 3 or 4 eGFR toxicities for Study 201585, including in the Extension Phase, are presented in Table 54.

3.1.4. Proteinuria

Week 48 Phase III/IIIB Results

Urine Albumin/Creatinine and Protein/Creatinine Ratio Assessments

Urine albumin/creatinine ratio and protein/creatinine ratio were evaluated to further assess any impact of study treatment on renal function (particularly glomerular function).

In Studies 201584 and 201585, the median urine albumin/creatinine ratios and protein/creatinine ratios showed little change in either treatment group up to Week 48, confirming there was no adverse effect on renal tubular function. There were no significant differences between the treatment groups in either study (GSK Doc. # 2017N345267_00 Section 7.6.3; GSK Doc. # 2018N370336_00 Section 7.7.3).

In Study 207966, there were no clinically relevant differences between treatment groups for proteinuria results (GSK Doc. # 2019N406358_01 Section 7.2.3).

Longer-term Phase III Results

At the end of the MP in Study 201584, urine protein/creatinine showed no median change in the CAB + RPV Q4W group compared with a small increase in the CAR group (GSK Doc. # 2019N421511_00 Section 9.1). There were no median changes in urine albumin/creatinine ratio in either treatment group. Lastly, a higher proportion of subjects had negative proteinuria in the CAB + RPV Q4W (79%) group compared with the CAR (68%) group (GSK Doc. # 2019N421511_00 Section 7.5.3).

In Study 201585, urinalysis dipstick results demonstrated that values did not significantly change over time or between treatment groups. A summary of results by visit is presented for CAB + RPV Q4W and for Extension Switch to CAB + RPV Q4W groups (Data Source: GSK Doc. # 2019N399072_00 Table 13.36 and Table 13.37). A summary of urine laboratory parameters changes from Baseline by visit for CAB + RPV Q4W and for Extension Switch to CAB + RPV Q4W is presented (Data Source: GSK Doc. # 2019N399072_00 Table 13.38 and Table 13.39).

3.1.5. Retinol Binding Protein

These assessments were only done in Studies 201584 and 201585.

In Studies 201584 and 201585, retinol binding protein was also evaluated to further assess for any impact of study treatment on renal function given a majority of subjects were switching from a TDF-containing regimen (Section 1.3.3).

There were no clinically significant changes in retinol binding protein (Table 73), indicating that CAB + RPV treatment had no impact on renal tubule function.

Table 73 Summary of Changes from Baseline in Retinol Binding Protein for Pooled Studies 201584 and 201585 - Week 48 Analysis - Maintenance Phase (Safety Population)

Treatment	N	Actual Relative Time	n	Mean	SD	Median	Q1	Q3	Min.	Max.
Retinol Binding Protein (mg/dL)										
CAB + RPV Q4W	591	Baseline	584	4.8	1.356	4.8	3.9	5.7	1	14
		Week 48	536	-0.4	0.960	-0.4	-0.9	0.1	-6	3
CAR	591	Baseline	580	4.8	1.359	4.8	4.0	5.6	1	11
		Week 48	546	-0.2	0.936	-0.1	-0.7	0.3	-5	3

Data Source: ISS/ISE Table 3.118.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

3.1.6. Creatine Kinase

Results for AEs potentially related to rhabdomyolysis are presented in Section 2.1.6.9. There were no cases of rhabdomyolysis attributed to treatment with CAB + RPV during Studies 201584, 201585, and 207966.

Week 48 Phase III/IIIB Results

During the MP (Week 48 analysis) in Studies 201584 and 201585, 122 subjects in the CAB + RPV Q4W group and 94 subjects in the CAR group had post-Baseline-emergent elevated CK levels (Table 74). Grade 3 and 4 elevations of CK were observed in 47 (8%) subjects for CAB + RPV Q4W through 48 weeks of treatment, compared with 26 (4%) subjects in the CAR group. Approximately half of these were Grade 4 elevations (≥20xULN) in each treatment group. These CK elevations were transient, asymptomatic, and generally associated with subjects reporting strenuous exercise and/or weightlifting.

In Study 207966, results were similar to those observed in Studies 201584 and 201585, and there were no clinically relevant differences between the Q8W and Q4W groups for CK results (Table 74). All CK elevations were generally explained by physical exertion on the part of the subject or occurred in association with a reported increase in strenuous activity such as weightlifting (GSK Doc. # 2019N406358_01 Section 7.1.5.3.9).

Table 74 Summary of Maximum Post-Baseline Intensity CK (IU/L) Elevations in Studies 201584, 201585, 201584+201585 Pooled, and 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Grade	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
1	37 (13)	19 (7)	23 (7)	18 (6)	60 (10)	37 (6)	41 (8)	32 (6)
2	9 (3)	19 (7)	6 (2)	12 (4)	15 (3)	31 (5)	22 (4)	19 (4)
3	13 (5)	4 (1)	9 (3)	9 (3)	22 (4)	13 (2)	7 (1)	9 (2)
4	10 (4)	10 (4)	15 (5)	3 (<1)	25 (4)	13 (2)	9 (2)	14 (3)

Data Source: ISS/ISE Table 3.123; GSK Doc. # 2019N406358_01 Table 3.43.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Longer-term Phase III Results

At the end of the MP in Study 201584, toxicities for CK occurred in 30% of subjects in the CAB + RPV Q4W group and 23% of subjects in the CAR group (GSK Doc. # 2019N421511_00 Section 7.5.1.4). Maximum Grade 3 and 4 emergent CK toxicities were observed in 12% of subjects in the CAB + RPV Q4W group and 5% of subjects in the CAR group. CK elevations were transient, asymptomatic, and often associated with strenuous exercise (see Section 2.1.6.9).

Grade 3 or 4 CK toxicities for Study 201585, including in the Extension Phase, are presented in Table 54.

Phase IIB Results

At EOS in Study LAI116482, of subjects who had a treatment-emergent abnormality in CK, the proportion with a maximum toxicity of Grade 3 or 4 was similar between the CAB +RPV and EFV groups (Table 75). At Week 160 in Study 200056, of subjects who had a treatment-emergent laboratory abnormality in CK, 5% had a maximum toxicity of Grade 3 and 5% had a maximum toxicity of Grade 4.

Table 75 Summary of Maximum Post-Baseline Grade 3 and 4 Intensity Creatine Kinase (IU/L) Elevations in Phase IIB Studies LAI116482 (EOS) and 200056 (Week 160) (Safety Maintenance Populations)

	Study LAI116482 (EOS)					Study 200056 (Week 160)		
	CAB 10 mg + RPV N=52 n (%)	CAB 30 mg+ RPV N=53 n (%)	CAB 60 mg + RPV N=55 n (%)	CAB + RPV Subtotal N=160 n (%)	EFV 600 mg + 2 NRTIs N=47 n (%)	CAB + RPV Q8W N=115 n (%)	CAB + RPV Q4W N=115 n (%)	Subtotal IM CAB + RPV N=230 n (%)
Grade 3	3 (6)	2 (4)	4 (7)	9 (6)	3 (6)	5 (4)	7 (6)	12 (5)
Grade 4	6 (12)	6 (11)	5 (9)	17 (11)	5 (11)	6 (5)	6 (5)	12 (5)

Data Source: GSK Doc. # 2019N404586_00 Table 8.38 and GSK Doc. # 2018N380094_00 Table 8.1061.
Note: In Study LAI116482, at or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm in Study LAI116482 completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

At Week 160 in Study 200056, 1 subject in the Extension Switch Population had a CK value with a maximum toxicity of Grade 3, and no subjects had a CK value with a maximum toxicity of Grade 4 (Data Source: GSK Doc.# 2018N380094_00 Table 8.1066).

3.1.7. Lipase

Results for AEs potentially related to pancreatitis are presented in Section 2.1.6.10.

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, post-Baseline emergent lipase elevations were observed in both treatment groups at comparable frequencies for Grade 1 and 2 occurrences, although a slightly higher incidence was observed in the CAB + RPV Q4W group for Grade 3 and 4 events (Table 76). The majority of these changes were Grade 1 or 2 and were asymptomatic.

In Study 207966, results were similar to those observed in Studies 201584 and 201585, and there were no clinically relevant differences between the Q8W and Q4W groups for lipase results (Table 76).

Table 76 Summary of Maximum Post-Baseline Intensity Lipase (U/L) Elevations in Studies 201584, 201585, 201584+201585 Pooled, and 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
Grade	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
1	20 (7)	24 (8)	30 (10)	25 (8)	50 (8)	49 (8)	40 (8)	44 (8)
2	24 (8)	23 (8)	22 (7)	20 (6)	46 (8)	43 (7)	31 (6)	44 (8)
3	14 (5)	7 (2)	9 (3)	3 (<1)	23 (4)	10 (2)	13 (2)	4 (<1)
4	4 (1)	1 (<1)	6 (2)	5 (2)	10 (2)	6 (1)	3 (<1)	6 (1)

Data Source: ISS/ISE Table 3.123; GSK Doc. # 2019N406358_01 Table 3.43.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Longer-term Phase III Results

At the end of the MP in Study 201584, toxicities for lipase occurred in 27% of subjects in the CAB + RPV Q4W group and 23% of subjects in the CAR group (GSK Doc. # 2019N421511_00 Section 7.5.1.5). Maximum Grade 3 or 4 lipase toxicities were observed in 7% of subjects in the CAB + RPV Q4W group and 5% of subjects in the CAR group.

Grade 3 or 4 lipase toxicities for Study 201585, including in the Extension Phase, are presented in Table 54.

Phase IIB Results

At EOS in Study LAI116482, of subjects who had a treatment-emergent abnormality in lipase, most had a maximum toxicity ≤Grade 2 (Table 77).

Table 77 Summary of Maximum Treatment-Emergent Laboratory Toxicities for Lipase in Study LAI116482 at End of Study (Safety Maintenance Population)

	CAB 10 mg + RPV (N=52) N (%)	CAB 30 mg + RPV (N=53) N (%)	CAB 60 mg + RPV (N=55) N (%)	CAB + RPV Subtotal (N=160) N (%)	EFV 600 mg + 2 NRTIs (N=47) N (%)
Grade 1	9 (17)	9 (17)	8 (15)	26 (16)	9 (19)
Grade 2	9 (17)	8 (15)	11 (20)	28 (18)	7 (15)
Grade 3	5 (10)	1 (2)	6 (11)	12 (8)	0
Grade 4	2 (4)	0	2 (4)	4 (3)	0

Data Source: GSK Doc.# 2019N404586_00 Table 8.38.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

At Week 160 in Study 200056, of subjects who had a treatment-emergent abnormality in lipase, the largest proportion of subjects for both the Safety Maintenance and Extension Switch Populations had a maximum toxicity of ≤Grade 2 (Table 78).

Table 78 Summary of Maximum Maintenance and Extension Period Treatment-Emergent Lipase Toxicity (Relative to Maintenance Baseline) and During Extension Period (Relative to Extension Baseline) in Study 200056 at Week 160 (Safety Maintenance and Extension Switch Populations)

	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	IM Total N=230 n (%)	Optimized Q8W IM[c] N=34 n (%)	Optimized Q4W IM[d] N=10 n (%)	Optimized IM Total N=44 n (%)
Grade 1	9 (8)	9 (8)	18 (8)	3 (9)	1 (10)	4 (9)
Grade 2	12 (10)	12 (10)	24 (10)	4 (12)	0	4 (9)
Grade 3	5 (4)	7 (6)	12 (5)	1 (3)	0	1 (2)
Grade 4	3 (3)	0	3 (1)	0	1 (10)	1 (2)

Data Source: GSK Doc. # 2018N380094_00 Table 8.1061 and Table 8.1066.
a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 weeks.
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 weeks.
c. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension Period.
d. Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension Period.

3.1.8. Lipid Parameters

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, most of the treatment-emergent cholesterol and triglycerides abnormalities were Grade 1 or Grade 2 (Table 79). More Grade 1 cholesterol abnormalities occurred in the CAB + RPV Q4W group than in the CAR group. The differences in the changes in lipid profile between the groups were not clinically significant (Data Source: ISS/ISE Table 3.119).

In Study 207966, results were similar to those observed in Studies 201584 and 201585, and there were no clinically relevant differences between the Q8W and Q4W groups for cholesterol and triglyceride results (Table 79).

Table 79 Summary of Maximum Post-Baseline-Emergent Elevations for Lipid Parameters in Studies 201584, 201585, 201584+201585 Pooled, and 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

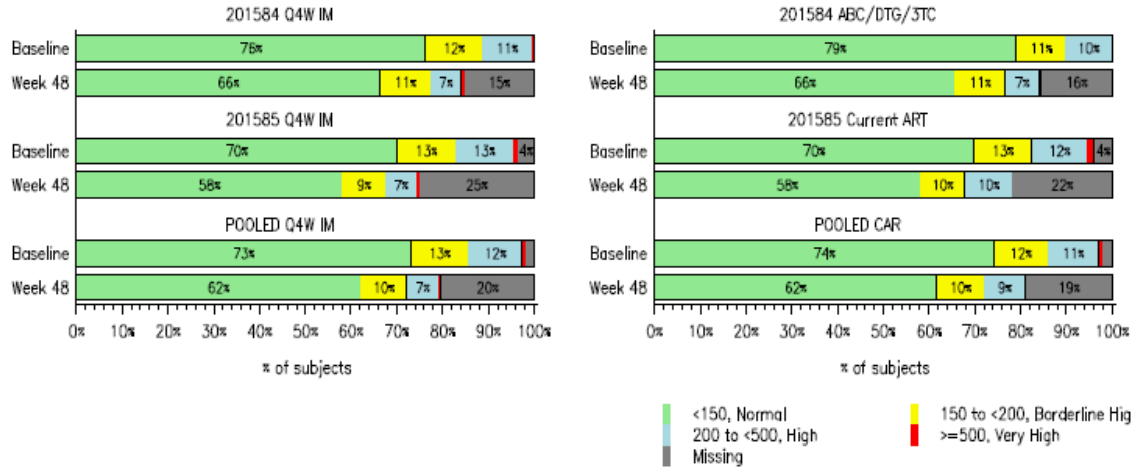
	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)	CAB + RPV Q8W (N=591) n (%)	CAB + RPV Q4W (N=591) n (%)
Cholesterol (mmol/L)								
Grade 1	30 (11)	18 (6)	39 (13)	14 (5)	69 (12)	32 (5)	50 (10)	52 (10)
Grade 2	15 (5)	8 (3)	10 (3)	17 (6)	25 (4)	25 (4)	31 (6)	30 (6)
Grade 3	0	0	0	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)
Grade 4	0	0	0	0	0	0	0	0
Triglycerides (mmol/L)								
Grade 1	14 (5)	24 (8)	20 (6)	25 (8)	34 (6)	49 (8)	51 (10)	42 (8)
Grade 2	3 (1)	5 (2)	6 (2)	6 (2)	9 (2)	11 (2)	11 (2)	3 (<1)
Grade 3	2 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)	4 (<1)	2 (<1)
Grade 4	0	0	0	0	0	0	0	2 (1)

Data Source: ISS/ISE Table 3.123; GSK Doc. # 2019N406358_01 Table 3.43.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

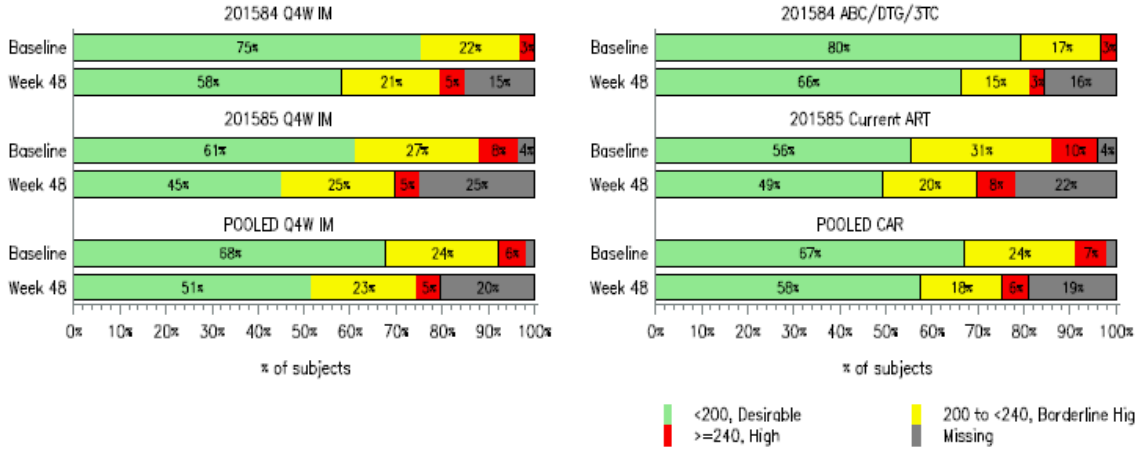
In Studies 201584 and 201585, results for fasting lipid NCEP categories at Week 48 vs. Baseline for triglycerides, total cholesterol, LDL, and HDL were similar in the 2 treatment groups (Figure 16). Shifts in laboratory values over the studies were similar between treatment groups and not clinically relevant for triglycerides, total cholesterol, HDL cholesterol, and LDL cholesterol, and TC/HDL ratio (Data Source: ISS/ISE Table 3.137, Table 3.138, Table 3.139, Table 3.140, Table 3.141, respectively).

Figure 16 Triglycerides, Total Cholesterol, LDL, and HDL at Week 48 vs. Baseline in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis – Maintenance Phase (Safety Population)

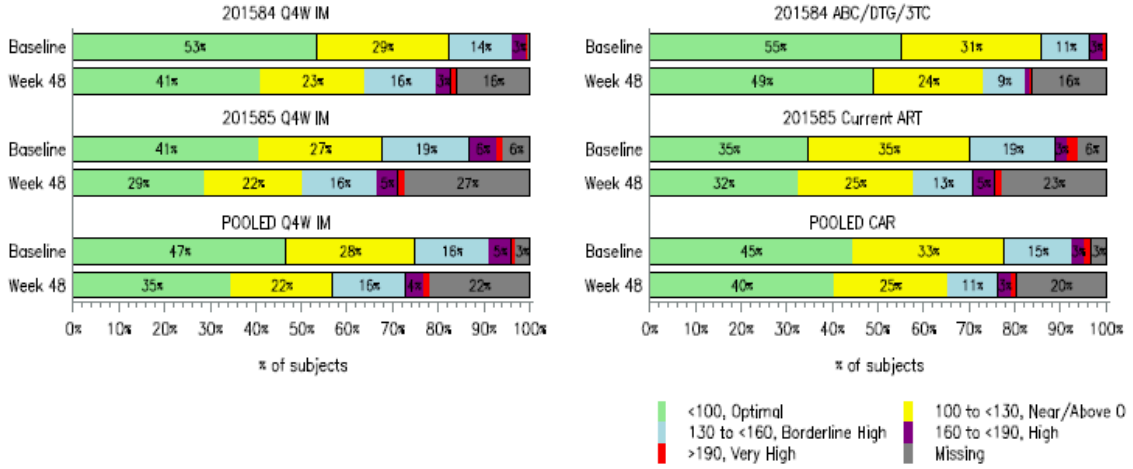
A. Triglycerides (mg/dL)



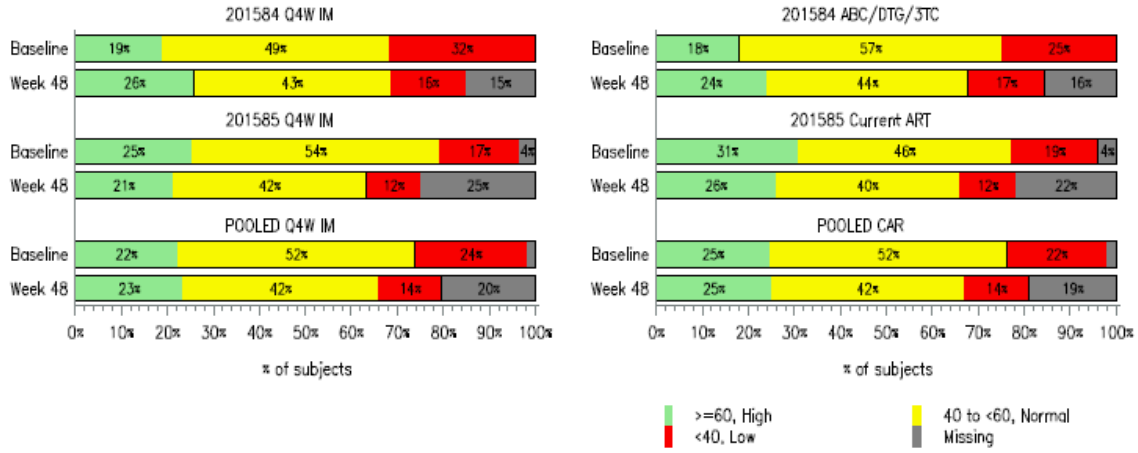
B. Total Cholesterol (mg/dL)



C. LDL Cholesterol (mg/dL)



D. HDL Cholesterol (mg/dL)



Data Source: ISS/ISE Figure 3.25.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Study 207966, minimal increases in medians for total cholesterol, LDL cholesterol, and cholesterol/HDL ratio were noted for the Q4W group at Week 48 (Data Source: GSK Doc. # 2019N406358_01 Table 3.54 and Figure 3.16). The change is not considered clinically significant. Results for triglycerides and HDL at Week 48 were similar in the 2 treatment groups. There were no clinically relevant patterns in changes in fasting lipids from Baseline category to maximum post-Baseline category (shifts) in either treatment group (GSK Doc. # 2019N406358_01 Section 7.2.4).

Longer-term Phase III Results

No clinically relevant patterns in changes in NCEP fasting lipids from Baseline category to maximum post-Baseline category for the MP in Study 201584 were observed in either treatment group for triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, or

TC/HDL ratio (GSK Doc. # 2019N421511_00 Section 7.5.4). Of the 264 CAB + RPV Q4W subjects with both a Day 1 and post-Baseline total cholesterol result, 50 (19%) subjects shifted from a desirable total cholesterol category to high or borderline high category. One subject shifted from a high Baseline total cholesterol category to a desirable category post-Baseline. Of the 268 CAR subjects with both a Day 1 and post-Baseline result, 34 (13%) subjects shifted from a desirable total cholesterol category to high or borderline high category. No subjects shifted from a high Baseline total cholesterol category to a desirable category post-Baseline.

Grade 3 or 4 NCEP fasting lipids toxicities for Study 201585, including in the Extension Phase, are presented in Table 54.

Phase IIB Results

At EOS in Study LAI116482, of subjects who had a treatment-emergent abnormality in lipids, most had a maximum toxicity ≤Grade 2 (Table 80).

Table 80 Summary of Maximum Treatment-Emergent Laboratory Toxicities for Lipids in Study LAI116482 at End of Study (Safety Maintenance Population)

	CAB 10 mg + RPV N=52 n (%)	CAB 30 mg + RPV N=53 n (%)	CAB 60 mg + RPV N=55 n (%)	CAB + RPV Subtotal N=160 n (%)	EFV 600 mg + 2 NRTIs N=47 n (%)
Cholesterol (mmol/L)					
Grade 1	17 (33)	17 (32)	19 (35)	53 (33)	9 (19)
Grade 2	6 (12)	12 (23)	15 (27)	33 (21)	10 (21)
Grade 3	3 (6)	0	3 (5)	6 (4)	4 (9)
Grade 4	0	0	0	0	0
LDL Cholesterol Calculation (mmol/L)					
Grade 1	14 (27)	16 (30)	13 (24)	43 (27)	8 (17)
Grade 2	6 (12)	11 (21)	14 (25)	31 (19)	6 (13)
Grade 3	4 (8)	2 (4)	7 (13)	13 (8)	4 (9)
Grade 4	0	0	0	0	0
Triglycerides (mmol/L)					
Grade 1	0	0	0	0	0
Grade 2	1 (2)	4 (8)	3 (5)	8 (5)	1 (2)
Grade 3	1 (2)	0	3 (5)	4 (3)	1 (2)
Grade 4	0	0	1 (2)	1 (<1)	0

Data Source: GSK Doc.# 2019N404586_00 Table 8.38.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

At Week 160 in Study 200056, of subjects who had a treatment-emergent abnormality in lipids, the largest proportion of subjects for both the Safety Maintenance and Extension Switch Populations had a maximum toxicity of ≤Grade 2 (Table 81). There were no Grade 4 elevations of cholesterol, LDL cholesterol (calculated), or triglycerides.

Table 81 Summary of Maximum Maintenance and Extension Period Treatment-Emergent Lipase Toxicity (Relative to Maintenance Baseline) and During Extension Period (Relative to Extension Baseline) in Study 200056 at Week 160 (Safety Maintenance and Extension Switch Populations)

	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	IM Total N=230 n (%)	Optimized Q8W IM[c] N=34 n (%)	Optimized Q4W IM[d] N=10 n (%)	Optimized IM Total N=44 n (%)
Cholesterol (mmol/L)						
Grade 1	32 (28)	30 (26)	62 (27)	6 (18)	1 (10)	7 (16)
Grade 2	15 (13)	21 (18)	36 (16)	5 (15)	1 (10)	6 (14)
Grade 3	1 (<1)	3 (3)	4 (2)	0	0	0
Grade 4	0	0	0	0	0	0
LDL Cholesterol Calculation (mmol/L)						
Grade 1	24 (21)	24 (21)	48 (21)	4 (12)	1 (10)	5 (11)
Grade 2	12 (10)	11 (10)	23 (10)	6 (18)	2 (20)	8 (18)
Grade 3	2 (2)	7 (6)	9 (4)	0	0	0
Grade 4	0	0	0	0	0	0
Triglycerides (mmol/L)						
Grade 1	0	0	0	0	0	0
Grade 2	1 (<1)	4 (3)	5 (2)	0	0	0
Grade 3	2 (2)	3 (3)	5 (2)	1 (3)	0	1 (2)
Grade 4	0	0	0	0	0	0

Data Source: GSK Doc. # 2018N380094_00 Table 8.1061 and Table 8.1066.

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 weeks.
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 weeks.
c. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension Period.
d. Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension Period.

3.1.9. Bone Biomarkers

Week 48 Phase III Results

These assessments were only done in Studies 201584 and 201585.

Bone biomarkers (Bone specific alkaline phosphatase, Procollagen type 1-Npropeptide [P1NP], type 1 collagen cross-linked C-telopeptide [CTX], Osteocalcin, and 25 hydroxy-Vitamin D) in the CAB + RPV Q4W treatment regimen had a more favorable bone profile indicating less bone turnover compared with CAR in Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.142 and Table 3.143).

Longer-term Phase III Results

In Study 201584, median values for bone specific alkaline phosphatase and vitamin D decreased from Maintenance Baseline (Day 1) to Week 96 in both groups (GSK Doc. # 2019N421511_00 Section 9.2). The decrease observed in vitamin D was greater in the CAR group compared with the CAB + RPV Q4W group based on geometric mean ratio to baseline (p=0.009); for bone specific alkaline phosphatase, the decrease based on geometric mean ratio to baseline was not significantly different between the treatment groups (p=0.765). The median osteocalcin value increased slightly from Maintenance Baseline (Day 1) to Week 96 in the CAB + RPV Q4W group compared with a decrease observed in the CAR group. The decrease observed in osteocalcin was greater in the CAR group compared with the CAB + RPV Q4W group based on geometric mean ratio to baseline (p<0.001). Median values for procollagen 1 N-terminal propeptide and type I collagen C-telopeptides increased from Maintenance Baseline (Day 1) to Week 96 in both groups. The increase based on geometric mean ratio to baseline was not significantly different between the treatment groups for either procollagen 1 N-terminal propeptide (p=0.089) or type I collagen C-telopeptides (p=0.889).

In Study 201585, bone biomarker results demonstrated that values did not significantly change over time or between treatment groups. A summary of changes from Baseline at Week 48 and Week 96 is presented for CAB + RPV Q4W and at Week 96 for Extension Switch to CAB + RPV Q4W (Data Source: GSK Doc. # 2019N399072_00 Table 13.40 and Table 13.41).

3.2. Hematology

Week 48 Phase III/IIIB Results

Overall, the changes from Baseline in hematology values for Studies 201584 and 201585 were not clinically relevant (Data Source: ISS/ISE Table 3.120 and Table 3.121). Post-Baseline emergent hematology abnormalities were mostly Grade 1 or Grade 2 (Data Source: ISS/ISE Table 3.129). 8 subjects had Grade 3 hematology abnormalities: hemoglobin (2 CAB + RPV Q4W; 3 CAR), neutrophils (1 CAB + RPV Q4W; 1 CAR), and platelets (0 CAB + RPV Q4W; 1 CAR). 3 subjects had Grade 4 hematology abnormalities (1 CAB + RPV Q4W [reduction in neutrophils]; 2 CAR [reduction in platelets, reduction in neutrophils]). No occurrences resulted in SAEs or required hospitalization for myeloid growth factors.

No trends were identified when hematology results were stratified by age, sex, or race (Data Source: ISS/ISE Table 3.130, Table 3.131, Table 3.132).

During the OLI Period, all hematology abnormalities were Grade 1 with the exception of one Grade 2 occurrence (neutrophils, not related) (Data Source: ISS/ISE Table 3.133).

In Study 207966, there were no clinically relevant differences between treatment groups for hematology parameters (GSK Doc. # 2019N406358_01 Section 7.2.2).

Longer-term Phase III Results

At the end of the MP in Study 201584, hematology toxicity grades were observed in 15% of subjects in the CAB + RPV Q4W group and 12% of subjects in the CAR group (GSK Doc. # 2019N421511_00 Section 7.5.2). There were no significant overall differences between the 2 treatment groups. Maximum hematology toxicities were mainly Grade 1 or 2. One subject (<1%) in the CAB + RPV Q4W group (hemoglobin) and 3 subjects (1%) in the CAR group (hemoglobin 2 subjects; platelets 1 subject) had Grade 3 hematology toxicities. There were no Grade 4 hematology toxicities in the CAB + RPV Q4W group. Two subjects (<1%) in the CAR group had Grade 4 toxicities (platelets, neutrophils).

In Study 201585, hematology laboratory values did not significantly change over time or between treatment groups (Data Source: GSK Doc. # 2019N399072_00 Table 13.30, Table 13.31). During the Extension Phase, no new Grade 3 or Grade 4 hematology abnormalities were reported in either treatment group (Data Source: GSK Doc. # 2019N399072_00 Table 13.34, Table 13.35).

Phase IIB Results

At EOS in Study LAI116482, there were no clinically significant trends in treatment-emergent hematology abnormalities (GSK Doc.# 2019N404586_00 Section 7.6.3). Changes from Baseline in hematology parameters were relatively small with large standard deviations relative to the mean changes.

At Week 160 in Study 200056, overall, there were few graded hematology toxicities across all treatment arms; 19% across randomized IM arms and 23% in the optimized IM arms (GSK Doc. # 2018N380094_00 Section 7.6.2). There were few Grade 3 and 4 treatment-emergent hematology toxicities in the randomized IM arms (3%) and none reported in the optimized IM arms.

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1. Vital Signs

Week 48 Phase III/IIIB Results

In Studies 201584 and 201585, there were no clinically relevant differences across treatment groups with regard to vital signs, including blood pressure, pulse rate, and temperature (Data Source: ISS/ISE Table 3.149).

In Study 207966, no clinically significant changes from Baseline in vital signs were observed in either treatment group (GSK Doc. # 2019N406358_01 Section 7.3).

Longer-term Phase III Results

In Study 201584, no clinically relevant differences were observed in mean change from Maintenance Baseline (Day 1) to Week 96 in vital signs including blood pressure, pulse rate, and temperature (GSK Doc. # 2019N421511_00 Section 7.6.1).

In Study 201585, mean vital sign (blood pressure, pulse rate, temperature) values did not significantly change over time or between treatment groups. A summary of changes from Baseline by visit is presented for CAB + RPV Q4W and for Extension Switch to CAB + RPV Q4W groups (Data Source: GSK Doc. # 2019N399072_00 Table 13.52 and Table 13.53).

Phase IIB Results

At EOS in Study LAI1116482, no significant patterns of changes in vital signs were identified in any treatment group (GSK Doc. # 2019N404586_00 Section 7.8).

In Study 200056, no clinically relevant differences were observed in mean change from Baseline to Week 160 in vital signs including blood pressure, pulse rate, and temperature for both the randomized IM and optimized IM arms (GSK Doc. # 2018N380094_00 Section 7.7).

4.2. Weight/BMI

A summary of AEs potentially related to weight gain is provided in Section 2.1.6.8.

Week 48 Phase III/IIIB Results

Body weight and BMI were recorded at Baseline and Week 48 during the Phase III/IIIB studies. Weight gain is considered an AESI for CAB since it is labelled as an adverse reaction for the structurally related INSTI, DTG.

In Studies 201584 and 201585, an overall trend towards slight weight gain was observed at Week 48 for subjects in the CAB + RPV Q4W group (median change of 1.5 kg vs. 1.0 kg for the CAR group), with numerous outliers on the upper end for both treatment groups (Table 82 and Figure 17). BMI also slightly increased in the CAB + RPV Q4W group compared with the CAR group (median change 0.50 vs. 0.35 kg/m^2). In Study 201584, weight was collected at Induction Baseline, so the weight changes occurred over the Induction Period (20 weeks) + 48 weeks of the MP. In contrast, in Study 201585, weight was collected at Day 1.

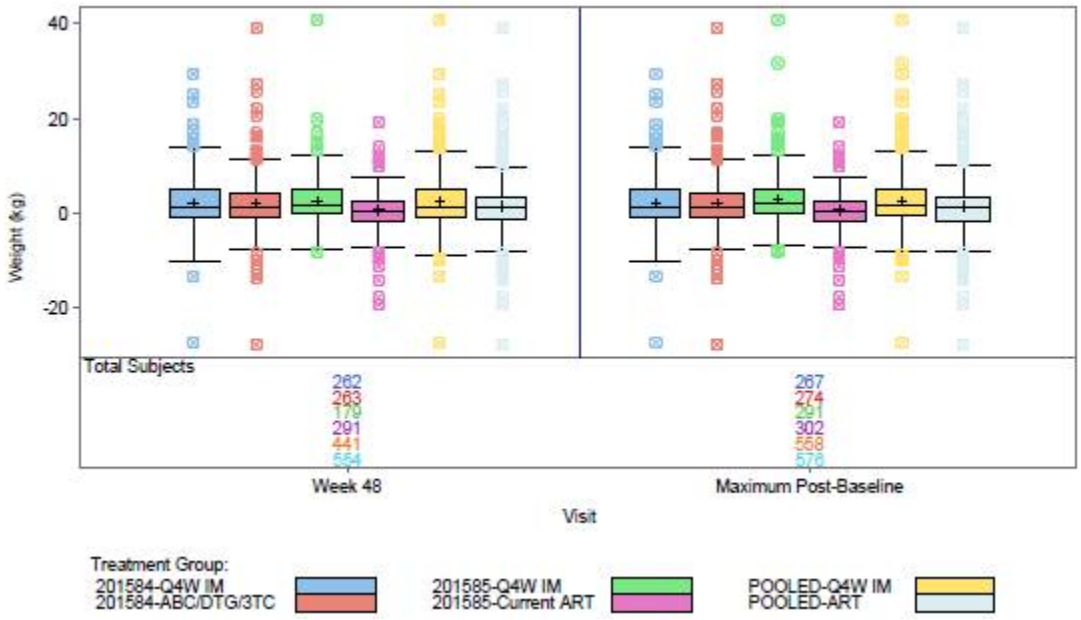
In pooled Studies 201584 and 201585, 1 subject had an AE of weight decreased in the CAB + RPV Q4W group whereas, in the CAR group, 4 subjects had AEs of weight decreased (Data Source: ISS/ISE Table 3.12).

Table 82 Summary of Change from Baseline for Weight (kg) in Studies 201584, 201585, and 201584+201585 Pooled – Week 48 Analysis – Maintenance Phase (Safety Population)

Study	Treatment	N	Actual Relative Time	n	Mean (kg)	SD	Median	Min.	Max.
201584	CAB + RPV Q4W	283	Baseline	283	75.71	14.552	74.00	46.3	125.6
			Week 48	262	2.18	5.960	1.30	-27.5	29.6
			Maximum Post-Baseline	267	2.27	5.933	1.40	-27.5	29.6
	CAR	283	Baseline	283	75.12	15.641	74.00	36.0	148.0
			Week 48	263	1.98	6.160	1.50	-28.0	39.0
			Maximum Post-Baseline	274	2.00	6.152	1.50	-28.0	39.0
201585	CAB + RPV Q4W	308	Baseline	308	77.69	15.901	76.00	41.2	139.4
			Week 48	179	2.58	5.224	1.80	-8.1	40.9
			Maximum Post-Baseline	291	2.85	5.420	2.00	-8.1	40.9
	CAR	308	Baseline	308	79.50	17.877	77.55	48.2	162.8
			Week 48	291	0.44	4.060	0.30	-19.4	19.2
			Maximum Post-Baseline	302	0.43	4.019	0.30	-19.4	19.2
Pooled Studies 201584 and 201585	CAB + RPV Q4W	591	Baseline	591	76.74	15.289	75.00	41.2	139.4
			Week 48	441	2.34	5.670	1.50	-27.5	40.9
			Maximum Post-Baseline	558	2.57	5.674	1.80	-27.5	40.9
	CAR	591	Baseline	591	77.40	16.971	75.20	36.0	162.8
			Week 48	554	1.17	5.217	1.00	-28.0	39.0
			Maximum Post-Baseline	576	1.18	5.200	1.00	-28.0	39.0

Data Source: ISS/ISE Table 3.149.
Note: For Study 201585, Baseline is the last observation before first dose in Maintenance Phase. For Study 201584, Baseline is Week -20 (Induction Baseline).
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Figure 17 Change from Baseline in Weight Over Time in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis – Maintenance Phase (Safety Population)



Data Source: ISS/ISE Figure 3.15.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

In Studies 201584 and 201585, no subjects had BMI changes from underweight to obese categories, although some subjects (<1%) had BMI changes from normal to obese in both groups (Table 83). Shifts in BMI were most notable in female subjects, with shifts from normal to overweight (n=18 [11%] in the CAB + RPV Q4W group vs. n=7 [4%] in the CAR group) and from overweight to obese (n=12 [7%] in the CAB + RPV Q4W group vs. n=6 [4%] in the CAR group) (Data Source: ISS/ISE Table 1.16).

Most subjects had minor shifts in their BMI, including some who had a decrease in BMI at Week 48, although most shifts were increases. It is unclear if this increase in weight was due to increased adiposity since body composition was not measured in these studies. Notably, weight gain shifts affected both CAB + RPV Q4W and CAR groups.

Table 83 Summary of Shift in BMI Categories from Baseline to Maximum Post-Baseline in Studies 201584+201585 Pooled - Week 48 Analysis – Maintenance Phase (ITT-E Population)

				Maximum Post-Baseline Result				
Study	Treatment	N	Baseline Result	<Normal n (%)	Normal n (%)	Overweight n (%)	Obese n (%)	Total n (%)
201584	CAB + RPV Q4W	271	<Normal	3 (1)	1 (<1)	0	0	4 (1)
			Normal	1 (<1)	123 (45)	26 (10)	1 (<1)	151 (56)
			Overweight	0	6 (2)	59 (22)	13 (5)	78 (29)
			Obese	0	1 (<1)	4 (1)	33 (12)	38 (14)
			Total	4 (1)	131 (48)	89 (33)	47 (17)	271 (100)
	CAR	277	<Normal	6 (2)	4 (1)	1 (<1)	0	11 (4)
			Normal	1 (<1)	124 (45)	28 (10)	3 (1)	156 (56)
			Overweight	0	8 (3)	55 (20)	10 (4)	73 (26)
			Obese	0	0	7 (3)	30 (11)	37 (13)
			Total	7 (3)	136 (49)	91 (33)	43 (16)	277 (100)
201585	CAB + RPV Q4W	294	<Normal	3 (1)	2 (<1)	1 (<1)	0	6 (2)
			Normal	0	101 (34)	23 (8)	1 (<1)	125 (43)
			Overweight	0	3 (1)	85 (29)	17 (6)	105 (36)
			Obese	0	0	2 (<1)	56 (19)	58 (20)
			Total	3 (1)	106 (36)	111 (38)	74 (25)	294 (100)
	CAR	302	<Normal	1 (<1)	0	0	0	1 (<1)
			Normal	1 (<1)	121 (40)	15 (5)	0	137 (45)
			Overweight	0	5 (2)	82 (27)	12 (4)	99 (33)
			Obese	0	0	7 (2)	58 (19)	65 (22)
			Total	2 (<1)	126 (42)	104 (34)	70 (23)	302 (100)
Pooled Studies 201584 and 201585	CAB + RPV Q4W	565	<Normal	6 (1)	3 (<1)	1 (<1)	0	10 (2)
			Normal	1 (<1)	224 (40)	49 (9)	2 (<1)	276 (49)
			Overweight	0	9 (2)	144 (25)	30 (5)	183 (32)
			Obese	0	1 (<1)	6 (1)	89 (16)	96 (17)
			Total	7 (1)	237 (42)	200 (35)	121 (21)	565 (100)
	CAR	579	<Normal	7 (1)	4 (<1)	1 (<1)	0	12 (2)
			Normal	2 (<1)	245 (42)	43 (7)	3 (<1)	293 (51)
			Overweight	0	13 (2)	137 (24)	22 (4)	172 (30)
			Obese	0	0	14 (2)	88 (15)	102 (18)
			Total	9 (2)	262 (45)	195 (34)	113 (20)	579 (100)

Data Source: ISS/ISE Table 1.17.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
Note: BMI Normal: 18.5 - 24.99 kg/m^2, Overweight: 25 - 29.99 kg/m^2, Obese: ≥30 kg/m^2.

In Study 207966 at Week 48, median change from Baseline in body weight was +1.00 kg in both treatment groups (Data Source: GSK Doc. # 2019N406358_01 Table 3.63). Median change from Baseline in BMI was +0.345 kg/m^2 in the Q8W group and +0.300 kg/m^{2}in the Q4W group.

At Week 48, notable shifts occurred for BMI in a subgroup of subjects with normal BMI at Baseline to overweight (Table 84). In addition, there was a shift towards weight gain in a subgroup of subjects who were overweight at Baseline and obese at Week 48;

however, the proportion of subjects who were overweight at Baseline and shifted to Normal at Week 48 (ie, lost weight) was similar. Proportions were similar between treatment groups for both of these notable shifts.

Table 84 Summary of Shift in BMI Categories from Baseline to Week 48 in Study 207966 - Week 48 Analysis - Maintenance Phase (Safety Population)

			Week 48					
Treatment	N	Baseline Result	Missing n (%)	<Normal n (%)	Normal n (%)	Over-weight n (%)	Obese n (%)	Total n (%)
CAB + RPV Q8W	522	<Normal	0	1 (25)	3 (75)	0	0	4 (<1)
		Normal	13 (6)	1 (<1)	177 (79)	**31 (14)**	1 (<1)	223 (43)
		Overweight	9 (5)	0	**17 (9)**	141 (77)	**15 (8)**	182 (35)
		Obese	6 (5)	0	0	8 (7)	99 (88)	113 (22)
		Total	28 (5)	2 (<1)	197 (38)	180 (34)	115 (22)	522 (100)
CAB + RPV Q4W	523	<Normal	0	8 (80)	2 (20)	0	0	10 (2)
		Normal	10 (5)	0	178 (84)	**24 (11)**	1 (<1)	213 (41)
		Overweight	17 (8)	0	**19 (9)**	152 (75)	**14 (7)**	202 (39)
		Obese	6 (6)	0	1 (1)	4 (4)	87 (89)	98 (19)
		Total	33 (6)	8 (2)	200 (38)	180 (34)	102 (20)	523 (100)

Data Source: GSK Doc. # 2019N406358_01 Table 3.64.
Note: No BMI results were missing at Baseline. BMI Normal: 18.5 - 24.99 kg/m^2, Overweight: 25 - 29.99 kg/m^2, Obese: ≥30 kg/m^2.

Results for maximum change in post-Baseline weight were similar to results at Week 48 (Data Source: GSK Doc. # 2019N406358_01 Table 3.64).

Longer-term Phase III Results

At the end of the MP in Study 201584, overall, both treatment groups had a similar median (range) weight gain at Week 96 of 2.00 (-24.6 to 25.4) kg and 2.00 (-17.3 to 35.7) kg in the CAB + RPV Q4W and CAR groups, respectively (GSK Doc. # 2019N421511_00 Section 7.6.2). Median BMI (range) increased by 0.60 (-8.9 to 10.3) kg/m^2 in the CAB + RPV Q4W group compared with an increase of 0.60 (-5.9 to 12.7) kg/m^2 in the CAR group.

In Study 201585, mean weight and BMI values did not significantly change over time or between treatment groups. A summary of changes from Baseline by visit is presented for CAB + RPV Q4W and for Extension Switch to CAB + RPV Q4W groups (Data Source: GSK Doc. # 2019N399072_00 Table 13.52 and Table 13.53).

Phase IIB Results

At EOS in Study LAI116482, subjects who continued to be in the study at that time had a median weight gain of 6.5 kg since Baseline (Table 85). BMI was not calculated in Study LAI116482.

Table 85 Summary of Observed Change from Baseline in Weight (kg) in Study LAI116482 at End of Study (Safety Population)

Change	CAB 10 mg + RPV N=60 n (%)	CAB 30 mg + RPV N=60 n (%)	CAB 60 mg + RPV N=61 n (%)	CAB + RPV Subtotal N=181 n (%)	EFV 600 mg + 2 NRTIs N=62 n (%)
n	31	34	43	108	40
Mean	7.89	7.86	5.64	6.99	0.44
SD	7.398	9.871	8.650	8.716	6.850
Median	6.90	6.60	4.70	6.50	-1.10
Q1	3.10	0.80	0.30	0.95	-2.60
Q3	10.40	12.00	10.70	11.00	5.10
Minimum	-1.9	-11.6	-14.7	-14.7	-16.4
Maximum	32.2	32.0	22.6	32.2	13.9

Data Source: GSK Doc.# 2019N404586_00 Table 8.58.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

In Study 200056, the randomized IM arms had a median (IQR) weight gain of 3.05 (0.05, 6.80) kg at Week 160 compared with Baseline (Week -20) (Data Source: GSK Doc. # 2018N380094_00 Table 8.1086). The optimized IM arms had a median (IQR) weight gain of 1.20 (-0.50, 4.30) kg compared with the Extension Baseline at Week 100 (GSK Doc. # 2018N380094_00 Table 8.1087). Median BMI increased by 0.90 (0, 2.10) kg/m^2 in the randomized IM arms and 0.40 (-0.30, 1.30) kg/m^2 in the optimized IM arms.

Conclusion

A trend towards higher average and median weight gain was observed at Week 48 in Studies 201584 and 201585 for subjects in the CAB + RPV Q4W group compared with the CAR group. This is consistent with a trend for weight gain observed over time during the Phase IIB studies. Median weight change in Study 207966 was the same (+1.00 kg) in the Q8W and Q4W groups.

4.3. Electrocardiograms

Details regarding AEs potentially related to QT prolongation are provided in Section 2.1.6.5.

Week 48 Phase III/IIIB Results

During Studies 201584 and 201585, 98% of subjects treated with CAB and RPV or CAR had normal or not clinically significant abnormal ECGs (Data Source: ISS/ISE Table 3.148).

Non-centralized collection (local collection at sites) of ECGs was performed in Studies 201584 and 201585 consistent with the protocols. The method of QT correction was collected in the eCRF. At Baseline, 406 subjects in the CAB + RPV Q4W group and 420 subjects in the CAR group had ECGs with QTcF correction, while 402 subjects in the CAB + RPV Q4W group and 417 subjects in the CAR group had ECGs with QTcB correction. RR interval was not routinely collected and is necessary to derive QTcB and/or QTcF. Therefore, in some cases, QTcF and QTcB values could not be derived (without using an approximation based on average HR). If a QTcB value was collected in the eCRF, however, then QTcF was backcalculated in the analysis dataset (and vice versa), as described in the individual study RAPs (Study 201584 CSR; Study 201585 CSR).

ECGs were routinely collected for all subjects at protocol defined timepoints. Per protocol, in the CAB + RPV Q4W group, additional ECGs were collected pre-dose at Week 4b, 2 hours post-dose at Week 4b, and 2 hours post-dose at Week 48.

In the pooled analysis, there were few QTc outliers (change from Baseline >60 msec or absolute QTc value >500 msec) (Data Source: ISS/ISE Table 3.147; GSK Doc. # 2019N406358_01 Table 3.91 and Table 3.94; GSK Doc. # 2017N345267_00 Table 3.99 and Table 3.101).

A summary of change from Baseline in QTcF and QTcB intervals for pooled Studies 201584 and 201585 is presented in Table 86 and Table 87, respectively. Higher rates of QT prolongation were observed in the CAB + RPV Q4W group compared with the CAR group. In these subjects, triplicate ECGs did not confirm a maximum change from Baseline corrected QT value >60 msec and all subjects remained on study.

Through 48 weeks in Studies 201584 and 201585, all subjects had QTcF intervals ≤500 msec. 1 subject had a pre-dose QTcB interval and 2 subjects had a post-dose QTcB interval >500 msec in the CAB + RPV Q4W treatment group (Data Source: ISS/ISE Table 3.147). All subjects with QTc values >500 msec remained on study drug.

None of the corrected QT prolongations were considered clinically significant. No clinically significant QTcF or QTcB prolongation was observed during the CAB + RPV development program. No cases of serious ventricular arrhythmias such as TdP were observed.

Table 86 Summary of QTcF Interval Maximum Change from Baseline for Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

Actual Relative Time (Timepoint, msec) Category	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)
n	188	181	208	193	396	374
≤30	162 (86)	171 (94)	192 (92)	186 (96)	354 (89)	357 (95)
>30 to ≤60	24 (13)	9 (5)	13 (6)	6 (3)	37 (9)	15 (4)
>60	2 (1)	1 (<1)	3 (1)	1 (<1)	5 (1)	2 (<1)

Data Source: ISS/ISE Table 3.146.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

Table 87 Summary of QTcB Interval Maximum Change from Baseline for Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

Actual Relative Time (Timepoint, msec) Category	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)
n	184	178	208	193	392	371
≤30	147 (80)	170 (96)	171 (82)	182 (94)	318 (81)	352 (95)
>30 to ≤60	30 (16)	6 (3)	30 (14)	10 (5)	60 (15)	16 (4)
>60	7 (4)	2 (1)	7 (3)	1 (<1)	14 (4)	3 (<1)

Data Source: ISS/ISE Table 3.146.
Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.

PK/PD analyses were conducted for QTc in Studies 201584 and 201585. Additional details are provided in m2.7.2.

In Study 207966, change from Baseline in ECG parameters at Week 48 was similar between the treatment groups (GSK Doc. # 2019N406358_01 Section 7.5).

Isolated instances of QTcF results of potential clinical concern were observed in single subjects, and no patterns were apparent (Table 88). In all cases when the QTcF result of potential clinical concern was measured pre-dose, the post-dose value was below the threshold of concern. No subject had a result of potential clinical concern on more than 1 occasion, and no AEs of concern for potential QT prolongation were reported for these subjects (Data Source: GSK Doc. # 2019N406358_01 Listing 19 and Listing 57).

Table 88 QTcF Results of Potential Clinical Significance in Study 207966 – Week 48 Analysis - Maintenance Phase (Safety Population)

Category Time	Treatment Group	By-Subject Details: Demographics/ Exposed to CAB + RPV in Study 201585?	By-Subject Details: Study Day/ QTcF Results
Interval >500 msec[a]			
Week 48 pre-dose	CAB + RPV Q4W	50-to-60 yo BF/ No	Day 343 QTcF @ ~0900 was **505** msec QTcF @ ~1130 was 415 msec
Change From Baseline >60 msec			
Day 1 post-dose	CAB + RPV Q4W	60-to-70 yo BM/ Yes, for 1 to 24 weeks	Day 1 QTcF @ ~1100 was 313 msec (BL) QTcF @ ~1430 was 395 msec (+**83** msec change from BL)
Week 48 pre-dose	CAB + RPV Q8W	40-to-50 yo WF/ No	Day 347 QTcF @ ~0900 was 470 msec (+**63** msec change from BL) QTcF @ ~1200 was 449 msec (+42 msec change from BL)
	CAB + RPV Q4W	20-to-30 yo WM/ No	Day 347 QTcF @ ~1000 was 496 msec (+**111** msec change from BL) QTcF @ ~1300 was 422 msec (+37 msec change from BL)
Week 48 post-dose	CAB + RPV Q4W	50-to-60 yo WM/ No	Day 349 QTcF @ ~1100 was 394 msec (+10 msec change from BL) QTcF @ ~1330 was 448 msec (+**64** msec change from BL)

Data Source: GSK Doc. # 2019N406358_01 Table 3.61, Table 3.62, and Listing 23.
BM=black male; BF=black female; WF=white female; WM=white male; yo=year old.
Note: The first of the 2 values for each subject is pre-dose and the second is post-dose. Values of potential clinical concern are shown in **bold**.
a. No subjects in either treatment group had a QTcF interval >500 msec at Baseline, Day 1 post-dose, or Week 48 post-dose.

QT prolongation information is summarized in GSK Doc. # 2019N406358_01 Section 7.1.5.3.5.

Longer-term Phase III Results

At the end of MP in Study 201584, mean and median changes in corrected QT interval were small and similar between treatment groups (GSK Doc. # 2019N421511_00 Section 7.3.3.1.5). At Week 96 pre-dose, QTcF changes from Baseline >60 msec occurred in 1/159 (<1%) subject in the CAB + RPV Q4W group and 1/166 (<1%) subject in the CAR group. Worst-case post-Maintenance Baseline QTcF changes from Baseline of >60 msec occurred in 2/190 (1%) subjects in the CAB + RPV Q4W group and 3/183 (2%) subjects in the CAR group. No subjects in either treatment group with a QTcF measurement had a QTcF prolongation at Week 96 pre-dose >500 msec or a worst-case post-Maintenance Baseline QTcF prolongation >500 msec.

In Study 201585, at Week 96 (pre-dose), no subjects in either treatment group had QTcB or QTcF prolongation >500 msec (Data Source: GSK Doc. # 2019N399072_00 Table 13.48 and Table 13.49).

At Week 96 (pre-dose), no subjects in the CAB + RPV Q4W group had a QTcB change from Baseline >60 msec during the Extension Phase in Study 201585. At Week 96 (pre-dose), 1 subject in the Extension Switch to CAB + RPV Q4W group had a change from Baseline >60 msec with QTcB but not with QTcF. This subject did not have any AEs related to QT prolongation and the QTcB value at Week 96 pre-dose was 468 msec (Data Source: GSK Doc. # 2019N399072_00 Table 13.50 and Table 13.51).

At Baseline, ECG results were normal or abnormal and not clinically significant in 94% of the CAB + RPV Q4W group and in 96% of the Extension Switch to CAB + RPV Q4W group in Study 201585 (Data Source: GSK Doc. # 2019N399072_00 Table 13.44 and Table 13.45). Abnormal ECG findings were clinically significant in the opinion of the investigator in 6% and 4% of subjects in each treatment group, respectively.

At Week 96 in Study 201585, ECG results were normal or abnormal and not clinically significant in 100% of the CAB + RPV Q4W group (Maintenance + Extension Phase) and in 90% of the Extension Switch to CAB + RPV Q4W group. Abnormal ECG findings were clinically significant in 3 (10%) subjects in the Extension Switch to CAB + RPV Q4W group. These abnormalities were described by the investigator as sinus bradycardia, incomplete right bundle branch block, and sinus arrhythmia (Data Source: GSK Doc. # 2019N399072_00 Table 13.44, Table 13.45, and Listing 116). None of the ECG abnormalities led to discontinuation of study drug (Data Source: GSK Doc. # 2019N399072_00 Listing 108).

Change from Baseline in ECG parameters at Week 96 was similar in the Extension Phase compared with those from the CAB + RPV Q4W group in the Maintenance Phase in Study 201585 (Data Source: GSK Doc. # 2019N399072_00 Table 13.46 and Table 13.47). None of the changes in mean heart rate, QRS duration, QTc, QTcB, QTcF, PR, or RR interval were clinically significant.

Phase IIB Results

At EOS in Study LAI116482, the proportion of subjects with a QTcF interval >60 msec was similar in the CAB + RPV and EFV groups (5% each) (Table 89).

Table 89 Maximum On-treatment Change in QTcF Interval in Study LAI116482 at End of Study (Safety Population)

	CAB 10 mg + RPV N=60 n (%)	CAB 30 mg + RPV N=60 n (%)	CAB 60 mg + RPV N=61 n (%)	CAB + RPV Subtotal N=181 n (%)	EFV 600 mg + 2 NRTIs N=62 n (%)
n	60	57	59	176	60
≤30 msec	46 (77)	39 (68)	39 (66)	124 (70)	49 (82)
>30 to ≤60 msec	11 (18)	15 (26)	17 (29)	43 (24)	8 (13)
>60 msec	3 (5)	3 (5)	3 (5)	9 (5)	3 (5)

Data Source: GSK Doc. # 2019N404586_00 Table 8.56.
Note: At or shortly following their Week 96 visit, all CAB + RPV subjects were switched to the selected dose (CAB 30 mg + RPV 25 mg) and entered the Open-label Phase; the summary is through EOS (Week 312) but subjects are shown in the CAB group into which they were randomized at the beginning of the study.
Note: Subjects in the EFV arm completed study participation at Week 96. Although the exposure time for this group was less than for CAB + RPV subjects, the data are provided for comparison purposes.

At Baseline in Study 200056, QTcB and QTcF results were ≤450 msec in >99% and 100% of the randomized IM arms, respectively. At Week 160, QTcB and QTcF results were ≤450 msec in 97% and 99%, respectively (GSK Doc. # 2018N380094_00 Section 7.8.1). Six (3%) subjects (1 Q8W, 5 Q4W) had QTcB results >450 but ≤480 msec and 2 (1%) subjects (2 Q4W) had QTcF results >450 but ≤480 msec. No subjects in the randomized IM arms had any QTc result >500 msec. In the optimized IM arms, at the Extension Baseline, QTcB and QTcF results were ≤450 msec in 98% subjects. There was no change in QTcB results at Week 160 for QTcB results with a slightly better rate in QTcF results with 100% of subjects ≤450 msec. No subjects in the optimized IM arms had any QTc result >500 msec.

Conclusion

Treatment with CAB + RPV did not have clinically relevant effects on the QT interval.

4.4. Suicidal Ideation or Behavior

Suicidality was monitored prospectively using the eC-SSRS throughout the CAB + RPV development program, in line with FDA guidance to industry. Details regarding AEs potentially related to suicidal ideation or behavior are provided in Section 2.1.6.6.

Week 48 Phase III/IIIB Results

The clinical events of suicidal ideation and behavior leading to the validated true positive post-Baseline alerts are documented in the PSRAE (and AE or SAE forms) (PSRAE listings for Studies 201584 and 201585: Data Source: GSK Doc. # 2017N345267_00 Listing 26; GSK Doc. # 2018N370336_00 Listing 24).

The definitions of behavioral suicidal events used in eC-SSRS are based on those used in the Columbia Suicide History Form [Posner, 2007; Posner, 2011]. The eC-SSRS was self-administered by subjects via telephone or using a computer/tablet connected to the internet. Assessments administered via the eC-SSRS include Levels 1 to 9, with positive alerts sent to the Sponsor and site for suicidal ideation (Level 4 or 5) or any suicidal behavior (Levels 6 to 9). Levels 1 to 3 of ideation are distinct from Levels 4 and 5 because they do not include any intent to act. If a subject had only Level 1 to 3 ideation or non-suicidal self-injurious behavior, a positive alert was not sent to the Sponsor or the site, but all reports were still expected to be reviewed by the site.

In Studies 201584 and 201585, results from the suicidality assessments indicated that 28 (5%) subjects in the CAB + RPV Q4W group and 33 (6%) subjects in the CAR group reported any (Level 1 to 9) suicidal ideation or behavior (Data Source: ISS/ISE Table 3.150).

Based on the eC-SSRS source table and the real-time log of known incorrect subject entries (based on information provided by the site in response to the ERT alert), there were 9 subjects with positive ERT alerts post-Baseline (3 subjects in the CAB + RPV Q4W group; 6 subjects in the CAR group; Table 90).

Table 90 Summary of Subjects with Post-Baseline Suicidal Ideation or Behavior Alerts in Studies 201584, 201585, and 201584+201585 Pooled - Week 48 Analysis - Maintenance Phase (Safety Population)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585	
	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)	CAB + RPV Q4W (N=308) n (%)	CAR (N=308) n (%)	CAB + RPV Q4W (N=591) n (%)	CAR (N=591) n (%)
Suicidal Ideation or Behavior Alerts (4-9)						
Any event	4 (1)	5 (2)	3 (<1)	7 (2)	7 (1)	12 (2)
Consistent with investigator clinical assessment?						
Yes- AE/SAE	1 (<1)	3 (1)	1 (<1)	3 (<1)	2 (<1)	6 (1)
Yes- non-AE/SAE	0	0	1 (<1)	0	1 (<1)	0
No	3 (1)	2 (<1)	2 (<1)	4 (1)	5 (<1)	6 (1)

Data Source: ISS/ISE Table 3.150.

More positive alerts that resulted in AE/SAEs were reported for the CAR group compared with the CAB + RPV Q4W group. 11 subjects were confirmed to have either entered responses into the eC-SSRS in error or were confirmed by the investigator through an interview not to have any suicidal risk.

Based on the AEs entered by the site/investigator, the incidence of subjects who reported suicidal ideation or behavior post-Baseline was low in both treatment groups. Most of these AEs of suicidal ideas or behaviors were identified through the eC-SSRS alerts.

Based on analyses of the eC-SSRS in Study 207966, a similar proportion of subjects (Q8W: 2%, 12 subjects; Q4W: 4%, 21 subjects) in each treatment group reported any (Level 1 to 9) suicidal ideation or behavior (Data Source: GSK Doc. # 2019N406358_01

Table 3.65). There were no subjects with AEs of suicide or suicide attempt (Data Source: GSK Doc. # 2019N406358_01 Table 3.71).

Possible suicidality-related data showed 5 (<1%) subjects in each treatment group had positive alerts (Table 91). Out of these, 2 subjects (1 Q8W; 1 Q4W) had positive PSRAEs.

- Q8W: This subject had a medical history of depression and past suicide attempt. During the study, the subject was hospitalized for major depression and substance-induced psychotic disorder with suicidal ideation due to [redacted] abuse. Both SAEs were considered not related to study drug and neither led to withdrawal of study drug. A full case narrative is provided in GSK Doc. # 2019N406358_01 Section 13.
- Q4W: This subject had a medical history of depression, bipolar disorder, and anxiety, and reported past suicide attempt. During the study, the subject had a nonserious, nonrelated AE of major depression and admitted to having thoughts of suicidal ideation at the Week 48 eC-SSRS assessment. The subject remained in the study.

Table 91 Summary of Subjects with Post-Baseline Suicidal Ideation or Behavior Alerts in Study 207966 - Week 48 Analysis – Maintenance Phase (Safety Population)

	CAB + RPV Q8W (N=522) n (%)	CAB + RPV Q4W (N=523) n (%)
Suicidal ideation or behavior alerts (4-9)		
Any event	5 (<1)	5 (<1)
Consistent with investigator clinical assessment?[a]		
Yes- AE/SAE	1 (<1)	1 (<1)
Yes- non-AE/SAE	2 (<1)	0
No	2 (<1)	4 (<1)

Data Source: GSK Doc. # 2019N406358_01 Table 3.65.
Note: Incomplete calls/web assessments were excluded if and only if a complete call/web assessment was recorded on the same day.
Note: Percentages were based on the number of subjects with at least one post-baseline assessment.
a. Subjects may have more than one clinical assessment category reported.

Longer-term Phase III Results

At the end of the MP in Study 201584, 1 additional subject in the CAB + RPV Q4W group and no additional subjects in the CAR group had positive suicidal ideation or behavior alerts since the Week 48 analysis (Table 90), of which 1 and 3 alerts were confirmed by investigator clinical assessment for the CAB + RPV Q4W and CAR groups, respectively, which was unchanged since the Week 48 analysis (Table 92). PSRAE data showed 1 subject in the CAB + RPV Q4W group with an AE of suicidal ideation and 2 subjects in the CAR group with AEs of suicidal ideation and suicide

attempt (GSK Doc. # 2019N421511_00 Section 7.6.4). None of these AEs were considered to be related to study drug.

Table 92 Summary of Subjects with Post-Baseline Suicidal Ideation or Behavior Alerts in Study 201584 at Week 100 – Maintenance Phase (Safety Population)

	CAB + RPV Q4W (N=283) n (%)	CAR (N=283) n (%)
Number of subjects with at least 1 on-treatment eC-SSRS assessment	281	280
Suicidal ideation or behavior (1-9)		
AE	16 (6)	18 (6)
Suicidal ideation (1-5)[a]		
Any suicidal Ideation	15 (5)	16 (6)
1 – Passive: wish to be dead	7 (2)	9 (3)
2 – Active: Non-specific (no method, intent, plan)	0	2 (<1)
3 – Active: Method, but no intent or plan	7 (2)	2 (<1)
4 – Active: Method and intent, but no plan	1 (<1)	1 (<1)
5 – Active: Method, intent, and plan	0	2 (<1)
Suicidal behavior (6-9)[b]		
Any suicidal behavior	5 (2)	5 (2)
6 – Preparatory acts or behavior	2 (<1)	1 (<1)
7 – Aborted attempt	3 (1)	2 (<1)
8 – Interrupted attempt	1 (<1)	2 (<1)
9 – Non-fatal actual attempt	2 (<1)	3 (1)
Self-Injurious behavior, no suicidal attempt	2 (<1)	2 (<1)
Suicidal ideation or behavior alerts (4-9)		
AE	5 (2)	5 (2)
Consistent with investigator clinical assessment?[c]		
Yes - AE/SAE	1 (<1)	3 (1)
Yes – non-AE/SAE	0	0
No	4 (1)	2 (<1)

Data Source: GSK Doc. # 2019N421511_00 Table 3.111.
Note: Incomplete calls are excluded if and only if a complete call is recorded on the same day.
Note: Percentages are based on the number of subjects with at least 1 post Maintenance Baseline (Day 1) eC-SSRS assessment.
Note: In the Data Source tables and figures, the CAB + RPV Q4W group is listed as Q4W IM and the CAR group as ABC/DTG/3TC.
a. Maximum post Maintenance BL (Day 1) suicidal ideation for each subject.
b. Subjects may have more than one type of suicidal behavior reported under 'Any suicidal behavior'.
c. Subjects with multiple 'suicidal ideation or behavior alerts (4-9)' may be reported under more than one clinical assessment category.

In Study 201585, no new subjects with suicidal ideation or behavior were reported in the CAB + RPV Q4W group during the Extension Phase. Two subjects in the Extension Switch to CAB + RPV Q4W group had suicidal ideations or behaviors. A summary of

subjects with post-Baseline suicidal ideation or behavior at Week 96 for the CAB + RPV Q4W and Extension Switch to CAB + RPV Q4W groups is presented in Table 93.

Table 93 Summary of Subjects with Post-Baseline eC-SSRS Suicidal Ideation or Behavior for Maintenance (up to 52 Weeks) + Extension (Post 52 Weeks) Phases in Study 201585 at Week 96 (Safety and Extension Switch Populations)

	CAB + RPV Q4W Day 1 to Week 52 (N=308) n (%)	CAR Day 1 to Week 52 (N=308) n (%)	CAB + RPV Q4W Day 1 to Week 96 (N=308) n (%)	Extension Switch to CAB + RPV Q4W Week 52 to Week 96 (N=174) n (%)
Number of subjects with at least 1 post-Baseline C-SSRS assessment	307	307	307	151
Any suicidal Ideation	**13 (4)**	**15 (5)**	**13 (4)**	**2 (1)**
1 – Passive: wish to Be Dead	6 (2)	6 (2)	6 (2)	1 (<1)
2 – Active: Non-Specific (no method, intent, plan)	2 (<1)	3 (<1)	2 (<1)	0
3 – Active: Method, but no intent or plan	3 (<1)	2 (<1)	3 (<1)	0
4 – Active: Method and intent, but no plan	1 (<1)	3 (<1)	1 (<1)	0
5 – Active: Method, intent, and plan	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Suicidal Behavior (6-9)				
Any Suicidal Behavior	2 (<1)	6 (2)	2 (<1)	0
6 – Preparatory Acts or Behavior	1 (<1)	1 (<1)	1 (<1)	0
7 – Aborted Attempt	1 (<1)	4 (1)	1 <1)	0
8 – Interrupted Attempt	2 (<1)	2 (<1)	2 (<1)	0
9 – Non-Fatal Actual Attempt	0	1 (<1)	0	0
Self-Injurious behavior, No Suicidal Attempt	2 (<1)	0	2 (<1)	0
Suicidal Ideation or Behavior Alerts (4-9)				
Any event	3 (<1)	7 (2)	3 (<1)	1 (<1)
Consistent with investigator clinical assessment?				
Yes - AE/SAE	1 (<1)	3 (<1)	1 (<1)	0
Yes – non-AE/SAE	1 (<1)	0	1 (<1)	0
No	2 (<1)	4 (1)	2 (<1)	1 (<1)

Data Source: GSK Doc. # 2019N399072_00 in-text Table 18.
Note: Incomplete calls are excluded if and only if a complete call is recorded on the same day.
Note: For Post-Baseline, percentages are based on the number of subjects with at least 1 on-treatment C-SSRS assessment. For behavior, the numbers of subjects (n) are those with the specified behavior at least once during treatment. For ideation, n refers to the number whose maximum ideation at any on-treatment assessment is the specified ideation. Subjects may have more than 1 type of suicidal ideation or behavior.
Note: In the Data Source tables and figures, the CAB + RPV group is listed as Q4W IM, and Extension Switch to CAB + RPV subjects are listed as CAR group.

Phase IIB Results

At EOS in Study LAI116482, 4 CAB subjects and 1 EFV subject had positive suicidal indication alert(s) (Safety Population) (Data Source: GSK Doc. # 2019N404586_00 Section 7.5 and Table 8.60). Six subjects had PSRAEs (5 CAB and 1 EFV) (Data Source: GSK Doc. # 2019N404586_00 Table 8.61).

At Week 96 in Study 200056 (the most recent time point at which these data were analyzed), 33 subjects had positive assessments for suicidal ideation and/or behavior while on study; 16 subjects in Q8W IM arm, 12 subjects in Q4W IM arm, and 6 subjects in the oral CAB arm (GSK Doc. # 2017N337118_00 Section 7.6). Five subjects had PSRAEs (3 Q8W and 2 Q4W). (Data Source: GSK Doc. # 2017N337118_00 Table 8.1079).

Conclusion

Suicidality assessments were collected prospectively during Phase IIB and Phase III/IIIB studies. Validated true positive alerts for suicidality assessments occurred at a lower incidence in the CAB + RPV Q4W group compared with the CAR group during Studies 201584 and 201585 (Week 48 analysis). 2 subjects in Study 207966 (1 Q8W; 1 Q4W) had positive PSRAEs (Week 48 analysis).

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

Data from the pooled Phase III studies (201584 and 201585) conducted for the CAB + RPV program and from studies conducted with CAB alone are included in this section. Additional information from other studies is included as appropriate.

5.1. Intrinsic Factors

5.1.1. Sex, Age, and Race

Analyses of AEs by age, sex, and race were conducted for Studies 201584, 201585, and pooled Studies 201584 and 201585.

In general, the AE profile for CAB + RPV Q4W was comparable across age, sex, and race (Data Source: ISS/ISE Table 3.09, Table 3.08, Table 3.10, respectively). In the 201584 and 201585 pooled analysis, there was no significant difference noted in the number and types of AEs reported postBaseline between males (N=413 [96%] in the CAB + RPV Q4W group; N=323 [76%] in the CAR group) and females (N=148 [91%] in the CAB + RPV Q4W group; N=122 [73%] in the CAR group). Events occurring in subjects <50 years (N=465 [95%] in the CAB + RPV Q4W group; N=348 [75%] in the CAR group) and ≥50 years (N=96 [97%] in the CAB + RPV Q4W group; N=97 [78%] in the CAR group) were similar. No clinically significant difference was observed in the number of AEs reported among races in the CAB + RPV Q4W group; however, the majority of subjects were White, and there were relatively small numbers in the other groups.

5.1.2. Hepatitis B and/or C Virus Co-infection

5.1.2.1. Hepatitis B Co-infection

HIV-infected patients with evidence of HBV coinfection were excluded from the CAB + RPV development program. No conclusions can be made about the safety of CAB + RPV in HBV co-infected patients. In Studies 201584 and 201585, subjects who developed isolated ALT elevations (>5xULN, Grade 3 ALT elevation) and were identified to have acquired acute infectious hepatitis had CAB + RPV Q4W dosing withheld. Resumption of dosing with acute infection of HBV was not studied.

5.1.2.2. Hepatitis C Co-infection

Subjects receiving CAB + RPV who met LSC and were subsequently identified as having acquired HCV had further dosing withheld. Hepatic AEs have been reported in patients receiving CAR with underlying liver disease, including HCV co-infection. Chronic HCV infection has been identified as an independent risk factor for severe hepatotoxicity during treatment with CAR [Wit, 2002]. Asymptomatic subjects with stable HCV were allowed to enroll in the Phase IIB and III studies for CAB + RPV provided that certain criteria were met, including that these subjects did not have advanced liver disease and were assessed by the investigator that HCV treatment was not necessary during the first 48 weeks of the study. Subjects who had positive HCV serology at Baseline are summarized in Table 94.

Table 94 Summary of Subjects With Positive HCV Serology at Baseline in Studies 201584, 201585, 201584+201585 Pooled, and 207966 (ITT-E Populations)

	Study 201584		Study 201585		Pooled Studies 201584 and 201585		Study 207966[a]	
	CAB + RPV Q4W N=283 n (%)	CAR N=283 n (%)	CAB + RPV Q4W N=308 n (%)	CAR N=308 n (%)	CAB + RPV Q4W N=591 n (%)	CAR N=591 n (%)	CAB + RPV Q8W N=522 n (%)	CAB + RPV Q4W N=522[b] n (%)
Positive HCV serology at Baseline	19 (7)	9 (3)	23 (7)	31 (10)	42 (7)	40 (7)	5 (<1)	6 (1)

Data Source: GSK Doc. # 2017N345267_00 Section 5.4.2.1 and Table 1.25; GSK Doc. # 2018N370336_00 Section 5.4.2 and Table 1.19; GSK Doc. #◦2019N406358_01 Table 1.18.
Note: In the ISS Data Source tables, the CAB + RPV group is listed as Q4W IM. For Study 201584, CAR = ABC/DTG/3TC.
a. The data shown for Study 207966 may include subjects from Study 201585. Subjects listed in Study 207966 were HCV infected with a positive HCV antibody and HCV RNA.
b. 522/523 subjects had test results for HCV.

During Studies 201584 and 201585, 7% of subjects were co-infected with HCV (based on HCV serology alone at Baseline) and they had similar treatment outcomes as mono-infected HIV subjects. These subjects had no suggestion of advanced, chronic

HCV infection, advanced liver disease, liver fibrosis, or liver decompensation. The subjects in the CAB + RPV Q4W arm did not develop signs or symptoms of DILI during their study participation, although limited conclusions can be drawn about this small sub-population particularly in light of the lack of confirmatory HCV RNA in this population. None of the subjects with acute HCV during Studies 201584 and 201585 who met LSC resumed study drug treatment.

Similar results were observed in co-infected subjects in Study 207966 although <1% of Q8W subjects and 1% of Q4W subjects were presumed to be co-infected with HCV (HCV antibody and RNA positive). These subjects all had stable HCV with no suggestion of advanced chronic HCV infection, advanced liver disease, liver fibrosis, or liver decompensation and did not develop DILI during their study participation. A subject in Study 207966 with acute hepatitis C met LSC, subsequently received treatment for hepatitis, and resumed study drug treatment; see GSK Doc. # 2019N406358_01 Section 7.1.5.3.2. Another subject in Study 207966 who did not meet LSC but whose liver chemistries were monitored developed HCV infection but did not restart study treatment.

Five subjects acquired acute HCV during the Phase IIb studies (Study 200056) and then restarted the study drug after recovery. Sexual transmission was likely as it occurred in the wider context of an ongoing epidemic of acute HCV in MSM within certain geographical areas in the US and Europe [Kaplan-Lewis, 2015; Hagan, 2015].

One subject in Study 200056 with HCV co-infection and evidence of liver damage (Grade 3 or 4 fibrosis) accompanied by ongoing HCV replication (chronic active hepatitis) was treated with oral CAB, subsequently met protocol-defined LSC, and developed suspected moderate DILI (Data Source: GSK Doc. # 2018N380094_00 Table 49). Additional details of subjects with suspected DILI are presented in Section 2.1.6.2.

5.1.3. Hepatic Impairment

No dose adjustment in CAB (oral or LA) is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. No data are available in severe hepatic impairment (Child-Pugh Class C) for CAB.

Details of a study conducted with CAB in subjects with hepatic impairment are presented in m2.7.2.

5.1.4. Renal Impairment

No dose adjustment of oral CAB or CAB LA is required for patients with mild to moderate renal impairment. No dose adjustment of oral CAB or CAB LA is required for severe renal impairment (not on renal replacement therapy).

CAB is highly bound to plasma proteins; therefore, it is unlikely that it would be significantly removed by hemodialysis or peritoneal dialysis.

Details of a study conducted with CAB in subjects with renal impairment are presented in m2.7.2.

5.2. Extrinsic Factors

5.2.1. Effects of Food on Oral CAB

In Study 205696, 30 mg oral CAB administered with a high-fat meal modestly increased exposures of CAB by 14% to 17% (AUC0-∞ 163 mcg-h/mL) (Data Source: GSK Doc. # 2016N298724_00 Table 3.3); parameters remained below those observed with the highest dose of 60 mg (AUC0-τ 195 mcg-h/mL) studied in Study LAI116482. Therefore, exposure increase of CAB with food is not considered clinically relevant.

In Study LAI116482, all oral CAB doses (10 mg, 30 mg, 60 mg) were required to be taken with food when co-dosed with RPV (optional when CAB doses with 2 NRTIs during induction) and demonstrated comparable safety and tolerability profiles. CAB 30 mg exposures during the induction phase were comparable to those observed in Study 205696 and were below those observed for the CAB 60 mg exposures in Study LAI116482, providing sufficient safety cover. On the basis of data from these studies, it is recommended that CAB can be administered with or without food.

5.3. Drug Interactions

Overall, there are limited safety implications resulting from theoretical or actual DDI with CAB + RPV during active therapy and following treatment discontinuation. There are no limitations to alternative ART following CAB + RPV discontinuation. Refer to m2.7.2 for further discussion.

5.3.1. Effect of CAB on Other Drugs

Based on in vitro and in vivo data, CAB had low propensity to cause drug interactions.

Refer to m2.7.2 for further discussion.

5.3.1.1. Methotrexate

Co-administration of CAB has the potential to increase methotrexate plasma concentrations via inhibition of OAT1 and OAT3 transporters; however, co-administration has not been studied. The effect of CAB on methotrexate concentrations is expected to be similar to that of tenofovir, another OAT1 and OAT3 substrate, which was co-administered with CAB 10 mg, 30 mg, and 60 mg through 24 weeks and demonstrated a favorable renal safety profile. In the oral CAB Phase IIB Study LAI116482, 149/243 (61%) of subjects received TDF/FTC as background NRTIs at the start of the study and 94/243 (39%) received ABC/3TC (Data Source: GSK Doc. # 2013N168724_00 Table 11). Overall rates of graded renal safety lab abnormalities were similar between oral CAB and EFV regimens, and there were no graded CRCL abnormalities in any treatment arm. Additionally, mechanistic static

and PBPK modeling provide support that CAB is not a clinically relevant inhibitor of OAT1/OAT3 transporters. Steady-state CAB exposures following LA administration remain between mean CAB 10 mg and 30 mg once daily exposures. No dose adjustment is required when CAB is co-administered with OAT1/3 substrates, such as tenofovir, including sensitive substrates with narrow therapeutic indices, such as methotrexate.

5.3.2. Effect of Other Drugs on CAB

CAB is eliminated mainly through metabolism by UGT1A1. CAB is also a substrate of UGT1A9, Pgp, and BCRP; therefore, drugs that induce these enzyme/transporters may theoretically decrease CAB plasma concentration and reduce the therapeutic effect of CAB. Drugs that inhibit these enzymes/transporters may increase CAB plasma concentration, resulting in AEs. Based on PBPK modeling, strong inhibitors of UGT1A1, e.g., atazanavir or atazanavir/ritonavir, are not expected to significantly increase CAB exposure (m2.7.2). Inhibitors of Pgp and BCRP are not expected to increase CAB exposure significantly (m2.7.2). No upper limit of exposure associated with an increased incidence of AEs has been identified. PK/PD analyses following oral and LA CAB administration did not identify an association between plasma exposure and any safety parameter (m2.7.2). Thus, there is no limitation to the use of UGT inhibitors as part of an alternative ART regimen following CAB discontinuation or as a concomitant medication with CAB based on PBPK modeling.

5.4. Use in Pregnancy and Lactation

The safety of CAB as part of the CAB + RPV 2-drug regimen during human pregnancy and breastfeeding has not been established.

5.4.1. Pregnancy

No studies have been conducted with CAB in pregnant women, and pregnant women were excluded from the CAB + RPV development program. Subjects who became pregnant on study were required to discontinue investigational products.

During the clinical development program for CAB + RPV, FCBP were counseled on highly effective methods of avoiding pregnancy and required a negative pregnancy test at Day 1 before study medications could be started. FCBP were then retested on a regular basis (at least at every study visit) thereafter to identify pregnancies early. Females who became pregnant during a study had treatment discontinued and entered the LTFU phase of the study in which they were enrolled if they had received at least 1 injection. Information on pregnancy outcomes, gestational age at delivery, birth weights, and presence of any congenital abnormalities were sought during follow-up of female subjects who became pregnant on study. Reported AEs potentially related to safety in pregnancy are presented in Section 2.1.6.12.

During the CAB development program for HIV-1, 17 pregnancies have been identified in women exposed to CAB and 3 pregnancies have been identified in women exposed to

CAR (1 live birth, 1 spontaneous abortion, and 1 induced abortion) (Table 95). Of the 20 pregnancies in women exposed to CAB:

- 2 were ongoing at the time of document finalization
- 8 resulted in live birth
- 10 did not progress
    - 1 due to medical abortion
    - 1 due to missed abortion
    - 2 due to spontaneous abortion
    - 6 due to induced abortion

Table 95 Confirmed Pregnancies in CAB Development Program for HIV-1 Treatment

Age (years)/ Subject ID	Treatment at Time of Pregnancy Identification	Outcome	Week of Gestation
Study 201584			
30 to 40 [redacted]	CAR	Live birth - no congenital anomaly reported	37
20 to 30 [redacted]	CAR	Induced abortion	8
40 to 50 [redacted]	CAB LA + RPV LA Q4W	Live birth - no congenital anomaly reported	44
40 to 50 [redacted]	CAB oral + RPV oral	Live birth - no congenital anomaly reported	40
40 to 50 [redacted]	CAB LA + RPV LA Q4W	Missed abortion	~8
30 to 40 [redacted]	CAB LA + RPV LA Q4W	Live birth - no congenital anomaly reported	40
30 to 40 [redacted]	CAB LA + RPV LA Q4W	Induced abortion	~7
Study 201585			
30 to 40 [redacted]	CAB LA + RPV LA Q4W	Induced abortion	~5
30 to 40 [redacted]	CAB oral + RPV oral	Medical abortion due to fetus not developing ([redacted])	~8
20 to 30 [redacted]	CAB LA + RPV LA Q4W	Live birth - no congenital anomaly reported	38
30 to 40 [redacted]	CAB LA + RPV LA Q4W	Induced abortion	~6
40 to 50 [redacted]	CAR	Spontaneous abortion	5
Study 207966[a]			
40 to 50 [redacted]	CAB oral + RPV oral	Spontaneous abortion ([redacted] previous spontaneous abortions)	~8
20 to 30 [redacted]	CAB LA + RPV LA Q8W	Induced abortion	~8
20 to 30 [redacted]	CAB LA + RPV LA Q8W (off study)	Ongoing	NA
20 to 30 [redacted]	CAB oral + RPV oral	Induced abortion	~7
20 to 30 [redacted]	CAB LA + RPV LA Q4W	Live birth - no congenital anomaly reported	39
40 to 50 [redacted]	CAB LA + RPV LA Q4W	Ongoing	NA
Study 200056			
20 to 30 [redacted]	CAB LA + RPV LA Q4W	Live birth - no congenital anomaly reported	38
20 to 30 [redacted]	CAB LA + RPV LA Q4W (off study)	Induced abortion	10
30 to 40 [redacted]	CAB LA + RPV LA Q4W	Live birth (via Caesarean) - no congenital anomaly reported	37
30 to 40 [redacted]	CAB LA + RPV LA Q8W	Live birth - no congenital anomaly reported	36

Age (years)/ Subject ID	Treatment at Time of Pregnancy Identification	Outcome	Week of Gestation
Study 201767 (Phase I)			
20 to 30 [redacted]	CAB LA	Spontaneous abortion (possible early miscarriage)	1

Data Source: GSK Doc. # 2019N421511_00 Section 7.7, Section 7.8.6, and Section 15; GSK Doc. # 2018N370336_00 Section 7.9; GSK Doc. # 2019N406358_01 Section 7.7 and Section 13; GSK Doc. # 2017N337118_00 Section 7.10 and Section 11; and Data on file.
a. A fifth subject had an unconfirmed pregnancy and possible miscarriage.

Narratives for the subjects who became pregnant during the CAB + RPV development program are available in the respective CSRs:

Recommendations for Use in Pregnancy

The embryofetal development toxicity studies with CAB in rat and rabbit do not indicate a risk to the human fetus. In addition, the risk of delayed parturition and a higher rate of stillborn rat pups was observed in the high-dose arm of the CAB rat PPN study. These findings occurred when rats were exposed to 28 times the human dose of CAB that women are exposed to in the first trimester, with levels of CAB expected to decrease as pregnancy progresses. The clinical relevance of this finding is unknown (see Section 1.1.2.1). There were no adverse effects noted in rats that received >10 times the maximum anticipated exposure of CAB. Clinical pregnancy data with CAB are limited and have not identified a known risk. CAB as part of the CAB + RPV 2-drug regimen should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

5.4.2. Lactation

The safety of exposure of CAB as part of the CAB + RPV 2-drug regimen to infants through breastfeeding has not been established. Some treatment guidelines [EACS, 2017] recommend against breastfeeding to avert the risk of HIV transmission to the infant, and product labelling for CAB will include standard recommendations not to breastfeed.

Women who were breastfeeding infants were excluded from study participation. Women who had received CAB LA were recommended to refrain from breastfeeding until at least 12 months from the last injection to avoid potential exposure of the infant because nonclinical data suggest that CAB may be present in breast milk (see m2.6.6, Section 6.4).

5.5. Pooled Phase I Clinical Pharmacology Safety Summary

No safety findings of concern, additional to those identified from Phase II and III studies, were observed in a pooled safety analysis of 19 clinical pharmacology studies with CAB.

5.5.1. Pooled Phase I Clinical Pharmacology Safety Summary for CAB

In total, 509 subjects from 19 integrated clinical pharmacology studies were pooled in a separate safety analysis (Table 96). Due to the crossover design of many of the Phase I studies, some subjects received CAB and/or placebo (PBO) and/or at least 1 other protocol-defined medicinal product, either sequentially and/or in combination. In studies primarily evaluating CAB LA, all subjects received oral CAB preceding CAB LA except for Study LAI114433. Thus, the Total Safety Population does not necessarily equal the sum of the All CAB and All PBO treatment populations.

Table 96 Summary of Integrated Pharmacology Studies

Integrated Clinical Pharmacology Studies	Pooled safety analyses[a] from ITZ111451, ITZ111682, ITZ111839, ITZ112929, LAI114433[b], LAI115428[b], LAI116181 (CAB arm), LAI116585, LAI116815[b], LAI117008, LAI117009[c], LAI117011, LAI117020, LAI117010, 201479, 201480, 201741, 205696, 205712
Clinical Pharmacology Studies Completed or Ongoing and excluded from Integrated Analysis (i.e., after the [redacted] 20[redacted] cut-off)[d]	Completed reports: 200056 CSF PK sub-study and 201120 ECLAIR Ongoing at the [redacted] 20[redacted] cut-off: 201767

a. Comprises 19 completed Phase I studies in healthy adults, including 1 Phase I study in hepatically impaired subjects, 1 Phase I study in renally impaired subjects, and 2 Phase IIa studies in ART-naïve, HIV-infected adult subjects (ITZ111451 and ITZ112929).
b. Phase I studies primarily evaluating CAB LA in healthy adults (LAI114433, LAI115428, LAI116815).
c. Key clinical pharmacology study (i.e., investigates specific safety outcomes); LAI117009 is the definitive QTc study.
d. These are grouped in m2.7.4 under "Other Completed and Ongoing Studies in Adults" sections and limited to summaries of SAEs, pregnancies or fatalities in these studies.

5.5.1.1. Pooled Safety Analysis in Phase I Studies (Oral and LA CAB)

Clinical Pharmacology Studies Population

As of 18 October 2018, safety and PK have been evaluated in 19 completed and 1 ongoing ViiV sponsored pharmacology studies with oral CAB and CAB LA (Table 96). Subjects have been exposed to 1 to 3 oral doses of CAB ranging from 5 to 150 mg, repeat once daily doses of 30 mg up to 28 days in duration, single CAB IM or SC or repeat CAB IM for 4 months.

15 HIV-infected subjects have received repeat once daily doses of oral CAB in 2 Phase IIa studies: ITZ111451 Part C and ITZ112929.

19 studies have been completed and 1 Phase I/IIa ViiV-sponsored clinical pharmacology study (201767) is ongoing.

This meta-analysis was an update of a previously published analysis that included safety data from the 14 studies completed and published in 2016 [Lou, 2016].

Pooled Safety Analysis Overall Safety Summary

In this meta-analysis, a total of 509 subjects, including 494 healthy subjects and 15 HIV-infected subjects, were exposed to CAB oral and/or LA. Of these, 136 subjects received CAB LA. Of the total 509 subjects, 148 were female and 361 were male, with a median age of 34 years (range: 18-69). Seventy subjects, with a median age of 33 years (range: 18-54), received at least 1 dose of placebo and were included in the pooled analysis.

Deaths and Pregnancies

No deaths or pregnancies were reported in any of the completed clinical pharmacology studies.

Adverse Events Leading to Withdrawal

Based on the clinical pharmacology integrated analysis, there were 12 subjects (12/509, 2%) on CAB (oral or LA) and 1 subject on placebo who had AEs that led to discontinuation from the study. There were no safety trends noted leading to discontinuation of subjects across the clinical pharmacology studies.

Twelve subjects withdrew due to AEs (4 drug-related AEs: dizziness, rash, leukopenia, and elevation in ALT/AST/GGTP; 8 non-drug related AEs: jaundice, hematuria, arthropod bite, UTI, food poisoning, elevated ALT, pyrexia, and tendon rupture) (Data Source: Pooled Safety Analysis Phase 1 Table 8).

Non-Fatal Serious Adverse Events

Three subjects had 3 drug-related (CAB) Grade 3 or 4 AEs (elevated lipase, elevated ALT, lymphopenia).

There were 5 SAEs reported; one was reported as drug related (ALT elevation, Grade 3; Table 47). The other 4 non-drug-related SAEs were foot osteomyelitis (Grade 4), uterine fibroids (Grade 2), appendicitis (Grade 2), and seizure (Grade 2; see Section 2.1.6.7).

Non-ISR Adverse Events

AEs were reported at all studied doses. The most frequent (>5%) non-ISR AEs were headache (overall CAB rate of 14%: 9% in oral and 27% in LA), which occurred more frequently in CAB than in the CAB +RPV group (11%), and upper respiratory tract infection (overall CAB rate of 5%: 2% in oral and 12% in LA), versus 21% in the CAB + RPV group (Data Source: Pooled Safety Analysis Phase 1 Table 5). CAB was well tolerated across all studies with an overall incidence of 13% of any drug-related AEs and few drug-related withdrawals.

All non-ISR drug-related AE rates by severity grade and dosing regimen are summarized in Table 97.

Table 97 Non-ISR Drug-related AEs by Severity From 19 Pooled Phase I/IIA Completed CAB Clinical Pharmacology Studies (Safety Population)

	CAB ORAL (N=451)				CAB IM (N=118)		CAB SC (N=28)		CAB Overall (N=509)			
PT (≥2 subjects)	**Mild**	**Moderate**	**Severe**	**Grade 4**	**Mild**	**Moderate**	**Mild**	**Moderate**	**Mild**	**Moderate**	**Severe**	**Grade 4**
Any AE, n (%)	**39 (9)**	**8 (2)**	**2 (<1)**	**1 (<1)**	**10 (8)**	**4 (3)**	**2 (7)**	**0**	**49 (10)**	**12 (2)**	**2(<1)**	**1 (<1)**
Headache	14 (3)	3 (<1)	0	0	2 (2)	2 (2)	2 (7)	0	17 (3)	5 (<1)	0	0
Nausea	7 (2)	1 (<1)	0	0	0	0	0	0	7 (1)	1 (<1)	0	0
Abdominal pain	3 (<1)	1 (<1)	0	0	1 (<1)	0	1 (4)	0	5 (<1)	1 (<1)	0	0
Dizziness	4 (<1)	0	0	0	0	0	0	0	4 (<1)	0	0	0
Insomnia	5 (1)	0	0	0	0	0	0	0	5 (<1)	0	0	0
Decreased appetite	3 (<1)	0	0	0	0	0	1 (4)	0	4 (<1)	0	0	0
ALT increased	1 (<1)	0	1 (<1)	0	1(<1)	0	0	0	2 (<1)	0	1 (<1)	0
Dyspepsia	2 (<1)	0	0	0	1 (<1)	0	0	0	3 (<1)	0	0	0
Abnormal dreams	2 (<1)	0	0	0	0	0	0	0	2 (<1)	0	0	0
Constipation	3 (<1)	0	0	0	0	0	0	0	3 (<1)	0	0	0
Fatigue	2 (<1)	0	0	0	0	0	0	0	2 (<1)	0	0	0
Pain in extremity	1 (<1)	0	0	0	1 (<1)	0	0	0	2 (<1)	0	0	0
Rash	1 (<1)	0	0	0	1(<1)	0	0	0	2 (<1)	0	0	0
Vomiting	2 (<1)	0	0	0	0	0	0	0	2 (<1)	0	0	0
Leukopenia	2 (<1)	0	0	0	0	0	0	0	2 (<1)	0	0	0
Neutropenia	2 (<1)	0	0	0	0	0	0	0	2 (<1)	0	0	0
Lymphope-nia	0	0	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)
Lipase increase	0	0	1 (<1)	0	0	0	0	0	0	0	1 (<1)	0

Data Source: Pooled Safety Analysis Phase 1 Table 7.

ISRs

ISRs associated with CAB or RPV LA injection were very common (CAB IM: 77% of exposed subjects, CAB SC: 96% of exposed subjects, RPV IM: 95% of exposed subjects) but generally mild with no Grade 3 or Grade 4 ISR AEs. The most frequent ISRs for IM and SC dosing, respectively, were pain, erythema, and nodules; the incidence of nodules was higher with SC dosing (79% of subjects) compared with IM dosing (19% of subjects). ISRs did not interfere with daily activities.

Median CAB IM ISR duration was ≤7 days for pain and erythema. Median ISR duration for nodules was 19 days for CAB IM, 53 days for CAB SC, and 56 days for RPV IM.

Table 98 summarizes the type of ISR events observed in/reported by subjects receiving CAB, RPV, or placebo injections.

Table 98 Summary of ISR AEs (Phase I/IIA Pooled Safety Analysis; Safety Population)

	CAB IM (N=118)	CAB SC (N=28)	RPV IM (N=19)	PBO IM (N=8)	PBO SC (N=6)
Any ISR, n (%)	**91 (77)**	**27 (96)**	**18 (95)**	**2 (25)**	**3 (50)**
Pain	87 (74)	24 (86)	17(89)	2 (25)	2 (33)
Nodule (granulomas and cysts)	22 (19)	22 (79)	3 (16)	0	0
Erythema	17 (14)	22 (79)	2 (11)	0	1 (17)
Induration	14 (12)	7 (25)	1 (5)	0	0
Warmth at injection site	7 (6)	8 (29)	1 (5)	0	0
Pruritus	4 (3)	5 (18)	0	0	0
Other	6 (5)	3 (11)	0	0	0
Swelling	1 (<1)	4 (14)	0	0	0
Ecchymosis (Bruise)	1 (<1)	3 (11)	0	0	1 (17)
Injection Site Bruising	1 (<1)	2 (7)	1 (5)	0	0
Injection Site Dryness	0	1 (4)	0	0	0
Injection Site Paresthesia	1 (<1)	0	0	0	0

Data Source: Pooled Safety Analysis Phase 1 Table 11.

ISR events are summarized according to toxicity grades observed in/reported by subjects receiving CAB, RPV, or placebo injections in Table 99.

Table 99 Summary of ISR Events (All Grades) in Phase I/IIA Pooled Safety Analysis (Safety Population)

ISR Events and Top 3 ISR AEs		CAB IM (N=257)	CAB SC (N=201	Overall CAB (N=458)	RPV IM (N=45)	PBO IM (N=3)	PBO SC (N=4)
Overall ISR, n (%)	**Any Grade**	**257 (100)**	**201 (100)**	**458 (100)**	**45 (100%)**	**3 (100)**	**4 (100)**
	Grade 1	228 (89)	199 (99)	427 (93)	39 (87)	3 (100)	4 (100)
	Grade 2	29(11)	2 (<1)	31 (7)	6 (13)	0	0
	Grade 3	0	0	0	0	0	0
Pain	Any Grade	171 (67)	48 (24)	219 (48)	37 (82)	3 (100)	2 (50)
	Grade 1	142 (55)	47 (23)	189 (41)	31 (69)	3 (100)	2 (50)
	Grade 2	29 (11)	1 (<1)	30 (7)	6 (13)	0	0
	Grade 3	0	0	0	0	0	0
Nodule (granulomas and cysts)	Any Grade	25 (10)	45 (22)	70 (15)	3	0	0
	Grade 1	25 (10)	45 (22)	70 (15)	3	0	0
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0
Erythema	Any Grade	19 (7)	46 (23)	65 (14)	2 (4)	0	1 (25)
	Grade 1	19 (7)	46 (23)	65 (14)	2 (4)	0	1 (25)
	Grade 2	0	0	0	0	0	0
	Grade 3	0	0	0	0	0	0

Data Source: Pooled Safety Analysis Phase 1 Table 12.
Events are cumulative; some subjects received more than 1 injection and may have had more than 1 ISR event/injection.

Clinical Laboratory Evaluations

No trends were noted during the conduct of the Phase I/IIa studies to suggest that CAB has a clinically significant effect on clinical chemistries.

Treatment-emergent maximum laboratory toxicities Grade ≥2 were reported in subjects for the following laboratory tests: total cholesterol (7%), lipase (4%), and CK (2%). A subject in the LAI115428 study developed a Grade 1 ALT elevation of 4.3xULN 118 days after initiation of CAB and 41 days after administration of TMC278LA, which was considered not related to study drug and resolved while on both drugs.

Adverse Events of Special Interest

One subject in a clinical pharmacology study (205712) had an ALT elevation (Grade 3) with normal bilirubin.

One seizure occurred in Study LAI116815 involving a subject with a pre-existing history of seizure (Table 51). The seizure occurred approximately 9 months after a single dose of CAB 400 mg IM, and approximately 6 months after CAB was no longer detectable in the serum. The seizure in this subject was not considered by the investigator or the Sponsor to be related to CAB.

QT Prolongation

In a randomized, placebo-controlled, 3-period cross-over trial (LAI117009; GSK Doc. # 2014N208600_00), 42 healthy subjects were randomized into 6 random sequences and

received 3 doses of oral administration of placebo, CAB 150 mg q 12 hours (Cmax approximately 3-fold of clinically therapeutic dose 30 mg qd), and a single dose of moxifloxacin 400 mg (active control). After baseline and placebo adjustment, the maximum time-matched mean QTcF for CAB was 2.62 msec (1-sided 95% upper CI: 5.26 msec). CAB did not prolong the QTc interval over 24 hours post dose (see m2.7.2 Section 2.1.5.6.3 for details).

Safety Data from Studies Not Included in the Pooled Analysis

Study 201767 is ongoing. To date, there were 2 non-drug-related SAEs, no deaths, and no significant vital signs or ECG abnormalities reported as AEs.

5.6. Medication Errors

The combination of a 2-drug injectable regimen using syringes for delivery is novel for some HCPs experienced in treating HIV patients. The different initiation and continuation doses for CAB and RPV and the unfamiliarity with vial dose/concentration could introduce additional complexity.

The investigational sites had the opportunity to record whether the subject received the correct treatment and whether the syringe device used for injection malfunctioned. Data gathered from CRFs regarding study drug exposure and device malfunction, along with communication with sites, were used to estimate the occurrence of medication errors. Medication error occurrences were not recorded as AEs unless a corresponding AE was recorded.

A total of 14,682 injections were administered during 48 weeks of Studies 201584 and 201585 (Data Source: ISS/ISE Table 3.110). Medication errors not associated with device malfunction were formally reported and were infrequent occurrences during these studies. These errors were reported to have occurred in 15 subjects, sometimes involving >1 drug, and sometimes involving >1 subject at the same investigative site. For most subjects (n=14), these involved receiving the wrong dose, and in 1 subject this involved receiving the right dose and drug but from the wrong study (Data Source: GSK Doc. # 2017N345267_00 Listing 66; GSK Doc. # 2018N370336_00 Listing 2). Of the 14 subjects receiving the wrong dose, 8 were due to underdose and 6 were due to overdose. In 11 subjects these errors occurred during the first 12 weeks of commencing CAB LA + RPV LA, suggesting an initial lack of familiarity with use of the product. No AEs were directly attributable to these errors. No evidence of lack of efficacy has been detected as determined by absence of suspected or confirmed virological failure following the occurrence of an error. There have been no reports of attempts to combine CAB + RPV into a single syringe.

Device malfunctions were reported infrequently with injections of CAB and RPV during Studies 201584 and 201585. 7 device malfunctions were recorded formally. In 4 subjects, it resulted in dosing errors causing underdose. This was noted by the site staff, and in 3 of the 4 subjects additional 'top up' injections were recorded as given to compensate for the lost study drug (Data Source: GSK Doc. # 2017N345267_00 Listing 66; GSK Doc. # 2018N370336_00 Listing 2).

In Study 207966, 8470 injections have been administered to 516 subjects in the Q8W group and 15,711 injections in 517 subjects in the Q4W group (Table 38) as of the data cut-off date (Section 1.1.4.1). There were few reports of dosing errors or device malfunctions.

- In the Q8W group, 1 subject was underdosed (received 2 mL instead of 3 mL) with both CAB + RPV; no dosing errors were reported in the Q4W group (GSK Doc. # 2019N406358_01 Section 7.1.5.4).
- Device malfunctions were reported for 4 subjects in the Q8W group and for 3 subjects in the Q4W group.

Overall, no discernable trends or systematic errors were identified, apart from an initial lack of familiarity of site staff administering drugs. It is likely that the observed errors represent the experience in a group of HCPs that initially lacked familiarity with the product and injection administration technique. The IFU developed for the marketed products will take these findings into consideration and use them to identify critical steps in the dispensing, preparation, and administration of the regimen.

5.7. Withdrawal Effects, Drug Abuse Potential, and Overdose

5.7.1. Withdrawal Effects

There is no clinical evidence to suggest withdrawal or rebound effects of CAB when administered alone or as part of the CAB + RPV 2-drug regimen. No studies to investigate the potential for withdrawal and rebound effects with CAB or CAB + RPV have been performed. These established classes of compounds have no known drug withdrawal or rebound potential.

5.8. Drug Abuse Potential

There are no data to suggest that CAB when administered alone or as part of the CAB + RPV 2-drug regimen has the potential for abuse or dependency, and abuse is not likely because the drug regimen is administered at the healthcare practitioner's clinic.

The INSTI class of compounds has no known drug abuse potential. The mechanism of action for this class does not involve receptors or neurotransmitters known to be involved in drug dependence (see m2.6.2, Section 3.1 for data related to potential off-target binding of CAB).

No studies to investigate the potential for abuse or dependency with CAB + RPV have been performed because:

- CAB and RPV are not centrally active,
- There is clear evidence that these compounds have low brain penetration,
- Mechanistically, CAB or RPV does not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, and

- Preclinical and clinical data available are not indicative of a potential for drug abuse.

In summary, there are no data suggesting that CAB + RPV has the potential for illicit use, abuse, or dependency.

5.8.1. Overdose

There is limited experience with CAB exposure higher than the doses used in the CAB + RPV development program. CAB and RPV have not been studied at doses higher than 800 mg IM every 12 weeks for CAB LA and 1200 mg IM every 8 weeks for 40 weeks for RPV LA. These higher doses were not associated with toxicity compared with the recommended doses for clinical practice.

5.9. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There have been no studies to investigate the effect of CAB administered alone or as part of the CAB + RPV 2-drug regimen on driving performance or the ability to operate machinery or impairment of mental ability.

Overall, given the pharmacology of CAB and available clinical evidence, there is no detrimental effect anticipated on the ability to drive or operate machinery or on mental ability. However, fatigue, dizziness, and somnolence have been reported in some subjects taking CAB + RPV and should be taken into consideration with regard to driving and operating machinery.

6. POST-MARKETING DATA

There are no post-marketing data on CAB as this drug product is not marketed in any country.

7. SAFETY CONCLUSIONS

A total of 2141 subjects have been exposed to CAB + RPV in Phase II and III/IIIB studies as of 18-OCT-2019 (Section 1.2.1).

Safety data across the Phase III/IIIB clinical studies (Studies 201584, 201585, and 207966), supported with data from Phase I and Phase II studies, support a favorable safety profile of CAB + RPV, both for dosing monthly and for dosing every 2 months.

Furthermore, the overall safety profile for CAB + RPV administered every 2 months was similar to the safety profile for CAB + RPV administered every month for both ISRs and systemic AEs.

There were no changes to the overall safety profile during long-term treatment. Overall, few additional subjects had AESIs, and no additional SAEs assessed as drug-related were reported since the Week 48 analysis in Studies 201584 (Week 96/100) and 201585

(Week 96). Therefore, conclusions from Studies 201584, 201585, and 207966 are based on data from the Week 48 analyses.

Common AEs

- In pooled Studies 201584 and 201585, ISRs were the most frequently reported AE but were generally well tolerated. The most common ISR was pain (77% of subjects), and ISRs were mild to moderate and self-limiting with few discontinuations (1% of subjects) due to ISRs or injection intolerance. The percentage of subjects reporting ISRs at each visit decreased over time.
- In Study 207966, results were similar. ISRs were generally mild and of short duration; furthermore, the frequencies and types of ISRs were similar to those observed in pooled Studies 201584 and 201585. The rate of withdrawals due to injection intolerability (1% in Q8W group and 2% in Q4W group) was similar to the rate in pooled Studies 201584 and 201585.
- In pooled Studies 201584 and 201585, the most frequently (≥10% in either group) reported non-ISR AEs were nasopharyngitis and upper respiratory tract infection, both of which were reported in similar proportions of subjects in the pooled CAB + RPV Q4W and CAR groups. Non-ISR AEs more commonly reported (≥5% difference) in the pooled CAB + RPV Q4W group compared with the CAR group were headache and pyrexia.
- In Study 207966, non-ISR AEs reported by ≥10% of subjects in either the Q8W or Q4W group were nasopharyngitis and upper respiratory tract infection. Headache (Q8W: 7%; Q4W: 7%) and pyrexia (Q8W: 5%; Q4W: 8%) were reported by a similar proportion of subjects in either group.
- Drug-related AEs, as identified by the investigator, were reported with a higher incidence with CAB + RPV Q4W compared with CAR in pooled Studies 201584 and 201585. The most common (>10 subjects per group) drug-related non-ISR AEs were headache, pyrexia, nausea, fatigue, asthenia, body temperature increased, myalgia, and dizziness.
- In Study 207966, results were similar. Drug-related non-ISR AEs reported by >10 subjects in either the Q8W or Q4W group were pyrexia, asthenia, fatigue, nausea, and headache.

Grade 3 and 4 AEs

- In pooled Studies 201584 and 201585, Grade 3 and Grade 4 AEs occurred at a higher incidence with CAB + RPV Q4W compared with CAR. This difference in these reported AEs was predominantly attributable to injection site reactions, acute viral hepatitis, and also laboratory findings of elevated creatine kinase and lipase.
- No Grade 3 non-ISR AEs were reported by ≥2 subjects in both the pooled studies and in Study 207966. Blood creatine phosphokinase increased was the only Grade 4 AE reported in both pooled Studies 201584 and 201585 and in Study 207966 among subjects treated with CAB + RPV.

Non-fatal SAEs and Deaths

- The incidence of SAEs reported in pooled Studies 201584 and 201585 was comparable between CAB + RPV Q4W and CAR. The most frequently reported SAE with CAB + RPV Q4W occurring in more than 1 subject was hepatitis A (n=4). Only 2 SAEs were considered study drug-related by the investigator: 1 subject in the CAB + RPV Q4W treatment group had an SAE of right knee mono-arthritis and 1 subject in the CAR treatment group had an SAE of suicidal ideation.
- In Study 207966, results were similar in that no trends were apparent. Three SAEs were reported in more than 1 subject in either treatment group: pneumonia, appendicitis, and hemorrhoids. SAEs reported as possibly drug related occurred with a frequency of <1% in both groups, and each SAE PT was reported once (pancreatitis acute, injection site abscess, and presyncope in the Q8W group and hypersensitivity in the Q4W group).
- Four subjects were reported to have post-injection reactions that were SAEs; 3 with apparent IV injection of RPV (based on PK). The fourth case was not confirmed because a suitably timed post-dose PK sample was not collected. In Study 200056, 1 case was reported. In Study 207966, 3 cases were reported. No specific AEs have been identified with CAB subjects with unexpectedly high PK. The SAEs of post-injection reactions were transient in nature and did not result in clinically significant sequelae.
- Among subjects receiving CAB + RPV during Phase III/IIIB Studies 201584, 201585, and 207966, 1 death was reported. The death (Q8W group in Study 207966) was reported 522 days after the first dose of CAB + RPV and 98 days after the subject's last dose of study drug. The cause of death was sepsis as a result of complications of acute pancreatitis (pancreatitis assessed as possibly related to study drug by the investigator). Based upon the long latency period and possible confounders, the Sponsor does not believe the evidence supports the study drugs being causative in this instance.
- There were 2 deaths during Phase III/IIIB studies in subjects in the CAR group (both accidental in nature).
- During Phase II studies, there were 6 fatalities. Of these 6 fatalities, 1 death (myocardial infarction) was considered study drug related (CAB + RPV) by the investigator. The subject had been on treatment for approximately 3 years and had several risk factors for cardiovascular disease.

AEs Leading to Withdrawal

- The rate of discontinuation was low overall for pooled Studies 201584 and 201585. 22 (4%) subjects in the CAB + RPV Q4W group and 9 (2%) subjects in the CAR group had AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase. The most common AEs leading to withdrawal for CAB + RPV Q4W were acute viral hepatitis (n=9) and ISRs (n=5). Individual AEs leading to withdrawal had an incidence of <1%.

- In Study 207966, the rate of AEs leading to withdrawal was low (2%) with no distinct patterns of AEs between the treatment groups.

AEs of Special Interest

- There were no cases of serious reactions such as DILI or HSR in Studies 201584 and 201585 with CAB + RPV Q4W. One possible case of DILI was reported during OLI in Study 207966. No cases of DILI have occurred during CAB LA + RPV LA treatment. In Studies 201584 and 201585, there was a higher incidence of Grade 3/4 ALTs and subjects who met LSC in the CAB + RPV Q4W treatment regimen compared with the CAR regimen, which was due to the higher incidence of the acute viral hepatitis occurring in subjects in the CAB + RPV Q4W group.
- During Phase I and Phase II studies, DILI was identified in 5 subjects receiving oral CAB (incidence was <1%).
- The incidence of neuropsychiatric AEs was low (up to 6% of subjects) during Studies 201584 and 201585 with CAB + RPV Q4W. The incidence of anxiety, depression, and sleep disorders with CAB + RPV Q4W was 1% to 4%. There were no serious neuropsychiatric events with CAB + RPV Q4W with 2 withdrawals (1 subject for depression suicidal and 1 subject for anxiety). In Study 207966, neuropsychiatric AESIs of depression, anxiety, and sleep disorders were reported in 2% to 7% of subjects in either treatment group, with few events leading to withdrawal.
- Weight gain was observed in Studies 201584 and 201585 with a pooled median weight gain of 1.5 kg with CAB + RPV Q4W when compared with 1.0 kg median weight gain with CAR (Week 48 analysis). This difference was more pronounced in Study 201585 with median weight gain of 1.8 kg with CAB + RPV Q4W compared with a median weight gain of 0.3 kg with CAR. It is unclear if this weight increase was due to increased adiposity as body composition was not measured in this trial. Subjects in both the Q4W and Q8W groups in Study 207966 had a median weight gain of 1.0 kg during the MP (Week 48 analysis). Similar trends with increased weight with CAB + RPV have been observed with treatment with CAB + RPV during Phase IIB studies with a median weight gain of 3.05 kg over 160 weeks (approximately 3 years) in Study 200056 and 6.50 kg at EOS (between 5 and 6 years of treatment) in Study LAI116482.
- Treatment with CAB + RPV Q4W or Q8W appears to have no clinically relevant effect on the following AESIs: QT prolongation, seizures, rhabdomyolysis, pancreatitis, or impact on creatinine.

Oral Treatment

- There were few safety events observed with oral treatment (OLI) during Studies 201584, 201585, and 207966. The overall safety profile observed with oral CAB + RPV is similar to that observed overall with the CAB + RPV treatment regimen (with the exception of ISRs). One possible case of DILI was reported during OLI in Study 207966.

Laboratory Assessments

- In pooled Studies 201584 and 201585, the majority (74.7% CAB + RPV Q4W, 80.2% CAR) of the maximum post-baseline emergent clinical chemistry abnormalities were Grade 1 or Grade 2 in intensity. With the exception of creatine kinase and lipase (higher frequency in CAB + RPV Q4W), there were similar frequencies of Grade 3/4 clinical chemistry abnormalities between the treatment groups. No clinically relevant differences were observed overall in Grade 3 and Grade 4 post-Baseline emergent abnormalities between the CAB + RPV Q4W and CAR groups.
- In Study 207966, no clinically relevant patterns in changes for chemistry, hematology, or lipids from Baseline category for the Maintenance Phase through Week 48 were observed in either treatment group.

Intrinsic Factors

- Results from Studies 201584 and 201585 do not suggest any effect of age, sex, or race on the safety profile of CAB.
- In Studies 201584, 201585, 207966, and 200056, medication errors and device malfunctions were infrequent occurrences, and no AEs were directly attributable to these errors.
- Co-infection with hepatitis
    - In Studies 201584 and 201585, 42/591 subjects on CAB + RPV Q4W and 40/591 subjects on CAR were identified as co-infected with HCV at Baseline. The subjects included in the study did not have advanced chronic HCV. The subjects in the CAB + RPV Q4W arm did not develop signs or symptoms of DILI during their study participation, although limited conclusions can be drawn about this small sub population. In Study 207966, fewer subjects (11/1044) were determined to be co-infected with HCV at Baseline, and results were similar.
    - HIV-infected patients with evidence of HBV co-infection were excluded from the CAB + RPV clinical program as CAB + RPV does not have activity against HBV. No conclusions can be made about the safety of CAB + RPV in HBV co-infected patients.
- No dose adjustment of CAB (oral or LA) is required for patients with mild or moderate hepatic impairment. No data are available in severe hepatic impairment.
- No dose adjustment of CAB (oral or LA) is required for patients with mild to severe renal impairment (creatinine clearance ≤30 mL/min and not on dialysis). No data are available in patients with end-stage renal disease on renal replacement therapy.

Special Populations

- The safety of CAB during human pregnancy and breastfeeding has not been established; CAB should be used during pregnancy only if the expected benefit justifies the potential risk to the fetus.

2.7.5 REFERENCES

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2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Biopharmaceutical Studies						
ITZ111682	To evaluate relative bioavailability of oral tablet	Open-label, single dose, randomized, parallel study	Healthy subjects	CAB 10 mg oral solution, single dose, fasted CAB 10 mg (2 x 5 mg) tablet, single dose, fasted CAB 10 mg (2 x 5 mg) tablet, single dose, fed	45 enrolled 45 completed	Completed CPSR
LAI116815	To evaluate the relative bioavailability of 2 new formulations of [redacted] of CAB 400 mg LA given IM compared with the current formulation ([redacted] nm [redacted])	Open label, single-dose, parallel study	Healthy subjects	Lead in (all treatments) CAB 30 mg QD for 14 days Midazolam 3 mg probe x 2 doses (n=12) Treatment A: 400 mg IM ([redacted] nm) Treatment B: 400 mg IM ([redacted] µm) Treatment C: 400 mg IM ([redacted] µm)	43 enrolled 33 completed	Completed CPSR
LAI117020	To assess the relative bioavailability of 2 30-mg sodium salt tablet formulations of CAB and to evaluate the effect of a moderate-fat meal on the bioavailability of the selected tablet formulation	Randomized, 2-part, open label, crossover study	Healthy subjects	Treatment A: CAB 30 mg [redacted], fasted Treatment B: CAB 30 mg [redacted], fasted Treatment C: CAB 30 mg [redacted], fasted	Part A: 24 enrolled 22 completed Part B: 15 enrolled 15 completed	Completed CPSR
201741	To evaluate the relative bioavailability of 4 new CAB 30 mg sodium salt tablet formulations ([redacted]) compared with a tablet of the current sodium salt formulation	Single center, randomized, open label, 2-cohort, 3-way cross-over study	Healthy subjects	Cohort 1 Treatment A = CAB 30 mg [redacted], reference Treatment B = CAB 30 mg [redacted], [redacted] mg [redacted]; [redacted] Treatment C = CAB 30 mg [redacted], [redacted] mg [redacted], [redacted] Cohort 2	37 enrolled 36 completed	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
				Treatment A = CAB 30 mg [redacted] reference Treatment D = CAB 30 mg [redacted] mg [redacted] Treatment E = CAB 30 mg [redacted] mg [redacted]		
LAI116585	To evaluate the relative bioavailability of 2 new CAB 30 mg free acid capsule formulations compared with a tablet of the current sodium salt formulation in the fasted state	Randomized, open-label, balanced, 3-way crossover study	Healthy adults	CAB 30 mg free acid in capsule (2 different formulations) CAB 30 mg tablet sodium salt formulation	18 enrolled 18 completed	Completed CPSR
Pharmacokinetic Studies Using Human Biomaterials						
205712	To compare steady state of CAB 30 mg oral dose once daily with or without rifabutin 300 mg once daily	Phase 1, open label, fixed-sequence, 2-period, crossover study	Healthy Subjects	Period 1: CAB 30 mg once daily for 14 days Period 2: CAB 30 mg once daily + Rifabutin 300 mg once daily for 14 days	15 Enrolled 12 Completed	Completed CPSR
LAI116181	To assess the potential for a drug interaction between CAB and rilpivirine	Open-label, repeat-dose, single sequence, 3-period study	Healthy subjects	CAB 30 mg QD for 12 days; oral tablet RPV 25 mg QD for 12 days; oral tablet CAB 30 mg QD + RPV 25 mg QD for 12 days	Cohort 1: 16 enrolled 16 completed Cohort 2: 12 enrolled 11 completed	Completed CPSR
LAI117010	To evaluate the effect of rifampin on the PK of oral CAB	Phase I, single-center, open label, fixed-sequence cross-over study	Healthy subjects	Treatment A - Single dose CAB 30 mg oral tablet (Day 1) Treatment B - RIF 600 mg oral tablet QD for 13 days (Days 8-20)	15 enrolled 15 completed	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
				Treatment C - Single dose CAB 30 mg on Day 21 + RIF 600 mg QD for 8 days (Days 21-28)		
LAI117011	To evaluate the effect of CAB 30 mg on the PK of an oral contraceptive containing levonorgestrel and ethinyl estradiol	Open label, fixed sequence crossover study	Healthy adult female subjects	EE/LNG for 10 days; oral tablet EE/LNG + CAB 30 mg QD for 11 days; oral tablet	20 enrolled 19 completed	Completed CPSR
ITZ111839	To assess the potential for a drug interaction between CAB and etravirine	Open-label, repeat dose, 2-period, single-sequence study	Healthy subjects	CAB 30 mg QD for 10 days; oral tablet CAB 30 mg QD + ETV 200 mg q12h for 14 days; oral tablet	12 enrolled 12 completed	Completed CPSR
Pharmacokinetic Studies						
201479	To compare plasma PK parameters of CAB in subjects with hepatic impairment to healthy controls matched in gender, age, and BMI	Phase 1, open-label, parallel group, 2-part, single-dose adaptive study	Adults with moderate and mild hepatic impairment and matched healthy control subjects with normal hepatic function	CAB 30 mg single dose oral tablet	16 enrolled 16 completed	Completed CPSR
201480	To compare plasma PK parameters and safety of CAB in subjects with severe renal impairment with that in healthy matched control subjects	Phase I, open-label, multiple center, single dose, parallel-group study	Human subjects with severely impaired renal function who do not require renal replacement therapy compared with matched healthy	CAB 30 mg single dose oral tablet	16 enrolled 16 completed	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
			subjects with normal renal function			
ITZ111451	Part 1: To assess safety, tolerability and PK of oral single doses Part 2: To assess safety, tolerability and PK of oral repeat doses Part 3: To evaluate safety, tolerability, and antiviral activity of oral CAB in HIV-infected subjects	Part 1: Single dose escalation Part 2: Repeat dose escalation for 10 days Part 3: Placebo-controlled, monotherapy for 10 days followed by 3-drug ART	Part 1: Healthy subjects Part 2: Healthy subjects Part 3: HIV-infected subjects	Part 1: CAB 5, 10, 25, 50 mg, placebo, oral suspension; single-dose, fasted Part 2: CAB 5, 10, 25 mg, placebo, oral suspension; QD x 14 days, fasted Part 3: CAB 30 mg or placebo, QD x 10 days, fasted	Part 1: 18 enrolled 17 completed Part 2: 30 enrolled 30 completed Part 3: 11 enrolled 10 completed	Completed CPSR
LAI114433	To assess safety, tolerability, and PK of a single dose of injectable CAB	Placebo-controlled, single dose escalation	Healthy subjects	CAB 100 mg IM CAB 100 mg SC CAB 200 mg IM CAB 200 mg SC CAB 400 mg IM CAB 400 mg SC CAB 800 mg IM	72 enrolled 58 completed	Completed CPSR
LAI117008	To determine the total recovery and relative excretion of total radioactivity in urine and feces after a single, oral solution dose of [^{14}C]-CAB and to describe the PK of plasma CAB following a supratherapeutic oral dose of CAB	Open-label, single-dose, mass balance study Open-label, placebo-controlled, randomized, single-dose study	Healthy adult subjects	Part A: Treatment A: [^{14}C]CAB 30 mg oral solution Part B: Treatment B: CAB 150 mg (5 x 30-mg tablets) Placebo	Part A: 6 enrolled 6 completed Part B: 10 enrolled 10 completed Total: 16 enrolled 16 completed	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
LAI115428	To investigate the safety, tolerability, and PK of CAB LA following each IM or SC dose and to investigate the safety, tolerability, and PK of RPV LA IM doses when given in combination with CAB LA IM doses	Phase 1, randomized, open-label, repeat-dose, parallel study	Healthy subjects	Lead-in (all cohorts): CAB 30 mg; oral tablet for 21 days Cohort 1: CAB 800 mg IM, then 200 mg SC q month x 3 doses Cohort 2: CAB 800 mg IM, then 200 mg IM q month x 3 doses; RPV 1200 mg IM (month 3) and 900 mg IM (month 4) Cohort 3: CAB 800 mg IM, then 400 mg IM q month x 3 doses; RPV 1200 mg IM (month 3) and 600 mg IM (month 4) Cohort 4: CAB 800 IM q 3 months x 2 doses	47 enrolled; 40 completed for oral 40 enrolled; 37 completed for injection 31 entered; 30 completed for long term safety	Completed CPSR
205696	To evaluate the effect of a high fat/high calorie meal on the PK of CAB	Single center, randomized, open-label, 2-way crossover study	Healthy subjects	Treatment A: CAB 30 mg tablet, fasted Treatment B: CAB 30 mg tablet, fed	24 enrolled 22 completed	Completed CPSR
201120 (ECLAIR)	To evaluate the safety, tolerability and acceptability of long acting injections of the HIV integrase inhibitor, CAB, in HIV uninfected men	Phase IIa, randomized, double-blind, placebo-controlled study	Healthy subjects at low risk of acquiring HIV	Arm 1: Daily oral CAB (30 mg tablets) for 4 weeks, followed by a 1-week washout period, followed by intra-muscular (IM) injections of 800 mg of CAB LA at 3 time points at 12 week intervals at Week 5, Week 17, and Week 29. Arm 2: Daily oral matching placebo and IM saline placebo injections on the same schedule as Arm 1.	127 enrolled; Enrolled in a 5:1 ratio of CAB treatment and placebo 104 completed (84 on CAB treatment and 20 on placebo)	Week 41 Completed Full CSR Week 81 Completed Abbreviated CSR
ITZ112929	To evaluate the safety, tolerabilitiy, and ART activity	Phase IIa, double-blind, randomized,	HIV-infected adult subjects	CAB 5 mg or placebo QD x 10 days	9 enrolled 9 completed	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	of oral CAB in HIV-infected subjects without prior HIV integrase inhibitor therapy	placebo-controlled study, monotherapy for 10 days followed by 3-drug ART				
2015N258625_00	To evaluate CAB as a perpetrator of DDIs of substrates (co-medications) cleared via UGT1A3, UGT1A9, OAT1, OAT3, MATE1, or MATE2-K	In vitro data were incorporated into mechanistic models to further investigate the drug-drug interaction potential of cabotegravir and determine the need to conduct a clinical drug-drug interaction study upon co-administration in clinical development. The test system for this analysis was limited to calculations using a static (static with respect to each probe substrate (where possible) mathematical model for the prediction of increases in AUC of UGT1A3, UGT1A9, OAT1, OAT3, MATE1 or MATE2-K substrates in the presence of CAB.	This analysis used appropriate exposure values such as Cmax obtained from the literature, including LAI115428 (healthy subjects).	CAB Cmax (20.48 uM) was obtained from the literature [Spreen, 2014] to assess the impact of CAB as an inhibitor on various enzymes and transporters.	N/A	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
2018N389974_01	To assess CAB drug-drug interaction potential using Simcyp v17.1 PBPK software. The PBPK model was used to evaluate the clinical relevance of the OAT1 and/or OAT3 inhibition potential of CAB to predict any change in exposure of OAT1/3 substrates. The PBPK model was further evaluated to assess the DDI potential of CAB as a victim drug when dosed with UGT1A1/ UGT1A9 inhibitors or inducers.	The developed model for CAB was verified by comparing the simulated PK profiles of the PBPK model against single and multiple oral dosing clinical PK studies in healthy volunteers, healthy adults with UGT1A1 poor metabolizer phenotype, and severe renally impaired patients.	Healthy subjects	Oral CAB 30mg single dose or repeat dose once daily	Data from multiple studies incorporated into model	Completed CPSR
CAB Population PK Report (2018N384611_01)	To further characterize CAB PK based on data from healthy subjects and HIV-1 infected patients following administration as oral tablet and LA injection	Population PK analysis was performed in the following sequence of steps: (1) exploratory data analysis, (2) base model development, (3) covariate analysis, (4) model refinement, (5) model evaluation, and (6) evaluation of clinical relevance of covariates. Studies Analyzed:	Healthy and HIV-1 infected subjects	LAI116585, LAI117010, LAI117020, 201741, 201479, 201480, 205696: CAB 30 mg (sodium salt tablets) PO single dose LAI117011: 30 mg (sodium salt tablets) PO QD × 11 days LAI116482: 10 mg tablet PO QD × 24 weeks; 30 mg tablet PO QD × 24 weeks; 60 mg (2 × 30mg) PO QD × 24 weeks LAI115428: 30 mg PO QD x 14 days LAI116815: Oral: 30mg PO QD, at SS LA: 400mg IM single dose (200 nm particle size only) 200056: Oral lead-in/induction 30 mg PO QD × 20 weeks, then switch to 1) 800mg IM × 1, then 400mg IM Q4W; or	1650 total subjects 458 Healthy subjects 1192 HIV-infected patients	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
		LAI116585; LAI117010; LAI117011; LAI117020; 201741; 201479; 201480; 205696; LAI116482 (LATTE); LAI115428; LAI116815; 200056 (LATTE2); 201120 (ECLAIR); 201103 (HPTN077); 201584 (FLAIR); 201585 (ATLAS)		2) 800mg IM × 1, then 600mg IM at Week 4, then 600mg IM Q8W starting at Week 8 201103: Oral lead-in 30 mg QD × 4 weeks, 1-week washout, then Arm 1: 800 mg IM Q12W × 3 Arm 2: 600 mg IM at Week 5, Week 9, and then Q8W × 3 201120: Oral lead-in 30mg QD × 4 weeks, 1-week washout, then 800 mg IM Q12W × 3 201584: Following a 20-week induction period, oral lead-in 30 mg PO QD × 4 weeks, switch to 600 mg IM × 1, then 400 mg IM Q4W 201585: Oral lead-in 30 mg PO QD × 4 weeks, switch to 600 mg IM × 1, then 400 mg IM Q4W		
Human Pharmacodynamic Studies						
LAI117009	To evaluate the effect of repeat oral doses of CAB 150 mg on cardiac conduction as assessed by baseline-adjusted, maximum time-matched QTcF effect compared with placebo and a single oral dose of moxifloxacin	Randomized, partial blind, repeat-dose, 3-period, balanced crossover study	Healthy subjects	Treatment A: 3 doses of CAB 150 mg (5 x 30 mg tablets) q 12 hours Treatment B: 3 doses of CAB placebo (5 tablets) q 12 hours Treatment C: A single dose of moxifloxacin 400 mg (one 400 mg tablet)	42 enrolled 36 completed	Completed CPSR
LAI116482 (LATTE) **Global Study**	Primary: • Dose selection of CAB for further evaluation of CAB + RPV Secondary: • To evaluate the safety,	Phase IIb, randomized, partially blind, dose ranging with an active control	HIV positive, antiretroviral naive	Treatment A – CAB 10 mg + NRTIs Treatment B – CAB 30 mg + NRTIs Treatment C – CAB 60 mg + NRTIs Treatment D – EFV + NRTIs Post Week 24, Treatments A, B and C discontinue NRTIs and initiate RPV	Total – 244 enrolled Treatment A – 60 Treatment B – 60 Treatment C –	Ongoing Week 24 Completed Full CSR Week 48

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	efficacy and tolerability of 10, 30, and 60 mg of CAB once daily both in combination with 2 NRTIs and as part of a 2-drug combination maintenance ART regimen with RPV, relative to EFV. • To evaluate the effect of 10, 30, and 60 mg of CAB on selected virologic and immunologic markers of HIV infection over 96 weeks.			Post Week 96, Treatment D completed the study and Treatments A, B and C continued on open-label 30 mg CAB+RPV	62 (61 treated) Treatment D – 62	Completed Full CSR Week 96 Completed Full CSR (CDISC) Week 144 Completed Synoptic CSR (legacy format) End of Study Completed Full CSR
200056 (LATTE-2) **Global Study**	• To evaluate CAB LA + RPV LA for the maintenance of virologic suppression following an induction of virologic suppression on an oral regimen of CAB plus abacavir/ lamivudine in HIV-1 infected, antiretroviral therapy-naïve adult subjects;	Phase IIb, Randomized, Parallel Group, Open Label	HIV-1 infected, antiretroviral therapy-naïve adult subjects	Induction Period (20 weeks): Oral CAB + abacavir/lamivudine (ABC/3TC) (or alternative NRTI backbone if HLA-B*5701 positive) Maintenance Period (2:2:1 randomization) (at least 96 weeks): IM CAB LA + RPV LA every 4 weeks, IM CAB LA + RPV LA every 8 weeks; Oral CAB + abacavir/lamivudine (ABC/3TC) (or alternative NRTI backbone if HLA-B*5701 positive) Extension Period: Subjects randomized to an IM dosing regimen in the Maintenance Period, remained on that regimen (either every 4 or	Induction Period: Oral CAB 30 mg - enrolled 310, 309 dosed; 292 completed Maintenance Period: 292 randomized into Maintenance 215 subjects included in the	Ongoing Week 32 Completed Full CSR Week 48 Completed Full CSR Week 96 Completed Full CSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	• To evaluate the impact of UGT1A1 genotypes on CAB PK in subjects who received both oral CAB and CAB LA. • An assessment of the PK of CAB and RPV in plasma and CSF			every 8 weeks until commercially available or program termination) Oral CAB subjects who successfully completed 96 weeks of oral therapy in the Maintenance Period were given the option to elect an optimized IM dosing regimen (either every 4 or every 8 weeks until commercially available or program termination): Optimized Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks during Extension. Loading dose injections with IM CAB LA 600 mg + RPV LA 900 mg begin at Week 100, followed by IM maintenance doses of CAB LA 400 mg + RPV LA 600 mg at Week 104 and continuing every 4 weeks thereafter. Optimized Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks during Extension. Loading dose injections with IM CAB LA 600 mg + RPV LA 900 mg begin at Week 100, followed by IM maintenance doses of CAB LA 600 mg + RPV LA 900 mg at Week 104 and continuing every 8 weeks thereafter. Amendment 06: US-specific. Addition of CSF substudy (15 Oct 2018)	retrospective exploratory evaluation of UGT1A1 genotypes CSF PK sub-study: 18 enrolled 18 completed;	Week 128 Completed Synoptic CSR Week 160 Completed Abbreviated CSR (CDISC) CSF Substudy Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
201584 (FLAIR) (2017N345267_00) **Global Study**	To evaluate the efficacy, safety, and tolerability of CAB LA + RPV LA for maintenance of virologic suppression following switch from an integrase inhibitor single tablet regimen	Phase III, randomized multicenter, parallel-group, open-label, non-inferiority study	HIV-1 infected antiretroviral therapy naive adult subjects	Induction Phase: Oral ABC/DTG/3TC FDC once daily for 20 weeks; subjects who were HLA-B*5701 positive received DTG + 2 NRTIs once daily Maintenance Phase: Arm 1: Switch to oral CAB 30 mg + RPV 25 mg once daily for 4 weeks, then IM CAB LA 600 mg + RPV LA 900 mg at Week 4, followed by IM CAB LA 400 mg + RPV LA 600 mg at Week 8 and then every 4 weeks thereafter for at least 96 weeks Arm 2: Continue oral ABC/DTG/3TC FDC once daily (or alternative DTG + 2 NRTIs) for at least 100 weeks Extension Period: Arm 1: Continue receiving CAB LA + RPV LA until they no longer derive clinical benefit, the treatment is no longer commercially available, or program termination Arm 2: Option to switch to CAB LA + RPV LA (with or without 4-week lead-in of oral CAB 30 mg + RPV 25 mg once daily) at Week 100. Loading dose injections with IM CAB LA 600 mg + RPV LA 900 mg begin at Week 100 (no oral lead-in) or Week 104, followed by IM maintenance doses of CAB LA 400 mg + RPV LA 600 mg at Week 104 (no oral lead-in) or	Induction Phase: 631 enrolled 629 treated Maintenance Phase: 566 randomized	Ongoing Week 48 Completed Full CSR (CDISC) Week 96 Completed Full CSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
				Week 108 and continuing every 4 weeks thereafter.		
201585 (ATLAS) (2018N370336_00) **Global Study**	To evaluate the efficacy, safety, and tolerability of switching to CAB LA + RPV LA from current INI- NNRTI-, or PI-based antiretroviral regimen	Phase III, randomized, multicenter, parallel-group, non-inferiority, open-label study	HIV-1-infected adults who are virologically suppressed	Maintenance Phase: Arm 1: Switch to daily oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks followed by Intramuscular (IM) CAB LA + RPV LA every 4 weeks (Q4W) for 48 weeks; Arm 2: Continue current ART regimen for at least 52 weeks. Following the Week 52 visit, eligible subjects were given the option to transition to study 207966 (comparing CAB + RPV Q4W to CAB + RPV Q8W) or to continue within the study 201585 Extension Phase. Extension Phase: Arm 1: continue IM dosing regimen (Q4W) through at least Week 96; Arm 2: option to complete study or switch to oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks followed by CAB LA + RPV LA Q4W through at least week 96. Participants can continue CAB LA + RPV LA Q4W until meeting protocol defined stopping criteria, products approved and commercially available or program termination)	Arm 1: 310 randomized Arm 2: 308 randomized	Week 48 Completed Full CSR (CDISC) Week 96 Completed Synoptic CSR
Efficacy and Safety Studies: Formal Integrated Analyses, Meta-analyses, Bridging analyses						
205162 Report No. 2016N297524	Meta-Analysis To evaluate the relationships between	Retrospective, non-interventional PGx analysis of data derived from 4	Phase I – Healthy subjects	PK PGx analysis: Oral CAB 30mg once daily for at least 8 days Tolerability analysis:	Total analyzed: 1364	Completed CPSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	UGT1A1 and UGT1A9 genotypes on oral CAB PK and tolerability	Phase I and 2 Phase II studies with subjects who received oral CAB 30 mg once daily for at least 8 days. The tolerability assessment data (ALT and total bilirubin change from Baseline) were derived from study LAI116482 with subjects who received oral CAB. Phase I studies: ITZ11839 LAI116181 LAI115428 LAI116815 Phase II studies: LAI116482 200056	Phase II - HIV positive, antiretroviral naive	Treatment received in LAI116482: Treatment A – CAB 10mg + NRTIs/ RPV Treatment B – CAB 30mg + NRTIs/ RPV Treatment C – CAB 60mg + NRTIs/ RPV		
Efficacy and Safety Studies: Other Clinical Study Reports						
207966 (ATLAS-2M) GSK Document No. 2019N406358_01 **Global Study**	To evaluate the efficacy, safety, and tolerability of CAB LA + RPV LA administered every 8 weeks or every 4 weeks	Phase IIIb, randomized, multicenter, parallel-group, non-inferiority, open-label study	HIV-1-infected adults who are virologically suppressed	Maintenance Phase: Arm 1- CAB LA + RPV LA every 4 weeks (Q4W): Cohort 1: Switch from oral standard of care to daily oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks followed by Intramuscular (IM) CAB LA 600 mg + RPV LA 900 mg at Week 4 and IM CAB LA 400 mg + RPV LA 600 mg	1049 Subjects randomized 1:1 in Q4W: Q8W	Ongoing Week 48 Completed Full CSR

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
				Q4W thereafter. Cohort 2: Continue with CAB LA 400 mg + RPV LA 600 mg Q4W after transition from the ATLAS study. Arm 2 CAB LA + RPV LA every 8 weeks (Q8W): Cohort 1: Switch from oral standard of care to daily oral CAB (30 mg) tablets + RPV (25 mg) tablets for 4 weeks followed by IM CAB LA 600 mg + RPV LA 900 mg at Week 4, Week 8, and Q8W thereafter. Cohort 2: Initiate IM CAB LA 600 mg + RPV LA 900 mg Q8W after transition from CAB LA 400 mg + RPV LA 600 mg Q4W in the ATLAS study. Extension Phase: Following Week 96, continue randomized IM dosing regimen (Q4W or Q8W) until participant no longer derives clinical benefit, meets protocol defined stopping criteria, products approved and commercially available, or program termination		
205741	Physician's Guidance Document for use of CAB with Named/Compassionate Patient Use in HIV	Phase III, ongoing, open-label program conducted in HIV-1 infected, ART-experienced adult subjects ≥18 years of age, with a demonstrated need for a long acting, injectable antiretroviral therapy including, but not limited to malabsorption or	Compassionate use in HIV-1-infected, antiretroviral-experienced adults	CAB 30mg QD oral determined on case-by-case basis; CAB LA 600 mg initial dose; CAB LA 400 mg maintenance doses (Q4W).	As of 17 April 2020, a total of 176 requests were submitted globally by the treating physicians under the ViiV/GSK NPP requesting compassionate use of CAB. Of the 176	Ongoing

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
		inability to achieve adequate drug levels via oral route.			submitted requests, 70 were approved, 106 were declined. The following countries have patients approved for compassionate use of CAB: Australia (1); Canada (2); Belgium (2); France (15); Italy (3); Portugal (1); Netherlands (2); South Korea (1); Spain (2); Switzerland (3); United Kingdom (21); and US (17). Of these 70 subjects, 47 are currently receiving CAB and 7 are pending CAB delivery. There were 3 deaths (2 deaths	

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
					occurred while the patient was receiving compassionate use and 1 death occurred after approval but before IP was received) and 13 additional cases that were subsequently withdrawn by physician or patient post approval involving 2 virologic failures, 3 subjects where clinical improvement obviated the continue need for LA dosing, 1 patient suffered traumatic brain injection prior to receiving the first dose of CU medication, 1 withdrew due to	

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
					exacerbation of pre-existing psychiatric disorder, 3 subjects declined participation in program after approval and 3 subjects were withdrawn for unknown reasons post approval.	
201767	To assess the PK of CAB LA in the blood plasma and anatomic locations associated with sexual HIV-1 transmission: VT, CT, CVF, RT, and RF	Phase 1, open label, multicompartment PK study	Healthy subjects	CAB oral 30 mg daily for 4 weeks; 14-42-day washout period followed by single 600 mg IM dose of CAB LA	19 enrolled 13 completed	Ongoing
201378 (HPTN 083) **Global Study**	Primary: ..To compare HIV incidence among participants randomized to oral CAB/CAB LA (oral lead in and injections) vs. oral TDF/FTC (Steps 1 and 2) To compare the safety of oral CAB/CAB LA vs. oral TDF/FTC. Secondary: .To compare HIV incidence	Phase IIb/III, randomized, multicenter, double-blind, double dummy, non-inferiority study	MSM or transgendered women who are HIV-uninfected and at risk for HIV acquisition, ≥18 years of age	**Step 1:** Arm A – **Daily oral CAB** (30 mg tablets) and oral TDF/FTC placebo for 5 weeks Arm B – **Daily oral TDF/FTC** (300 mg/200 mg fixed-dose combination tablets) and oral CAB placebo for 5 weeks **Step 2**: Arm A – **CAB LA** (600 mg as a single	N=5000 2500 for each Arm	Ongoing

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	among participants receiving CAB LA injections vs. oral TDF/FTC (each step independently and all steps in aggregate) To compare HIV incidence among participants receiving CAB LA injections vs. oral TDF/FTC (Steps 1, 2, and 3 combined) To compare HIV incidence among participants randomized to CAB LA injections vs. oral TDF/FTC while taking open label TDF/FTC (Step 3 only, descriptive) To compare the change in risk of HIV acquisition between CAB and oral TDF/FTC strategies (Arm A and Arm B) as participants progress from Step 2 to Step 3 To compare HIV incidence among the subgroups of participants receiving oral CAB/CAB LA vs. oral TDF/FTC by region, age, race, ethnicity, baseline risk, and gender identity To compare changes in			intramuscular [IM] injection at 2 time points 4 weeks apart and every 8 weeks thereafter) and daily oral TDF/FTC placebo. Arm B – **Daily oral TDF/FTC** (300/200 mg fixed-dose combination tablets) and IM placebo at 2 time points 4 weeks apart and every 8 weeks thereafter (matching vehicle, identical volume as active injectable product in Arm A). This step will continue until the required number of endpoints is reached. **Step 3:** Both arms: **Open-label daily oral TDF/FTC** no later than 8 weeks after the last injection (in order to cover the PK tail for Arm A participants), for up to 48 weeks. Participants will then transition to locally-available HIV prevention services, including services for pre-exposure prophylaxis, if available.		

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	renal function, liver function, and bone mineral density among participants receiving oral CAB/CAB LA vs. oral TDF/FTC To evaluate and compare rates of HIV drug resistance among participants who acquire HIV infection during the study among participants receiving oral CAB/CAB LA vs oral TDF/FTC To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.					
201739 (HPTN 084) **Global Study**	Primary: • To evaluate the relative efficacy and safety of oral CAB/CAB LA (oral run-in and injections, Steps 1 and 2) vs. daily oral TDF/FTC for HIV prevention (Steps 1 and 2). Secondary: • To compare HIV incidence among	Phase IIb/III, randomized, multicenter, open-label, superiority study	African women at risk of HIV acquisition ages 18-45	**Step 1, Oral Run-in Phase: Arm A – Daily oral cabotegravir (CAB) 30mg** for 5 weeks plus an HIV prevention package. **Arm B – Daily TDF/FTC** for 5 weeks plus an HIV prevention package. **Step 2, Injection Phase**: **Arm A – CAB LA** (a single 600mg IM injection at 2 time points 4 weeks apart and every 8 weeks thereafter) plus an HIV prevention package. **Arm B – Daily TDF/FTC** plus an HIV prevention package. Step 2 will continue until the required number of endpoints (125) is reached, estimated to be 81 weeks after enrolling the last participant. **Step 3, Follow-up Phase**:	N=3200 1600 for each Arm	Ongoing

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	participants receiving oral CAB/CAB LA vs. daily oral TDF/FTC (Steps 1, 2 and 3). • To evaluate relative efficacy of oral CAB/CAB LA vs. oral TDF/FTC in subgroups defined by the baseline factors of: age, herpes simplex virus-2 (HSV-2) serostatus, contraceptive method, and BMI. • To describe and model the relationship between HIV incidence and drug concentration, within each arm. • To describe the distribution and correlates of drug concentration, within each arm. • To compare the acceptability of and preferences for CAB LA vs. oral TDF/FTC.			**Regimen Arm A – Daily TDF/FTC** will be provided no later than 8 weeks after the last injection, for up to 48 weeks plus an HIV prevention package. Arm A participants will then transition to locally available HIV prevention services, including services for pre-exposure prophylaxis, if available. **Arm B – Daily TDF/FTC** will be offered plus an HIV prevention package. Participants may choose to discontinue oral TDF/FTC at this stage. Arm B participants then will transition to locally-available HIV prevention services, including services for pre-exposure prophylaxis, if available.		

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
201103 (HPTN 077) **Global Study**	To evaluate the safety, tolerability and pharmacokinetics of the investigational injectable HIV integrase inhibitor, CAB, in HIV-uninfected men and women	Phase IIa, multi-site, double-blind, 2-arm, randomized, placebo-controlled trial of the safety, tolerability, and acceptability of CAB LA	HIV-uninfected men and women at low to minimal risk for acquiring HIV infection, ages 18 to 65	Participants will be randomized to receive daily oral CAB (30 mg tablets) or daily oral placebo for 4 weeks, followed by a 1-week washout, to assess safety and tolerability before they receive injections. After safety and tolerability assessments from the oral phase have been completed (if no concerns are identified), participants will enter the injection phase of the study and will receive 2 intra-muscular (IM) gluteal injections of CAB LA (800 mg, administered as 2 400-mg injections) or placebo (matching vehicle control) at 3 study visits performed at 12-week intervals. A second cohort was added to explore an every 8-week dose (1 x 3 ml gluteal injection) with injections at Wk 0, Wk 4, and every 8 weeks thereafter for a total of 5 injections.	Enrolled: 199	Ongoing
209035 (POLAR)	Primary: • To demonstrate the antiviral activity of CAB LA + RPV LA every 2 months in virally-suppressed HIV-1 infected antiretroviral therapy ART-experienced participants.	Phase IIb, open-label, multicenter rollover study designed to assess the antiviral activity and safety of CAB LA + RPV LA administered every 2 months in approximately 100 adult HIV-1 infected participants from the Long Acting anTiretroviral	HIV-infected adult subjects	Participants choose to receive CAB LA (600 mg) + RPV LA (900 mg) at 2 timepoints 4 weeks apart and then every 2 months (Q2M) or the oral DTG (50 mg) + RPV (25 mg) once daily regimen for at least 12 months	N=98 (n=91, Q2M; n=7, oral DTG + RPV)	Ongoing

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	Secondary: • To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 2 months and oral DTG +RPV once daily. • To demonstrate the safety and tolerability of CAB LA + RPV LA every 2 months and oral DTG +RPV once daily. • To assess viral resistance in participants experiencing protocol-defined confirmed virologic failure • To characterize CAB and RPV concentrations and population pharmacokinetics	Treatment Enabling Study (LATTE) receiving oral CAB 30 mg + RPV 25mg once daily.				

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	and identify important determinants of variability • To assess participant reported health-related quality of life, injection tolerability/acceptability, and treatment satisfaction.					
206898	Primary: • To evaluate the safety and tolerability of the injectable agent, CAB LA injectable (600 mg dose administered every 4 weeks for 2 doses followed by every 8 weeks for 3 doses) through Week 5 to 41 in HIV-1 uninfected Chinese men. • To evaluate the plasma pharmacokinetics of	Phase 1, open-label, multi-site study to evaluate the PK, safety, tolerability, and acceptability of CAB LA in adult HIV uninfected Chinese male participants at low risk for HIV acquisition	Healthy male adult subjects	Daily oral CAB (30 mg tablets) for 4 weeks. Following confirmation of oral CAB safety and tolerability at the Week 4 visit, participants entered the injection phase and received CAB LA 600 mg (3 mL) IM injections at the following time points: Week 5, Week 9, Week 17, Week 25 and Week 33.	Planned number of subjects: Approximately 48 participants planned to enter the oral phase and approximately 40 participants planned to enter the injection phase of the study. Number of subjects enrolled: 48 subjects	Ongoing

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	CAB following repeat oral administration (Day 1 to Week 4) and CAB LA IM injections throughout the Injection Phase (Weeks 5 to 41). Secondary: • To evaluate the plasma pharmacokinetics of CAB LA trough during the Injection and Long-term Follow-up Phases (Week 5 to 89) • To evaluate the safety and tolerability of oral CAB in HIV uninfected Chinese men during the oral lead-in Phase (Day 1 to Week 4) • To evaluate the acceptability of CAB LA injections through 41 weeks. • To explore concentration-effect relationships for various safety and tolerability parameters if relevant.				have been enrolled and exposed to ≥1 dose of CAB oral and/or LA.	

2.7.6 Synopses of Individual Studies

<table>
<tr><th>Study Identifier (Identifier of Study Report)</th><th>Study Objective(s)</th><th>Study Design</th><th>Healthy Subjects or Diagnosis of Patients</th><th>Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)</th><th>Total No. of Subjects by Group Entered/ Completed</th><th>Study Reporting Status (Type of Report)</th></tr>
<tr>
<td>208580 (MOCHA)</td>
<td>Primary:
<u>Cohort 1 (continuing a background cART regimen):</u>
• To confirm the doses for oral CAB followed by injectable CAB LA in HIV-infected, virologically suppressed adolescents by evaluating:
  • Safety and multiple dose PK of oral CAB through Week 4;
  • Safety and multiple dose PK of CAB LA through Week 16.
• To confirm doses for injectable RPV LA in HIV-infected, virologically suppressed adolescents by evaluating safety and multiple dose PK of RPV LA through Week 16.
<u>Cohort 2 (discontinuing a background cART regimen):</u>
• To assess the safety of CAB LA + RPV LA through Week 24 in</td>
<td>Phase I/II, multi-center, open-label, non-comparative study to confirm the dose and evaluate the safety, tolerability, acceptability, and PK of oral CAB, long-acting injectable CAB (CAB LA), and long-acting injectable RPV (RPV LA)</td>
<td>Virologically suppressed HIV-1 infected children and adolescents aged 12 to <18 years</td>
<td>
<table>
<tr><th>Cohort</th><th>Step</th><th>Study Product Regimen and Administration</th></tr>
<tr><td rowspan="2">1C</td><td>1</td><td>CAB administered orally as one 30 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks, with or without food.</td></tr>
<tr><td>2</td><td>CAB LA administered as one IM injection in the gluteus medius at Week 4b (Step 2 Entry) study visit (600 mg/3 mL), at Week 8 (400 mg/2 mL), and at Week 12 (400 mg/2 mL).</td></tr>
<tr><td rowspan="2">1R</td><td>1</td><td>RPV administered orally as one 25 mg tablet once daily, beginning at the Entry visit, for 4-6 weeks, with a meal.</td></tr>
<tr><td>2</td><td>RPV LA administered as one IM injection in the gluteus medius at Week 4b (Step 2 Entry) study visit (900 mg/3 mL), at Week 8 (600 mg/2 mL), and at Week 12 (600 mg/2 mL).</td></tr>
<tr><td>2</td><td>3</td><td>CAB administered orally as one 30 mg tablet once daily AND RPV administered orally as one 25 mg tablet once daily, taken together and with a meal, beginning at the Entry visit for</td></tr>
</table>
</td>
<td>155 subjects planned; 23 subjects enrolled as of 27 April 2020</td>
<td>Ongoing</td>
</tr>
</table>

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	HIV-infected, virologically suppressed adolescents. Secondary: <u>Cohort 1</u> • To evaluate the tolerability and acceptability of CAB LA through Week 16 in HIV-infected, virologically suppressed adolescents. • To evaluate the tolerability and acceptability of RPV LA through Week 16 in HIV-infected, virologically suppressed adolescents. <u>Cohort 2</u> • To assess safety of oral CAB + oral RPV followed by CAB LA + RPV LA through Week 48 in HIV-infected, virologically suppressed adolescents. • To evaluate repeat-			<table><tr><td></td><td></td><td>4-6 weeks.</td></tr><tr><td></td><td>4</td><td>First injection: CAB LA administered as one 600 mg (3 mL) IM injection in the gluteus medius AND RPV LA administered as one 900 mg (3 mL) IM injection in the gluteus medius, at Week 4b (Step 4 Entry). Subsequent injections: CAB LA administered as a 400 mg (2 mL) IM injection in the gluteus medius muscle AND RPV LA administered as a 600 mg (2 mL) IM injection in the gluteus medius, every four weeks through Week 96.</td></tr></table>		

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	Study Objective(s)	Study Design	Healthy Subjects or Diagnosis of Patients	Treatment Details (Test Product(s); Dosage Regimen; Route; Duration)	Total No. of Subjects by Group Entered/ Completed	Study Reporting Status (Type of Report)
	dose pharmacokinetics of CAB LA + RPV LA through Week 24, and through Week 48 in HIV-infected, virologically suppressed adolescents. • To assess antiviral activity of CAB LA + RPV LA through Week 24, and through Week 48 in HIV-infected, virologically suppressed adolescents.					

3TC = Lamivudine
ABC = Abacavir
ART = Antiretroviral therapy
AUC = Area Under the Plasma Concentration-Time Curve
BMI = Body Mass Index
CAB = Cabotegravir
CPSR = Clinical Pharmacology Study Report
CSF = Cerebrospinal Fluid
CSR = Clinical Study Report
CT = Cervical Tissue
CVF = Cervicovaginal Fluid
DDI = Drug Drug Interaction
DTG = Dolutegravir
EE/LNG = Ethinyl estradiol/ levonorgestrol
EFV = Efavirenz
ETV = Etravirine
FDC = Fixed Dose Combination
FTC = Emitricitabine
HIV = Human Immunodeficiency Virus
HLA = Human Leukocyte Antigen
IM = Intramuscular
IND = Investigational New Drug Appliation
INI = Integrase Inhibitor
LA = Long Acting
[redacted] = [redacted]
MSM = Men Who Have Sex With Men
NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI = Nucleoside Reverse Transcriptase Inhibitor
OL = Open label
PGx = Pharmacogenetics
PI = Protease Inhibitor
PK = Pharmacokinetics
PO = Oral
Q4W = Once Every 4 weeks Dosing
Q8W = Once Every 8 weeks Dosing
QD = Once Daily
RF = Rectal Fluid
RIF = Rifampin
RPV = Rilpivirine
RT = Rectal Tissue
SC = Subcutaneous
TDF = Tenofovir Disoproxil Fumerate
UK = United Kingdom
US = United States
VT = Vaginal Tissue
Wk = Week

Individual Study Synopses for Clinical Studies

Synopsis for Study ITZ111682

Identifier: RM2008/00637/00 **Study Number:** ITZ111682

Title: A Single Dose, Randomized Study to Assess the Relative Bioavailability of Two Formulations and Food Effect on GSK1265744 in Healthy Male and Female Subjects

Investigators: The study was conducted at one site by two investigators: [redacted] MD, [redacted] PharmD

Study center: [redacted]

Publications: None at the time of this report.

Study period:

Initiation Date: 30 June 2008

Completion Date: 08 August 2008

Phase of development: I

Objectives:

Primary

- To evaluate the single-dose relative bioavailability of GSK1265744 10mg administered in either oral solution fasted, two 5mg tablets fasted, or two 5mg tablets following a moderate fat content meal.

Secondary

- To assess the safety and tolerability of GSK1265744 administered as single doses of oral tablets and oral solution.

Methodology: This was an open-label, single dose, randomized, single period, parallel study in healthy subjects to assess the relative bioavailability of GSK1265744 10mg administered as either oral solution, two 5mg tablets fed, or two 5mg tablets fasted. GSK1265744 concentrations following single dose administration of solution have been measurable for 14 days or more post dose because of the long t1/2 and the low lower limit of quantification (LLOQ) for the assay. Therefore, this study was parallel design instead of cross-over design requiring long washout periods between treatments.

Subjects were randomized to one of three treatments. Subjects in Treatment C were fed a moderate fat meal prior to dosing. GSK1265744 was administered in accordance with the following table:

Treatment	GSK1265744 Dose
A	GSK1265744 10mg oral solution
B	GSK1265744 two 5mg tablets, fasted
C	GSK1265744 two 5mg tablets, fed

The study consisted of a screening visit, one treatment period containing a single dose and serial plasma sample collections for 5 days, and a follow-up visit within 7 to 10 days following administration of investigational product. Screening procedures, used to determine eligibility, were performed within 30 days prior to receiving the first dose. Subjects participated in the study for up to 6 weeks.

Number of subjects: Forty-five subjects were planned to be enrolled with 15 subjects assigned to each of the three treatment groups.

Subject Disposition and Demographics:

Number of Subjects	**Treatment**			
	A	**B**	**C**	**Total**
Number of subjects planned, N:	15	15	15	45
Number of subjects entered, N:	15	15	15	45
Number of subjects included in Safety population, n (%):	15 (100%)	15 (100%)	15 (100%)	45 (100%)
Number of subjects included in PK population, n (%):	15 (100%)	15 (100%)	15 (100%)	45 (100%)
Number of subjects completed as planned, n (%):	15 (100%)	15 (100%)	15 (100%)	45 (100%)
Number of subjects withdrawn (any reason), n (%):	0	0	0	0
Demographics	**A**	**B**	**C**	**Total**
Age in Years, Median (min -max)	35.0 20 – 55	34.0 19 - 52	28.0 20 - 54	30.0 19 - 55
Sex, n (%)				
Female:	3 (20%)	1 (7%)	5 (33%)	9 (20%)
Male:	12 (80%)	14 (93%)	10 (67%)	36 (80%)
Body Mass Index (BMI), Median (min - max)	27.14 19.9-31.1	25.12 19.9-30.7	26.28 19.8-30.8	26.28 19.8-31.1
Height, Median (min - max)	175.0 158 - 185	175.0 163 - 196	180.0 163 - 188	175.0 158 - 196
Weight, Median (min -max)	78.50 60.8-103	86.60 57.6-94.8	79.80 64.0-102.1	78.50 57.6-103
Ethnicity, n (%)				
Hispanic or Latino:	3 (20%)	2 (13%)	2 (13%)	7 (16%)
Not Hispanic or Latino:	12 (80%)	13 (87%)	13 (87%)	38 (84%)
Race, n (%)				
African American/African Heritage	4 (27%)	2 (13%)	7 (47%)	13 (29%)
Asian – East Asian Heritage	0	0	1 (7%)	1 (2%)
Asian – South East Asian Heritage	1 (7%)	1 (7%)	0	2 (4%)
White – White/Caucasian/European Heritage	10 (67%)	10 (67%)	7 (47%)	27 (60%)
Mixed Race	0	2 (13%)	0	2 (4%)

Treatment A= 10 mg GSK1265744 Solution Fasted
Treatment B=Two 5 mg GSK1265744 Tablets Fasted
Treatment C=Two 5 mg GSK1265744 Tablets Fed

Diagnosis and main criteria for inclusion: Healthy men or women between 18 and 55 years of age, with a body weight ≥ 50 kg (110 lbs.) for men and ≥ 45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive).

Treatment administration: Subjects received the following treatments:

Treatment	Drug	Dose/Form/Route	Frequency/Duration	Batch Number
A	GSK1265744	10mg /solution /oral	Single dose	[redacted]
B	GSK1265744	Two 5mg / tablets/ oral (fasted)	Single dose	[redacted]
C	GSK1265744	Two 5mg / tablets/ oral (fed)	Single dose	[redacted]

Criteria for evaluation: The primary endpoints of the study included assessment of plasma GSK1265744 AUC(0-∞), AUC(0-t), C24 and Cmax.

The secondary endpoints of the study included plasma GSK1265744 t1/2, tlag, tmax, and CL/F, safety and tolerability parameters, including adverse events (AEs), concurrent medication, clinical laboratory screens, electrocardiograms (ECGs), and vital signs assessments.

Statistical methods: To estimate the relative bioavailability of two GSK1265744 formulations following the same single oral dose of 10mg of each formulation, and the effect of moderate fat meal on the single-dose pharmacokinetics of GSK1265744 oral investigational tablet, log-transformed values of PK parameters were analyzed by analysis of variance (ANOVA). This analysis considered treatment as fixed effect. The analysis was performed using the mixed linear models procedure within the SAS/STAT module of the SAS system. For each log-transformed PK parameter, point estimate and its associated 90% CI was constructed for the treatment differences between Treatments B-A and C-B and these differences and its 90% CIs were exponentiated to obtain the ratios of geometric least-squares (GLS) means and its 90% CIs.

2.7.6 Synopses of Individual Studies

Summary:

Safety: No serious adverse events, deaths, or withdrawals due to AEs were reported during this study. The most commonly reported AEs were headache (5 subjects) and nausea (2 subjects). All other AEs were reported by one subject each. More subjects receiving Treatment C reported AEs (5 subjects) compared to Treatments A (1 subject) and B (2 subjects). No severe AEs were reported. Two moderate AEs (abdominal pain and flatulence) were reported but were not considered related to investigational product by the investigator; all other AEs were mild in intensity.

All AEs	Treatment A N=15	Treatment B N=15	Treatment C N=15	Total N=45
Any AE, n (%)	1 (7%)	2 (13%)	5 (33%)	8 (18%)
Headache	1 (7%)	0	4 (27%)	5 (11%)
Nausea	1 (7%)	0	1 (7%)	2 (4%)
Catheter site infection	0	1 (7%)	0	1 (2%)
Arthropod bite	0	1 (7%)	0	1 (2%)
Eye injury	0	1 (7%)	0	1 (2%)
Abdominal pain	0	0	1 (7%)	1 (2%)
Flatulence	0	0	1 (7%)	1 (2%)
Vomiting	0	0	1 (7%)	1 (2%)
Back pain	0	0	1 (7%)	1 (2%)
Pruritus generalized	0	0	1 (7%)	1 (2%)

Treatment A= 10 mg GSK1265744 Solution Fasted
Treatment B=Two 5 mg GSK1265744 Tablets Fasted
Treatment C=Two 5 mg GSK1265744 Tablets Fed

No clinical laboratory values were reported as AEs. There were no Grade 3 or Grade 4 clinical laboratory abnormalities. One subject had Grade 2 total bilirubin at screening and on Day -1 during Treatment C. All other laboratory values were Grade 1 or less. No significant changes in vital signs or ECGs were reported during the study.

Pharmacokinetics: Selected PK parameters are summarized below.

Treatment	AUC(0-∞) (µg.h/mL)	AUC(0-t) (µg.h/mL)	Cmax (µg/mL)	Tmax[1] (h)	C24 (µg/mL)	t1/2 (h)	Tlag[1] (h)
A (n=15)	62.4 [55.7, 70.0] (21)	60.1 [53.9, 67.0] (20)	1.93 [1.76, 2.11] (16)	1.00 (0.50-2.00)	0.68 [0.62, 0.75] (18)	41.2 [38.1, 44.5] (14)	0.00 (0.00-0.00)
B (n=15)	44.7 [36.7, 54.5] (37)	42.8 [35.2, 52.0] (36)	1.13 [1.00, 1.28] (23)	2.50 (1.50-3.50)	0.51 [0.44, 0.60] (29)	38.5 [35.5, 41.9] (15)	0.00 (0.00-0.00)
C (n=15)	51.6 [46.4, 57.3] (19)	49.4 [44.8, 54.4] (18)	1.18 [1.10, 1.27] (13)	4.00 (2.50-6.00)	0.59 [0.53, 0.65] (19)	42.2 [38.8, 45.8] (15)	0.00 (0.00-0.50)

1. median (range)
Treatment A = GSK1265744 10mg oral solution, fasted
Treatment B = GSK1265744 two 5mg tablets, fasted
Treatment C = GSK1265744 two 5mg tablets, fed

Median GSK1265744 tmax was increased from 1h for solution to 2.5h for tablets administered without food, and median tmax was further prolonged to 4h following administration of tablets with a moderate fat meal. Median GSK1265744 terminal phase t1/2 was similar across treatments at 39-42h.

The results of the statistical comparison of GSK1265744 plasma PK parameters are presented in the table below.

Plasma GSK1265744 PK Parameter	**GLS Mean Ratio [90% CI]**	
	B/A (N=15/15)	C/B (N=15/15)
AUC(0-∞)	0.716 [0.610, 0.841]	1.15 [0.982, 1.36]
AUC(0-t)	0.712 [0.609, 0.831]	1.15 [0.988, 1.35]
Cmax	0.588 [0.528, 0.655]	1.04 [0.933, 1.16]
C24	0.745 [0.650, 0.853]	1.15 [1.01, 1.32]

Treatment A = GSK1265744 10mg oral solution, fasted
Treatment B = GSK1265744 two 5mg tablets, fasted
Treatment C = GSK1265744 two 5mg tablets, fed

The results of the comparison showed that the oral bioavailability of the tablet was less than the oral solution. Under fasted conditions, plasma GSK1265744 AUC(0-∞), Cmax, and C24 were lower by 28%, 41%, and 25%, respectively, following administration of the tablet compared to the solution formulation. GSK1265744 AUC(0-∞) and C24 were increased 15% and Cmax was unchanged following administration of the tablet formulation with food as compared to administration of tablets while fasting.

Conclusions:

- Tablet formulation under fasted conditions showed reduced rate and extent of absorption of GSK1265744 compared to the oral solution formulation. Plasma AUC(0-∞), Cmax, and C24 were on average 28%, 41%, and 25% lower following administration of tablets compared to solution, and median tmax was delayed from 1h following solution to 2.5h following tablets.
- The presence of food increased GSK1265744 AUC(0-∞) and C24 by 15% and had no effect on Cmax for the tablet formulation when compared to tablets administered in the fasted state.
- GSK1265744 was generally well tolerated in this study in healthy subjects. No serious adverse events, Grade 3/4 AEs, deaths, or withdrawals due to AEs were reported during this study. The most commonly reported AEs were headache and nausea. No significant clinical laboratory, vital signs, or ECG values were noted.

Date of Report: [redacted] 20[redacted]

Synopsis for Study LAI116815

Title: A Single-Center, Randomized, Open-Label, Study to Assess the Relative Bioavailability of New Formulations of GSK1265744 LAP in Healthy Adult Subjects

Investigator(s): [redacted], MD

Study Center(s): The study was conducted at one center at [redacted] United States [redacted]

Publication(s): None at the time of this report

Study Period: 14-JAN-2013 - 21-APR-2014

Phase of development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
To evaluate the relative bioavailability (RBA) of two new formulations of GSK1265744 400 mg long acting (LA) parenteral given intramuscularly (IM) compared to the current formulation ([redacted] nm [redacted])	Plasma GSK1265744 area under the concentration-time curve from time zero (pre-dose) to week 12 within a subject across all treatments (AUC[0-wk12]), concentration observed at week 12 (Cwk12) and maximum observed concentration (Cmax)

Objectives	Endpoints
Secondary	
To assess the safety, tolerability, and pharmacokinetics (PK) of oral GSK1265744 in healthy subjects. To assess the safety and tolerability of three formulations of GSK1265744 LA administered as a single 400mg dose IM To investigate the potential of GSK1265744 to inhibit or induce cytochrome P450 3A (CYP3A) enzymes using midazolam as a probe substrate following repeat dose oral administration of GSK1265744 To evaluate the RBA of the GSK1265744 400 mg LA ([redacted] nm [redacted]) in current formulation [redacted] ([redacted]) [redacted] with the historical data	Plasma GSK1265744 area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-∞]), area under the concentration-time curve from time zero (pre-dose) to week 4 within a subject across all treatments (AUC[0-wk4]), concentration observed at week 4 (Cwk4), area under the concentration-time curve from time zero (pre-dose) to week 8 within a subject across all treatments (AUC[0-wk8]), concentration observed at week 8 (Cwk8), terminal phase half-life (t½), time of occurrence of Cmax (tmax), and apparent clearance (CL/F) following the LA dosing. Plasma GSK1265744 AUC(0-wk12), AUC(0-wk4), Cwk12 and Cmax following LA administration of 400mg IM (unsplit) in Cohorts 3 and 8 of LAI114433 for historical control Route C material. Plasma GSK1265744 area under the concentration-time curve over the dosing interval (AUC[0-tau]), Cmax, t½, tmax, and CL/F following oral administration of GSK1265744 in the midazolam subgroup. Safety and tolerability parameters, including adverse events (AEs), concurrent medication, clinical laboratory screens, electrocardiogram (ECG), and vital signs assessments. Plasma AUC(0-∞), Cmax, area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments (AUC[0-t]), t1/2, lag time before observation of drug concentrations in sampled matrix (tlag), tmax, percentage of AUC(0-∞) obtained by extrapolation (%AUCex), and CL/F of midazolam following oral administration of midazolam alone and in combination with oral GSK1265744.

Methodology:

This was a single-center, randomized, open-label, 3 parallel treatment study in healthy adult subjects to assess the RBA of 2 new formulations of GSK1265744 (744) long

acting (LA) 400 mg IM compared to the current 744 LA 400 mg [redacted] formulation. The current formulation, Treatment A, was a [redacted] nm [redacted] formulation, Treatment B (test formulation) was prepared by [redacted] and had an approximate [redacted] μm, and Treatment C (test formulation) was prepared with a [redacted] and had a [redacted] μm. On Day -28, subjects started a 14-day oral lead-in period at a dose of 30 mg daily. The objective of the oral lead-in period was to minimize the chance of an unexpected drug hypersensitivity reaction occurring during 744 LA dosing. After a 14-day washout period, subjects were randomized to receive 1 of the 3 744 400mg intramuscular (IM) formulations. Subjects remained in the research unit for at least 4 hours after the dose of study drug for PK sampling and safety assessments. Subjects returned to the research unit for PK sampling and for study assessments as described in the Time and Events table.

A 3-cohort parallel treatment study design was chosen for this study due to the long half-life of 744 LA. Samples for determination of 744 concentrations were collected for 12 weeks post-injection which made a cross-over study design less viable. Subjects had safety laboratory assessments for 52 weeks post 744 LA IM injection.

During the oral lead-in period, a sub-study to examine the potential of 744 to inhibit or induce cytochrome P450 (CYP) 3A activity using midazolam as a probe was conducted (Group 1). Subjects received a single oral dose of 3 mg midazolam on the morning of Day -29, followed by 24 hours of serial PK collection. Subjects were then dosed with oral 744 30mg once daily (QD) for 14 days and returned to the research unit on Day -16. On Day -15, subjects were given a single dose of 30mg 744 followed by 24 hours of serial PK. On Day -14, subjects were co-administered midazolam + 744 followed by 24 hours of serial PK. All subjects underwent a 14-day washout period prior to IM dosing.

Diagnosis and Main Criteria for Inclusion:

Male or female healthy subjects aged between 18 and 65 years of age inclusive, with body mass index (BMI) within the range 18.5 to 31.0 kg/m^2 (inclusive) were included in this study.

Number of Subjects:

A total of 43 subjects were enrolled and received at least one dose of oral 744. Thirty-eight subjects entered the injection phase of the study with 37 completing the injection phase. Thirty-three subjects completed oral, injectable, and safety phases of the study.

Treatment Administration:

	Study Treatment				
Product name:	Oral GSK1265744	GSK1265744 injectable suspension Treatment A	GSK1265744 injectable suspension Treatment B	GSK1265744 injectable suspension Treatment C	midazolam
Formulation description:	GSK1265744B, lactose monohydrate, microcrystalline cellulose, hypromellose, sodium lauryl sulfate, croscarmellose sodium, magnesium stearate, Opadry film-coating, white OY-S-28876	Sterile Suspension for Injection			Each mL of syrup contains midazolam hcl equivalent to 2 mg midazolam compounded with artificial bitterness modifier, citric acid anhydrous, D&C Red #33, edetate disodium, glycerin, mixed fruit flavor, sodium benzoate, sodium citrate, sorbitol, and water; the pH is adjusted to 2.8 - 3.6 with hydrochloric acid
Dosage form:	Tablet	Injection			Syrup
Unit dose strength(s)/Dosage level(s):	30mg	400mg GSK1265744 Each vial contains 1.5 ml suspension of 200 mg/ml GSK1265744			3mg
Route/ Administration/ Duration:	Administer orally, once daily	Intramuscular Injection	Intramuscular Injection	Intramuscular Injection	Oral/single dose Administer by oral syringe.
Dosing instructions:	Taken orally, once a day in the morning with or without a meal.	Vortex suspension vial for 20 seconds to re-suspend sediments. Allow bubbles to subside, then use a syringe to withdraw the required volume of suspension for IM injection.			The syringe will be rinsed twice with 5mL to ensure the entire dose is administered + an additional 230mL of water. The total water amount should be 240mL with or without GSK1265744.
Physical description:	White to almost white oval tablet	White to slightly colored suspension	White to slightly colored suspension	White to slightly colored suspension	syrup
Manufacturer/ source of procurement:	GlaxoSmithKline				Commercially available
Method for individualizing dosage:	One 30mg tablet taken once a day.	Refer to the Study Reference Manual for Instructions for individualizing doses.			Clinical site to purchase commercial product
Batch Number	Lot No: [redacted] Batch No: N/A Input Batch No: [redacted]	[redacted]	[redacted]	[redacted]	NDC: 00054-3566-99 Lot No: [redacted]

Statistical Methods:

The sample size of 45 to obtain a minimum of 36 evaluable subjects was chosen based on subject variability of 744 to address the objectives of the study. Based on integrase GSK364735 first time in human study, within-subject variability CV% for midazolam AUC(0-∞) was 15%. With this assumption, 12 subjects provided more than 80% power to reject the two one-sided tests and conclude that 744 had no effect on midazolam AUC(0-∞) or AUC(0-t).

Unless stated otherwise, descriptive summaries included n, mean, standard deviation (SD), coefficient of variation (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-subject CV (%CVb) for continuous variables, whereas n and percent were used as summary statistics for categorical variables. Safety data was presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards. From the plasma concentration-time data, the following PK parameters were determined, as data permit: Cmax, tmax, AUC(0-t) and AUC(0-∞), and t½, also CL/F. Pharmacokinetic data was presented in graphical and/or tabular form and summarized descriptively. For each primary PK endpoint, point estimates and corresponding 90% CIs were constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

Summary

A total of 43 subjects were enrolled and dosed with at least one dose of oral 744. Of the 43 subjects, 38 subjects received an IM dose of 744 LA, and 33 (77%) completed the study. Ten (23%) subjects prematurely discontinued from the study. The reasons for discontinuation were lost to follow-up (3 [7%] subjects), followed by AEs, withdrawal of consent, investigators decision (2 [5%] subjects, each) and protocol deviation (1 [2%] subject).

2.7.6 Synopses of Individual Studies

Subject Disposition and Demography							
Number of Subjects	**MDZ (N=12)**	**744 Oral (N=43)**	**744 Oral + MDZ (N=12)**	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**	**Overall (N=43)**
Number of subjects randomized, n (%)	12 (100)	43 (100)	12 (100)	13 (100)	12 (100)	13 (100)	43 (100)
Number of subjects completed, n (%)	12 (100)	39 (91)	11 (92)	12 (92)	10 (83)	11 (85)	33 (77)
Number of subjects included in safety population, n (%)	12 (100)	43 (100)	12 (100)	13 (100)	12 (100)	13 (100)	43 (100)
Number of subjects included in PK concentration population, n (%)	12 (100)	12 (28)	12 (100)	13 (100)	12 (100)	13 (100)	39 (91)
Number of subjects included in 744 oral PK concentration population, n (%)	0	12 (28)	12 (100)	0	0	0	12 (28)
Number of subjects included in 744 LA PK concentration population, n (%)	0	0	0	13 (100)	12 (100)	13 (100)	38 (88)
Number of subjects included in Midazolam PK concentration population, n (%)	12 (100)	0	12 (100)	0	0	0	12 (28)
Number of subjects included in PK parameter population, n (%)	12 (100)	12 (28)	12 (100)	13 (100)	12 (100)	13 (100)	39 (91)
Number of subjects included in 744 Oral PK parameter population, n (%)	0	12 (28)	12 (100)	0	0	0	12 (28)
Number of subjects included in 744 LA PK Parameter population, n (%)	0	0	0	13 (100)	12 (100)	13 (100)	38 (88)
Number of subjects included in Midazolam PK summary population, n (%)	12 (100)	0	12 (100)	0	0	0	12 (28)
Number of subjects withdrawn (any reason), n (%)	0	4 (9)	1 (8)	1 (8)	2 (17)	2 (15)	10 (23)
Reasons for subject withdrawal, n (%)							
Adverse event	0	2 (5)	0	0	0	0	2 (5)
Protocol deviation	0	1 (2)	0	0	0	0	1 (2)
Lost to follow-up	0	0	0	1 (8)	2 (17)	0	3 (7)
Investigator discretion	0	1 (2)	1 (8)	0	0	0	2 (5)
Withdrew consent	0	0	0	0	0	2 (15)	2 (5)
Demographics	**MDZ (N=12)**	**744 Oral (N=43)**	**744 Oral + MDZ (N=12)**	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**	**Overall (N=43)**
Age in Years, Mean (SD)	35.3 (13.72)	34.8 (13.16)	35.3 (13.72)	36.6 (12.87)	37.3 (14.76)	32.0 (12.83)	34.8 (13.16)

2.7.6 Synopses of Individual Studies

Subject Disposition and Demography							
Number of Subjects	**MDZ (N=12)**	**744 Oral (N=43)**	**744 Oral + MDZ (N=12)**	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**	**Overall (N=43)**
Sex, n (%)							
Female:	4 (33)	8 (19)	4 (33)	4 (31)	0	3 (23)	8 (19)
Male:	8 (67)	35 (81)	8 (67)	9 (69)	12 (100)	10 (77)	35 (81)
BMI (kg/m^2), Mean (SD)	24.72 (2.508)	25.44 (3.271)	24.72 (2.508)	26.62 (2.862)	24.99 (2.717)	25.23 (3.660)	25.44 (3.271)
Ethnicity, n (%)							
Hispanic or Latino:	0	2 (5)	0	0	0	2 (15)	2 (5)
Not Hispanic or Latino:	12 (100)	41 (95)	12 (100)	13 (100)	12 (100)	11 (85)	41 (95)
Race, n (%)							
African American/African Heritage	2 (17)	10 (23)	2 (17)	3 (23)	1 (8)	4 (31)	10 (23)
White – White/Caucasian/European Heritage	10 (83)	33 (77)	10 (83)	10 (77)	11 (92)	9 (69)	33 (77)

Treatment: 744 Oral=GSK1265744B 30 mg PO 14-Day Lead-in RD; 744 Oral+MDZ=GSK1265744B 30 mg PO+ Midazolam 3 mg; MDZ=Midazolam; [redacted] nm=[redacted] mg [redacted] nm [redacted] ([redacted]); [redacted] µm=[redacted] mg [redacted] µm [redacted] ([redacted]); [redacted] µm=[redacted] mg [redacted] µm [redacted] ([redacted]).

Safety Results:

Subjects in all the treatment arms reported AEs. The System Organ Class (SOC) 'General Disorders and Administration Site Conditions' accounted for the majority of events in the following treatment groups: [redacted] nm (11 subjects [85%]), [redacted] µm (11 subjects [92%]) and [redacted] µm (10 subjects [77%]), reflecting the occurrence of injection site reactions (ISR).

Summary of All AEs by Cohort (SOC)						
SOC	**MDZ (N=12)**	**744 Oral (N=43)**	**744 Oral + MDZ (N=12)**	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**
Any event, n (%)	**2 (17)**	**20 (47)**	**5 (42)**	**11 (85)**	**12 (100)**	**11 (85)**
General disorders and administration site conditions	0	0	0	11 (85)	11 (92)	10 (77)
Infections and infestations	0	5 (12)	1 (8)	3 (23)	6 (50)	4 (31)
Nervous system disorders	2 (17)	5 (12)	3 (25)	2 (15)	4 (33)	3 (23)
Musculoskeletal and connective tissue disorders	0	1 (2)	0	1 (8)	4 (33)	5 (38)
Investigations	0	4 (9)	0	1 (8)	2 (17)	3 (23)
Injury, poisoning and procedural complications	0	1 (2)	0	2 (15)	5 (42)	1 (8)
Skin and subcutaneous tissue disorders	0	3 (7)	2 (17)	1 (8)	1 (8)	1 (8)
Gastrointestinal disorders	0	3 (7)	0	2 (15)	1 (8)	0
Respiratory, thoracic and mediastinal	0	1 (2)	0	0	2 (17)	1 (8)

Summary of All AEs by Cohort (SOC)						
SOC	**MDZ (N=12)**	**744 Oral (N=43)**	**744 Oral + MDZ (N=12)**	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**
Any event, n (%)	**2 (17)**	**20 (47)**	**5 (42)**	**11 (85)**	**12 (100)**	**11 (85)**
disorders						
Blood and lymphatic system disorders	0	1 (2)	0	0	0	1 (8)
Metabolism and nutrition disorders	0	0	0	1 (8)	0	1 (8)
Psychiatric disorders	0	1 (2)	0	0	1 (8)	0
Ear and labyrinth disorders	0	0	0	0	0	1 (8)
Eye disorders	0	1 (2)	0	0	0	0
Immune system disorders	0	0	0	1 (8)	0	0
Renal and urinary disorders	0	0	0	1 (8)	0	0

Treatment: 744 Oral=GSK1265744B 30 mg PO 14-Day Lead-in RD; 744 Oral+MDZ=GSK1265744B 30 mg PO+ Midazolam 3 mg; MDZ=Midazolam; [redacted] nm=[redacted] mg [redacted] nm [redacted] ([redacted]); [redacted] µm=[redacted] mg [redacted] µm [redacted] ([redacted]), [redacted] µm=[redacted] mg [redacted] µm [redacted] ([redacted]).

Injection Site Reactions (ISR): The most commonly reported ISR after IM administration of [redacted] nm, [redacted] µm, and [redacted] µm LA was pain, at 77%, 83%, and 69% incidence respectively, followed by less frequently observed nodules, induration, erythema, paraesthesia, tightness, and warmth.

The median duration of the three most commonly reported ISR events for [redacted] nm, [redacted] µm, and [redacted] µm are presented. The median duration for pain and induration were generally shorter, lasting ≤11days compared to nodules (granulomas and cysts). Subjects in the [redacted] nm group experienced shorter pain duration than subjects in [redacted] µm and [redacted] µm. Nodules resolved within 55 days in the [redacted] nm and [redacted] µm arms, while one subject in the [redacted] µm arm had a detectable nodule up to 181 days.

Summary of All ISR by IM Treatment			
ISR Event	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**
Any subject with any ISR event, n(%)	**11 (85)**	**11 (92)**	**10 (77)**
Injection site pain	10 (77)	10 (83)	9 (69)
Injection site nodule	4 (31)	5 (42)	2 (15)
Injection site induration	2 (15)	3 (25)	4 (31)
Injection site erythema	0	2 (17)	0
Injection site paraesthesia	0	1 (8)	0
Injection site reaction (tightness)	0	1 (8)	0
Injection site warmth	0	1 (8)	0

Treatment: [redacted] nm=[redacted] mg [redacted] nm [redacted] ([redacted]); [redacted] µm=[redacted] mg [redacted] µm [redacted] ([redacted]), [redacted] µm=[redacted] mg [redacted] µm [redacted] ([redacted]).

Summary of Duration (Days) for Top 3 744 LA ISR Events by Treatment			
ISR Event	**[redacted] nm (N=13)**	**[redacted] µm (N=12)**	**[redacted] µm (N=13)**
Pain, median (min-max)	3.0 (1-5)	5.0 (1-10)	6.0 (2-11)
Nodule (granulomas and cysts), median (min-max)	13.5 (3-55)	13.0 (5-55)	96.0 (11-181)
Induration, median (min-max)	11.0 (9-13)	3.0 (3-13)	7.0 (4-13)

Treatment: [redacted] nm= [redacted] mg [redacted] nm [redacted] ([redacted]);
[redacted] µm= [redacted] mg [redacted] µm [redacted] ([redacted]),
[redacted] µm= [redacted] mg [redacted] µm [redacted] ([redacted]).

ISRs were common but all mild in intensity, with the exception of a single Grade 2 or moderate ISR of pain reported by a subject in the [redacted] µm treatment arm. No Grade 3/4 ISR AEs were reported.

Summary of incidence, severity of ISRs across treatments by event			
Overall Injections	**[redacted] nm**	**[redacted] µm**	**[redacted] µm**
Subjects with injections (N)	**13**	**12**	**13**
Total injections (n)	13	12	13
Total ISR events (n)	16	25	16
Overall ISR			
Grade 1, n (%)	16 (100)	24 (96)	16 (100)
Grade 2, n (%)	0	1 (4)	0
Erythema			
Grade 1, n (%)	0	2 (8)	0
Grade 2, n (%)	0	0	0
Induration			
Grade 1, n (%)	2 (13)	3 (12)	4 (25)
Grade 2, n (%)	0	0	0
Nodule (granulomas and cysts)			
Grade 1, n (%)	4 (25)	5 (20)	2 (13)
Grade 2, n (%)	0	0	0
Pain			
Grade 1, n (%)	10 (63)	11 (44)	10 (63)
Grade 2, n (%)	0	1 (4)	0
Paraesthesia			
Grade 1, n (%)	0	1 (4)	0
Grade 2, n (%)	0	0	0
Warmth at injection site			
Grade 1, n (%)	0	1 (4)	0
Grade 2, n (%)	0	0	0
Other[a]			
Grade 1, n (%)	0	1 (4)	0
Grade 2, n (%)	0	0	0

Note: Based on the AE Data and summarized at the Event Level.
a. AEs for Injection Site Reaction (Tightness) is categorized into ISR 'Other' category.
Treatment: [redacted] nm= [redacted] mg [redacted] nm [redacted] ([redacted]);
[redacted] µm= [redacted] mg [redacted] µm [redacted] ([redacted]),
[redacted] µm= [redacted] mg [redacted] µm [redacted] ([redacted]).

Non-ISR Adverse Events:

The most frequently reported drug-related non-ISR AEs were nausea (n=3) and headache (n=2) reported during the oral lead-in period. Five subjects developed Grade 3/4 non-ISR AEs, of which three subjects had increased creatine phosphokinase (CPK) in NM 1 μm and 744 Oral treatment groups, one subject had joint dislocation in [redacted] μm treatment group, and one subject had an increased total bilirubin in [redacted] μm treatment group. None of the Grade 3 and 4 non-ISR events were considered to be related to study drug.

Two subjects were withdrawn from the study and did not receive 744 LA due to an AE during the oral lead-in period. One subject experienced Grade 1 leukopenia and the other had Grade 1 increases in AST, ALT, and GGT. Both AEs were considered by the investigator to be related to study drug.

One subject in [redacted] nm treatment group experienced a serious adverse event (SAE) of convulsion/seizure (preferred term/verbatim text) which was not considered to be related to study drug by the investigator due to prior subject history and lack of detectable GSK1265744 at the time of the episode. No deaths were reported during the study in any treatment group.

Pharmacokinetic Results:

PK parameters following oral and IM administration of each 744 LA formulation are summarized below.

Summary of Plasma 744 Pharmacokinetic Parameters Following Oral Dose Administration

Treatment	n	Cmax[a] (μg/mL)	AUC(0-τ)[a] (μg.h/mL)	CL/F[a] (L/hr)	tmax[b] (hr)
744 PO	12	7.01 (23)	120 (25)	0.25 (25)	2.00 (1.00-4.00)

a. geometric mean (CV%)
b. median (range)

Summary of Plasma 744 Pharmacokinetic Parameters Following IM Dose Administration				
PK Parameters	Treatment – Current Study, LAI116815			Study LAI114433 Cohorts 3 & 8
	[redacted] nm (n=13)	[redacted] µm (n=12)	[redacted] µm (n=13)	[redacted] nm (n=14)
AUC(0-∞)[a] (µg.h/mL)	2664[c] (20)	2717[c] (28)	2313[e] (18)	NR
AUC(0-wk4)[a] (µg.h/mL)	427 (118)	537 (132)	331 (121)	290 (46)
AUC(0-wk8)[a] (µg.h/mL)	905 (94)	1058[d] (107)	634 (103)	ND
AUC(0-wk12)[a] (µg.h/mL)	1266 (71)	1435[d] (85)	893 (85)	953[f] (54)
Cmax[a] (µg/mL)	0.91 (101)	1.27 (131)	0.70 (121)	0.70 (55)
Cwk4[a] (µg/mL)	0.77 (108)	0.80 (100)	0.50 (110)	0.48 (55)
Cwk8[a] (µg/mL)	0.56 (51)	0.58[d] (72)	0.38 (68)	ND
Cwk12[a] (µg/mL)	0.32 (71)	0.32[d] (81)	0.31 (49)	0.49[f] (61)
CL/F[a] (L/hr)	0.15[c] (20)	0.15[c] (28)	0.17[e] (18)	NR
t1/2[a] (hr)	371[c] (40)	421[c] (26)	615[e] (29)	NR
tmax[b] (day)	28.00 (4.00-84.1)	10.00 (2.0-56.9)	21.00 (4.0-84.0)	69.00 (2.0-213)

a. geometric mean (CV%)
b. median (range)
c. n=5
d. n=11
e. n=4
f. n=13

NR: Not Reported, data available within Clinical Pharmacology Study Report of LAI114433 (GlaxoSmithKline Document Number 2013N159605_00]; ND: Not Determined; [redacted] nm: [redacted] nm [redacted]; [redacted] µm: [redacted] µm [redacted]; [redacted] µm: [redacted] µm [redacted]; [redacted] nm [redacted].

A summary of plasma midazolam PK parameters following administration alone and after co-administration with oral 744 are presented below. The PK of midazolam after repeat oral doses of 744 revealed no significant change in AUC[0-τ], Cmax, t½, tmax, and CL/F relative to the PK parameters generated when midazolam was dosed alone.

Summary of Plasma Midazolam Pharmacokinetic Parameters Following Dose Administration								
Treatment	n	AUC(0-∞)[a] (ng.h/mL)	AUC(0-t)[a] (ng.h/mL)	Cmax[a] (ng/mL)	CL/F[a] (L/hr)	t1/2[a] (hr)	tlag[b] (hr)	tmax[b] (hr)
Midazolam	12	27.5 (53)	25.8 (53)	12.3 (40)	109 (53)	3.99 (37)	0.00 (0.0-0.0)	0.50 (0.3-0.5)
Midazolam + 744	12	29.7 (54)	28.3 (54)	13.4 (36)	101 (54)	3.95 (47)	0.00 (0.0-0.0)	0.50 (0.3-1.0)

a. geometric mean (CV%)
b. median (range)

Statistical Analysis:

744 LA PK parameters were analyzed using a mixed effects model with fixed effect terms for the treatment. Point estimates and corresponding 90% CIs were constructed for the ratio of the geometric mean of the test treatment ([redacted] μm, [redacted] μm) to the geometric mean of the reference treatment ([redacted] nm), μ(test)/μ(reference). The results of the statistical comparisons are shown below.

Summary of 744 LA PK Treatment Comparisons			
PK Parameters	GLS Mean Ratio [90% CI]		
	[redacted] μm vs [redacted] nm	[redacted] μm vs [redacted] nm	[redacted] nm Current Study vs. [redacted] nm Study 114433 Cohorts 3&8
AUC(0-∞)	1.02 [0.791, 1.32]	0.868 [0.663, 1.14]	ND
AUC(0-wk4)	1.26 [0.710, 2.23]	0.775 [0.442, 1.36]	1.47 [0.849, 2.56]
AUC(0-wk8)	1.17 [0.653, 2.09]	0.701 [0.401, 1.22]	ND
AUC(0-wk12)	1.13 [0.721, 1.78]	0.706 [0.458, 1.09]	1.33 [0.861, 2.05]
Cmax	1.39 [0.789, 2.43]	0.761 [0.439, 1.32]	1.31 [0.764, 2.26]
Cwk4	1.03 [0.609, 1.75]	0.653 [0.389, 1.10]	1.62 [0.972, 2.69]
Cwk8	1.04 [0.696, 1.55]	0.680 [0.463, 0.998]	ND
Cwk12	1.01 [0.670, 1.52]	0.970 [0.654, 1.44]	0.647 [0.437, 0.959]
CL/F	0.980 [0.758, 1.27]	1.15 [0.877, 1.51]	ND
t1/2	1.13 [0.793, 1.62]	1.66 [1.13, 2.42]	ND

[redacted] nm: [redacted] nm [redacted] ([redacted]); [redacted] μm: [redacted] μm [redacted] ([redacted]); [redacted] μm: [redacted] μm [redacted] ([redacted]); [redacted] nm [redacted]

ND: Not Determined

Pharmacokinetic parameters of midazolam were separately analyzed using a mixed effects model with fixed effect terms for treatment of midazolam alone and with 744. Subject was treated as a random effect in the model. The results of the statistical comparisons are presented below.

Summary of Midazolam PK Treatment Comparisons	
PK Parameter	**GLS Mean Ratio [90% CI] MDZ + 744 vs MDZ**
AUC(0-∞)	1.08 [0.962, 1.22]
AUC(0-t)	1.10 [0.954, 1.26]
Cmax	1.09 [0.944, 1.26]
CL/F	0.924 [0.822, 1.04]
t1/2	0.991 [0.893, 1.10]

MDZ=Midazolam; MDZ +744 =GSK1265744B 30 mg PO+ Midazolam 3 mg

Conclusions:

- This study did not identify any significant new safety issues associated with 744. Specifically there were no deaths, drug-related SAEs, or drug-related Grade 3/4 AEs. No clinically significant trends in post-dose laboratory abnormalities, vital signs or ECG values were noted.
- ISRs accounted for the majority of drug-related AEs, all of which were of mild to moderate intensity.
- 744 did not affect (induce or inhibit) the activity of CYP3A as evidenced by unchanged midazolam PK with co-administration.
- 744 AUC(0-Wk12) was similar between the [redacted] µm and [redacted] nm formulations. The [redacted] µm formulation resulted in reduced (~29%) exposure over 12-weeks relative to the 200 nm formulation. All treatments achieved a similar mean concentration 12 weeks after dosing.
- The [redacted] nm [redacted] formulation was selected for the future clinical development of 744 LA.

Effective Date: [redacted]

Synopsis for Study LAI117020

Name of company: ViiV Healthcare and the GlaxoSmithKline group of companies

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744

Study Number: LAI117020

Title: A Two Part, Single-center, Randomized, Open-label, Crossover Study to Assess the Relative Bioavailability of New Tablet Formulations of GSK1265744 in Healthy Adult Subjects.

Investigator: [redacted], MD

Study Center: [redacted], United States.

Publication: None at the time of this report.

Study Period: 26-FEB-2014 - 12-JUL-2014

Phase of development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
Part A • To evaluate the relative bioavailability of two new GSK1265744 (744) 30 mg sodium salt tablet formulations compared to a tablet of the current sodium salt formulation in the fasted state. **Part B** • To evaluate the effect of a moderate fat meal on the bioavailability of the selected tablet formulation	**Part A** • Plasma 744 AUC(0-∞), AUC(0-t), Cmax and C24. **Part B** • Plasma 744 AUC(0-∞), AUC(0-t), Cmax and C24.
Secondary	
Part A • To evaluate the relative bioavailability of two new 744 30 mg sodium salt tablet formulations compared to a tablet of the current sodium salt formulation in the fasted state. • To assess the safety and tolerability of 744 administered as a single 30 mg dose of the current sodium salt formulation in the fasted state and two new sodium salt	**Part A** • Plasma 744 t½, tlag, tmax, %AUCex, tlast and CL/F. • Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, ECG, and vital signs assessments.

Objectives	Endpoints
formulations. **Part B** • To evaluate the effect of a moderate fat meal on the bioavailability of the selected tablet formulation. • To further assess the safety and tolerability of 744 administered as a single 30 mg dose of the selected formulation from Part A.	**Part B** • Plasma 744 t½, tlag, tmax, %AUCex, tlast and CL/F. • Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, ECG, and vital signs assessments.

Methodology:

This study was designed to assess the oral bioavailability of two new GSK1265744 (744) formulations relative to the reference 744 sodium salt tablet formulation being used in the phase IIB studies (Part A) and the effect of a moderate-fat meal on the bioavailability of the selected tablet formulation (Part B). In Part A, 24 subjects were randomized and in Part B, 15 subjects from Part A were enrolled on a first come first serve basis. The table below outlines the overall study design.

Treatment	Part A N=24					Washout	Part B N = 15
A: Reference formulation fasted (reference)	Period 1	Wash-out At least 14 days	Period 2	Wash-out At least 14 days	Period 3	Up to 21 days	
B: Formulation 1 fasted							
C: Formulation 2 fasted							
Formulation 1 or 2 fed							Period 4

Treatment A = 744 30mg sodium salt current formulation, [redacted] mg [redacted] (reference)
Treatment B = 744 30mg formulation [redacted], [redacted] mg [redacted], fasted
Treatment C = 744 30mg formulation [redacted], [redacted] mg [redacted], fasted

In Part A, subjects were randomized to receive one of the following six sequences: ABC, ACB, BAC, BCA, CAB, and CBA. Subjects underwent a screening visit within 30 days of the first dose of study drug, three treatment periods separated by a 14-day washout, and a follow-up period.

The selection of formulation used in Part B was based on the preliminary PK analysis results of Part A. The decision to conduct Part B was based on the concentration at 24 h post-dose (C24) geometric least square (GLS) means ratio (GLS means ratio was equal to or greater than 0.9 was 50% or more (Prob[C24 ratio≥0.9]≥50%), area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC0-∞), maximum observed concentration (Cmax), and pharmaceutical development factors. Part B was not to be conducted if both new formulations were found to be clearly inferior to the current formulation. If none of the tablets passed the criteria, Part B was still to be conducted if the results of one of the formulations were narrowly outside of the criteria. Even though neither tablet met the criteria, the study team agreed that there might still be

value in understanding the food effect with one of these formulations for future planning. Therefore Part B was conducted.

GSK1265744 30 mg formulation, made from [redacted] drug substance was selected for testing in Fed condition in Part B.

In Part B, subjects were given moderate fat meal followed by a single dose of study drug administered within 30 minutes of completing the meal on Day 1.

Diagnosis and Main Criteria for Inclusion:

Healthy males and females aged between 18 to 65 years inclusive, with body weight ≥50 kg and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive) were enrolled in this study.

Number of Subjects:

A total of 24 subjects in Part A and 15 subjects in Part B were planned, enrolled and analyzed.

Treatment Administration:

In Part A, subjects were assigned to one of the six sequences in accordance with the randomization schedule as shown in table below

Treatment assignment for Part A			
Sequence	**Period 1**	**Period 2**	**Period 3**
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Treatment A = 744 30mg sodium salt current formulation, [redacted] mg [redacted], fasted (reference).
Treatment B = 744 30mg formulation [redacted], [redacted] mg [redacted], fasted.
Treatment C = 744 30mg formulation [redacted], , [redacted] mg [redacted], fasted.

In Part B, subjects were assigned to treatment B, 744 30 mg 208 mg, formulation [redacted] with a moderate fat meal as shown in table below:

Treatment Assignment for Part B	
Treatment (from Part A)	**Treatment in Period 4**
D	744+food

Treatment D = 744 30 mg treatment B, [redacted] mg [redacted], fed (moderate fat meal)

Statistical Methods:

No formal hypothesis was tested in Part A or B.

For each primary pharmacokinetic endpoint, point estimates and corresponding 90% confidence intervals were constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

Safety analyses: safety data were presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Pharmacokinetic analyses: plasma 744 concentration-time data were analyzed by non-compartmental methods with WinNonlin 5.2 or higher. From the plasma concentration-time data, the following pharmacokinetic parameters were determined, as data permitted: area under the plasma concentration-time curve (AUC[0-∞] and AUC[0- t]),Cmax,C24, apparent terminal phase half-life (t1/2), absorption lag time (tlag), time to Cmax (tmax), the percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time of last measurable concentration (tlast), and apparent oral clearance (CL/F).

Summary

Demographics:

Number of Subjects	Part A (Fasted)			Part B (Fed)	Overall N=24
	A: 744 30 mg (reference) N=22	B: [redacted] 744 30 mg N=24	C: [redacted] 744 30 mg N=24	D: [redacted] 744 30 mg N=15	
Number of subjects planned, [N]	24	24	24	15	24
Number of subjects randomized/enrolled, [N]	22	24	24	15	24
Number of subjects included in All subjects (safety) population, [n (%)]	22 (100)	24 (100)	24 (100)	15 (100)	24 (100)
Number of subjects included in PK population, [n (%)]	22 (100)	24 (100)	24 (100)	15 (100)	24 (100)
Number of subjects completed as planned, [n (%)]	22 (100)	23 (96)	23 (96)	15 (100)	22 (92)
Number of subjects withdrawn (any reason), [n (%)]	0	1 (4)	1 (4)	0	2 (8)
Number of subjects withdrawn for SAE, [n (%)]	0	0	0	0	0
Number of subjects withdrawn for AE, [n (%)]	0	0	0	0	0
Reasons for subject withdrawal, [n (%)]					
Protocol violation	0	1 (4)	0	0	1 (4)
Medical monitor decision or Investigator's discretion	0	0	1 (4)	0	1 (4)

Number of Subjects	Part A (Fasted)			Part B (Fed)	Overall N=24
	A: 744 30 mg (reference) N=22	**B: [redacted] 744 30 mg N=24**	**C: [redacted] 744 30 mg N=24**	**D: [redacted] 744 30 mg N=15**	
Demographics	A: 744 30 mg (reference) N=22	B: [redacted] 744 30 mg N=24	C: [redacted] 744 30 mg N=24	D: [redacted] 744 30 mg N=15	Overall N=24
Age in Years [Mean (SD)]	40.3 (12.87)	41.8 (13.29)	41.8 (13.29)	40.0 (13.56)	41.8 (13.29)
Sex [n (%)]					
Female	9 (41)	10 (42)	10 (42)	5 (33)	10 (42)
Male	13 (59)	14 (58)	14 (58)	10 (67)	14 (58)
BMI (kg/m2) [Mean (SD)]	26.66 (2.908)	26.77 (2.805)	26.77 (2.805)	26.74 (2.858)	26.77 (2.805)
Height (cm) [Mean (SD)]	172.71 (10.289)	172.96 (10.619)	172.96 (10.619)	173.60 (10.446)	172.96 (10.619)
Weight (kg) [Mean (SD)]	79.88 (13.741)	80.47 (13.893)	80.47 (13.893)	80.98 (14.325)	80.47 (13.893)
Ethnicity [n (%)]					
Hispanic or Latino	1 (5)	1 (4)	1 (4)	1 (7)	1 (4)
Not Hispanic or Latino	21 (95)	23 (96)	23 (96)	14 (93)	23 (96)
Race [n (%)]					
African American/African Heritage	5 (23)	5 (21)	5 (21)	3 (20)	5 (21)
White – White/Caucasian/European Heritage	17 (77)	19 (79)	19 (79)	12 (80)	19 (79)

A: 744 30 mg current formulation, [redacted] mg [redacted], fasted (reference)
B: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
C: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
D: 744 30 mg formulation [redacted], [redacted] mg [redacted], fed

Pharmacokinetic Results:

Plasma 744 exposure for both new candidate formulations was lower than for the reference formulation. Plasma 744 parameters (AUC(0-∞), Cmax and C24) were 29-36% lower following the test [redacted] tablet (Treatment B) and 42%-47% lower following the test [redacted] tablet (Treatment C) as compared to the reference tablet. The test [redacted] formulation was selected for Part B of the study, and food slightly increased but did not have a significant impact on 744 AUC(0-∞) or Cmax.

Summary of Selected Plasma 744 Pharmacokinetic Parameters Following Single Dose Administration[a]

Treatment	AUC(0-72) (hr*μg/mL)	AUC(0-∞) (hr*μg/mL)	Cmax (μg/mL)	C24 (μg/mL)	tmax[b] (hr)	t1/2 (hr)
A: 744 30 mg (reference) (Fasted) (N=22)	104 (19) [95.4,113]	141 (20) [129, 154]	3.70 (23) [3.35, 4.10]	1.64 (20) [1.50, 1.78]	2.00 (1.00 – 6.00)	37.8 (18) [35.0, 40.9]
B: [redacted] 744 30 mg (Fasted) (N=22)	72.0 (29) [63.4, 81.8]	98.8 (33) [85.6, 114]	2.38 (30) [2.09, 2.71]	1.16 (28) [1.03, 1.31]	3.00 (1.00 – 6.00)	38.4 (18) [35.5, 41.5]
C: [redacted] 744 30 mg (Fasted) (N=22)	60.3 (41) [50.7, 71.8]	82.0 (42) [68.6, 97.9]	1.98 (40) [1.68, 2.35]	0.94 (43) [0.78, 1.13]	3.00 (1.00 – 6.00)	36.3 (20) [33.3, 39.6]
B: [redacted] 744 30 mg (Fasted) (N=15 subset)	75.7 (23) [66.9, 85.6]	104 (27) [90.3, 121]	2.50 (27) [2.16, 2.90]	1.22 (23) [1.08, 1.38]	3.00 (1.00 – 6.00)	38.6 (18) [35.0, 42.7]
D: [redacted] 744 30 mg (Fed) (N=15)	83.4 (20) [74.6, 93.3]	113 (25) [98.4, 129]	2.71 (16) [2.48, 2.96]	1.36 (22) [1.21, 1.54]	3.03 (2.00 – 8.00)	37.2 (16) [34.0, 40.6]

Geometric Mean (Cvb%)[95% CI]
Median (range)
Treatments:
A: 744 30 mg current formulation, [redacted] mg [redacted], fasted (reference)
B: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
C: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
D: 744 30 mg formulation [redacted], [redacted] mg [redacted], fed

Plasma 744 PK Treatment Comparison

Plasma PK Parameter	Ratio of GLS Means (90% CI)		
	[redacted] 30 mg fasted vs Reference (B:A) (N=22)	**[redacted] 30 mg fasted vs Reference (C:A) (N=22)**	**[redacted] 30 mg fed vs [redacted] fasted (D:B) (N=15 subset)**
AUC(0-72) (hr*μg/mL)	0.690 (0.613, 0.777)	0.578 (0.513, 0.651)	1.102 (0.992, 1.224)
AUC(0-∞) (hr*μg/mL)	0.699 (0.622, 0.786)	0.580 (0.516, 0.652)	1.081 (0.978, 1.195)
Cmax (μg/mL)	0.640 (0.563, 0.727)	0.533 (0.469, 0.606)	1.081 (0.958, 1.220)
C24 (μg/mL)	0.707 (0.627, 0.798)	0.573 (0.508, 0.646)	1.117 (1.000, 1.248)
t1/2 (hr)	1.02 (0.973, 1.06)	0.961 (0.921, 1.00)	0.962 (0.921, 1.005)

Treatments:
A: 744 30 mg current formulation, [redacted] mg [redacted], fasted (reference)
B: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
C: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
D: 744 30 mg formulation [redacted], [redacted] mg [redacted], fed

Safety Results:

There were no deaths, no serious adverse events (SAEs), and no significant adverse events (AEs) reported in the study. All AEs were mild in intensity (Grade 1). None of the AEs were related to the investigational product. No subjects were withdrawn due an adverse event. An overview of adverse events is presented in the table below.

Overview of Adverse Events by Treatments

Preferred Term	Part A (Fasted)			Part B (Fed)	Overall N=24
	A: 744 30 mg (reference) N=22	B: [redacted] 744 30 mg N=24	C: [redacted] 744 30 mg N=24	D: [redacted] 744 30 mg N=15	
	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	1 (5)	1 (4)	6 (25)	1 (7)	9 (38)
Any AE related to investigational product	0	0	0	0	0
Catheter site pain	0	0	2 (8)	0	2 (8)
Catheter site swelling	1 (5)	0	0	0	1 (4)
Oropharyngeal pain	0	0	0	1 (7)	1 (4)
Burns second degree	0	0	1 (4)	0	1 (4)
Excoriation	0	0	1 (4)	0	1 (4)
Thermal burn	0	0	1 (4)	0	1 (4)
Headache	0	1 (4)	0	0	1 (4)
Dermatitis contact	0	0	1 (4)	0	1 (4)

A: 744 30 mg current formulation, [redacted] mg [redacted], fasted (reference)
B: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
C: 744 30 mg formulation [redacted], [redacted] mg [redacted], fasted
D: 744 30 mg formulation [redacted], [redacted] mg [redacted], fed

No consistent, treatment related or clinically significant changes in hematology, or clinical chemistry results were observed during this study. Vital signs values remained relatively unchanged throughout this study. There were no vital sign abnormalities of potential clinical concern noted. There were no clinically significant electrocardiogram (ECG) abnormalities observed in study.

Conclusions:

- Plasma 744 parameters (AUC(0-∞), Cmax and C24) were 29-36% lower following the test [redacted] tablet (Treatment B) and 42%-47% lower following the test [redacted] tablet (Treatment C) as compared to the reference tablet (Treatment A). Neither new formulation met the criteria for progression into Phase 3.

- Food did not affect 744 PK following administration of the test micronized tablet.
- There were no deaths, no serious AEs. No subjects were withdrawn due an adverse event.
- All AEs were mild in intensity. None of AEs were related to the investigational product.

Effective Date: [redacted]-[redacted]-20[redacted]

Synopsis for Study 201741

Name of company: ViiV Healthcare Limited

Name of finished product: N/A

Name of active substance: GSK1265744, Cabotegravir

Study Number: 201741

Title: A Phase 1, single-center, randomized, open-label, crossover study to assess the relative bioavailability of Phase III tablet formulation candidates in healthy adult subjects

Investigator: [redacted], MD

Study Center: [redacted], United States

Publication(s): None at the time of this report

Study Period: 10-MAR-2015 – 05-JUN-2015

Phase of development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
To evaluate the relative bioavailability of four new cabotegravir (CAB) 30 mg sodium salt tablet formulations ([redacted]) compared to a tablet of the current sodium salt formulation in the fasted state.	Plasma CAB area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-∞]), Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments (AUC [0-t]), maximum observed concentration (Cmax) and concentration at 24 hours post-dose (C24).
Secondary	
To evaluate the relative bioavailability of four new CAB 30 mg sodium salt tablet formulations ([redacted]) compared to a tablet of the current sodium salt formulation in the fasted state.	Plasma CAB terminal phase half-life (t ½) , lag time before observation of drug concentrations in sampled matrix (tlag), time of occurrence of Cmax (tmax), percentage of AUC(0-∞) obtained by extrapolation (%AUCex), area under the concentration-time curve from time zero to 72 hours post dose (AUC [0-72]), time of last measurable concentration (tlast) and apparent clearance following oral dosing (CL/F).
To assess the safety and tolerability of CAB administered as a single 30 mg dose of the Phase III tablet formulation candidates and the current sodium salt formulation in the fasted state.	Safety and tolerability parameters included adverse events, concurrent medication, clinical laboratory screens, electrocardiogram (ECG) and vital signs assessments.

Methodology: This was a single-center, randomized, open-label, two cohort, three-way crossover study in healthy adult subjects to assess the oral bioavailability of four new cabotegravir (CAB) formulations relative to the reference CAB sodium salt tablet with an 800 mg core weight used in Phase 2b studies. Thirty-six subjects were to be randomized into one of the six sequences in each of the two cohorts; subjects in Cohort 1 (n=18) received the current reference formulation (mg), the mg formulation with ( ) and , and subjects in Cohort 2 (n=18) received the current reference formulation, the mg formulation with .

Overall Study Design

Cohort	Subjects		Treatment periods					Follow-up
Cohort 1	N=18	30 day Screening period	Period 1	Wash-out At least 14 days	Period 2	Wash-out At least 14 days	Period 3	14 days after last dose
Cohort 2	N=18							
Cohort 1/Sequences 1-6 Treatment A = CAB 30 mg current formulation, reference Treatment B = CAB 30 mg new formulation , mg , Treatment C = CAB 30 mg new formulation , mg , **Cohort 2/Sequences 7-12** Treatment A = CAB 30 mg current formulation, reference Treatment D = CAB 30 mg new formulation , mg , Treatment E = CAB 30 mg new formulation , mg ,								

Subjects underwent a screening visit within 30 days of the first dose of study drug, three treatment periods, and a follow-up period. All treatments were administered as a single 30 mg dose of CAB under fasting conditions separated by a 14-day washout.

Participation in this study was 12 weeks (e.g., 30-day screening period, 3- treatment periods, 14 day wash-out between each dose, 7 - 14 day follow up period).

Diagnosis and Main Criteria for Inclusion: Healthy males and females aged between 18 to 65 years inclusive, with body weight ≥50 kg and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive) were enrolled in this study.

Number of Subjects: Thirty-seven healthy adult subjects were enrolled into the study and 36 subjects completed dosing and critical assessments.

Treatment Administration:

	Study Treatments				
Product name:	**Cabotegravir sodium (Reference)**	**Cabotegravir** [redacted]	**Cabotegravir** [redacted]	**Cabotegravir** [redacted]	**Cabotegravir** [redacted]
Formulation description:	GSK1265744B ([redacted]) [redacted]	GSK1265744B ([redacted]) [redacted]	GSK1265744B ([redacted]) [redacted]	GSK1265744B ([redacted]) [redacted]	GSK1265744B ([redacted]) [redacted]
Dosage form:	Film coated Tablet, [redacted] mg	Film coated Tablet, [redacted] mg	Film coated Tablet, [redacted] mg	Film coated Tablet, [redacted] mg	Film coated Tablet, [redacted] mg
Batch Number	PK Lot ID: [redacted]; Bulk Product Batch No. [redacted]	PK Lot ID: [redacted]; Bulk Product Batch No. [redacted]	PK Lot ID: [redacted]; Bulk Product Batch No. [redacted]	PK Lot ID: [redacted]; Bulk Product Batch No. [redacted]	PK Lot ID: [redacted]; Bulk Product Batch No. [redacted]
Unit dose strength/Dosage level:	Tablet strength: 30 mg Dose level: 1 tablet				
Route of Administration	Administer orally				
Dosing instructions:	Dose with 240 mL of water				
Manufacturer	GlaxoSmithKline				

Statistical Methods:

No formal hypothesis was tested.

Safety Analyses: Safety data was presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Pharmacokinetic Analyses: Plasma CAB concentration-time data were analyzed by non-compartmental methods with WinNonlin (Phoenix) 6.3. Calculations were based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters were determined, as data permitted: area under the plasma concentration-time curve [AUC(0-∞), AUC(0-72) and AUC(0- t)],

maximum observed plasma concentration (Cmax), concentration at 24 h post-dose (C24), apparent terminal phase half-life (t1/2), absorption lag time (tlag), time to Cmax (tmax), the percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time of last measurable concentration (tlast), and apparent oral clearance (CL/F).

Summary

A total of 37 subjects were enrolled in the study and 36 subjects completed all the treatment periods, with one subject withdrawn prematurely**.** The majority of subjects were African American/African Heritage (54%), not Hispanic/Latino (95%) and male (73%). The mean age was 32.4 years (SD: 9.62; range: 19 years to 57 years).

Demographics:

Subject Disposition and Demographics						
Number of Subjects	**CAB 30 mg ([redacted])**	**CAB 30 mg ([redacted])**	**CAB 30 mg ([redacted])**	**CAB 30 mg ([redacted])**	**CAB 30 mg ([redacted])**	**Overall**
Number of subjects planned [N]	36	18	18	18	18	36
Number of subjects randomized [N]	36	19	18	18	18	37
Number of subjects included in All subjects (safety) population [n (%)]	36 (100)	19 (100)	18 (100)	18 (100)	18 (100)	37 (100)
Number of subjects included in PK Concentration population [n (%)]	36 (100)	19 (100)	18 (100)	18 (100)	18 (100)	37 (100)
Number of subjects included in PK Parameter population [n (%)]	36 (100)	19 (100)	18 (100)	18 (100)	18 (100)	37 (100)
Number of subjects included in PK Summary population [n (%)]	36 (100)	18 (95)	18 (100)	18 (100)	18 (100)	36 (97)
Number of subjects completed as planned [n (%)]	36 (100)	18 (95)	18 (100)	18 (100)	18 (100)	36 (97)
Number of subjects withdrawn (any reason) [n (%)]	0	1 (5)	0	0	0	1 (3)
Reasons for subject withdrawal [n (%)]						
Other-Eligibility criteria not fulfilled	0	1 (5)	0	0	0	1 (3)

Subject Disposition and Demographics						
Demographics	**CAB 30 mg ([redacted]) N=36**	**CAB 30 mg ([redacted]) N=19**	**CAB 30 mg ([redacted]) N=18**	**CAB 30 mg ([redacted]) N=18**	**CAB 30 mg ([redacted]) N=18**	**Overall N=37**
Age in Years [Mean (SD)]	32.0 (9.43)	31.6 (10.09)	30.8 (9.65)	33.2 (9.32)	33.2 (9.32)	32.4 (9.62)
Sex [n (%)]						
Female	9 (25)	8 (42)	7 (39)	2 (11)	2 (11)	10 (27)
Male	27 (75)	11 (58)	11 (61)	16 (89)	16 (89)	27 (73)
BMI (kg/m^2) [Mean (SD)]	26.08 (3.279)	25.75 (2.785)	25.68 (2.851)	26.48 (3.697)	26.48 (3.697)	26.10 (3.236)
Height (cm) [Mean (SD)]	174.39 (8.816)	172.36 (9.361)	172.64 (9.550)	176.14 (7.896)	176.14 (7.896)	174.20 (8.771)
Weight (kg) [Mean (SD)]	79.46 (12.471)	76.66 (11.726)	76.74 (12.061)	82.18 (12.610)	82.18 (12.610)	79.35 (12.315)
Ethnicity [n (%)]						
Hispanic or Latino	2 (6)	1 (5)	1 (6)	1 (6)	1 (6)	2 (5)
Not Hispanic or Latino	34 (94)	18 (95)	17 (94)	17 (94)	17 (94)	35 (95)
Race [n (%)]						
African American/African Heritage	20 (56)	7 (37)	7 (39)	13 (72)	13 (72)	20 (54)
White – White/Caucasian/European Heritage	16 (44)	12 (63)	11 (61)	5 (28)	5 (28)	17 (46)

[redacted] = [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg current formulation, reference
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 3, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 4, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 5, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 6, [redacted] mg [redacted]

Safety Results

There were no deaths, no serious adverse events (SAEs), and no significant adverse events (AEs) reported in the study. All AEs were mild in intensity (Grade 1). None of the AEs were related to the investigational product. No subjects were withdrawn due to an AE. An overview of AEs is presented in the table below.

Overall Summary of All Subjects with Adverse Events (Safety Population):

Preferred Term	A: CAB 30 mg ([redacted]) N=36	B: CAB 30 mg ([redacted]) N=19	C: CAB 30 mg ([redacted]) N=18	D: CAB 30 mg ([redacted]) N=18	E: CAB 30 mg ([redacted]) N=18	Overall N=37
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	4 (11)	3 (16)	3 (17)	1 (6)	0	9 (24)
Any AE related to investigational product	0	0	0	0	0	0
Upper respiratory tract infection	0	1 (5)	0	1 (6)	0	2 (5)
Otitis media	1 (3)	0	0	0	0	1 (3)
Viral infection	0	1 (5)	0	0	0	1 (3)
Headache	1 (3)	1 (5)	0	0	0	1 (3)
Paraesthesia	1 (3)	0	0	0	0	1 (3)
Tympanic membrane hyperaemia	1 (3)	0	0	0	0	1 (3)
Eyelid oedema	0	0	1 (6)	0	0	1 (3)
Vessel puncture site pain	1 (3)	0	0	0	0	1 (3)
Neutrophil count decreased	1 (3)	0	0	0	0	1 (3)
Decreased appetite	0	0	1 (6)	0	0	1 (3)
Dermatitis	0	0	1 (6)	0	0	1 (3)
Haematoma	0	1 (5)	0	0	0	1 (3)

[redacted]=[redacted], [redacted]=[redacted]
CAB 30 mg ([redacted]) = CAB 30 mg current formulation, reference
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 3, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 4, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 5, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 6, [redacted] mg [redacted]

No consistent, treatment-related or clinically significant changes in hematology, or clinical chemistry results were observed during this study. No clinical meaningful change over time was observed in vital signs. One subject had 2 episodes of bradycardia, which were not reported as AEs and was not considered clinically significant by the Investigator. There were no clinically significant electrocardiogram (ECG) abnormalities observed in the study.

Pharmacokinetic Results:

Summary of Selected Plasma CAB Pharmacokinetic Parameters Following Single Dose Administration

Treatment	AUC(0-∞) (hr*μg/mL)	AUC(0-t) (hr*μg/mL)	Cmax (μg/mL)	C24 (μg/mL)	tmax[b] (hr)	t1/2 (hr)
A: Cohort1: CAB30mg ([redacted]) (n=18)	131 (33) [112, 154]	124 (30) [107, 143]	3.35 (24) [2.98, 3.76]	1.51 (25) [1.34, 1.71]	2.01 (0.5 – 6.0)	39.1 (23) [34.9, 43.8]
B: Cohort1: CAB30mg ([redacted]) (n=18)	135 (26) [119, 154]	128 (24) [114, 144]	3.43 (21) [3.10, 3.80]	1.58 (20) [1.43, 1.74]	3.00 (1.0 - 4.0)	38.4 (24) [34.3, 43.2]
C: Cohort1: CAB30mg ([redacted]) (n=18)	106 (27) [92.7, 121]	101 (27) [88.5, 115]	2.65 (29) [2.30, 3.05]	1.24 (26) [1.10, 1.41]	2.00 (1.0 - 4.0)	36.8 (23) [32.9, 41.3]
A: Cohort2: CAB30mg ([redacted]) (n=18)	142 (25) [126, 160]	135 (25) [120, 152]	3.48 (29) [3.01, 4.01]	1.65 (26) [1.45, 1.87]	2.01 (0.5 - 6.0)	38.6 (12) [36.4, 40.9]
D: Cohort2: CAB30mg ([redacted]) (n=18)	129 (26) [113, 147]	123 (26) [108, 140]	3.15 (27) [2.76, 3.59]	1.49 (27) [1.31, 1.71]	2.01 (0.5 - 6.0)	37.4 (14) [35.0, 40.1]
E: Cohort2: CAB30mg ([redacted]) (n=18)	106 (33) [90.4, 125]	101 (33) [86.1, 119]	2.60 (36) [2.19, 3.09]	1.12 (49) [0.89, 1.41]	2.00 (0.5 - 4.0)	38.0 (14) [35.4, 40.7]
A:Combined: CAB30mg ([redacted]) (n=36)	137 (29) [124, 150]	129 (27) [118, 142]	3.41 (26) [3.13 3.72]	1.58 (26) [1.45 1.72]	2.01 (0.5 – 6.0)	38.9 (18) [36.6, 41.3]

a. geometric mean (%CVb) [95% CI]
b. median (range)
CAB 30 mg ([redacted]) = CAB 30 mg current formulation, reference
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 3, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 4, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 5, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 6, [redacted] mg [redacted]

Plasma CAB PK Treatment Comparison

Plasma PK Parameter	Ratio of GLS Means (90% CI)			
	CAB30mg ([redacted]) vs. CAB30mg ([redacted]) (N=18)	CAB30mg ([redacted]) vs. CAB30mg ([redacted]) (N=18)	CAB30mg ([redacted]) vs. CAB30mg ([redacted]) (N=18)	CAB30mg ([redacted]) vs. CAB30mg ([redacted]) (N=18)
AUC(0-∞) (hr*μg/mL)	1.03 [0.931, 1.15]	0.809 [0.729, 0.897]	0.908 [0.793, 1.040]	0.747 [0.653, 0.855]
AUC(0-t) (hr*μg/mL)	1.04 [0.934, 1.15]	0.814 [0.735, 0.903]	0.91 [0.796, 1.04]	0.749 [0.655, 0.856]
Cmax (μg/mL)	1.03 [0.918, 1.15]	0.791 [0.708, 0.884]	0.905 [0.781, 1.05]	0.747 [0.644, 0.866]
C24 (μg/mL)	1.04 [0.937, 1.16]	0.823 [0.739, 0.917]	0.908 [0.762, 1.08]	0.68 [0.571, 0.809]
t1/2 (hr)	0.983 [0.931, 1.040]	0.942 [0.892, 0.995]	0.970 [0.938, 1.00]	0.984 [0.951, 1.02]

[redacted] = [redacted]. [redacted] = [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg current formulation, reference
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 3, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 4, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 5, [redacted] mg [redacted]
CAB 30 mg ([redacted]) = CAB 30 mg new formulation 6, [redacted] mg [redacted]

The [redacted] mg [redacted] formulation was bioequivalent to the reference formulation. Exposures following the [redacted] mg [redacted] formulation were reduced 9% relative to the reference formulation. Exposures following the [redacted] mg and [redacted] mg [redacted] formulations were reduced 18 - 21% and 25 – 32%, respectively, relative to the reference formulation. The apparent terminal phase t1/2 was similar between treatments, suggesting that differences in exposure for the test formulations resulted from differences in absorption rather than in elimination. The [redacted] formulation with [redacted] mg was bioequivalent to the reference formulation.

In summary, both test formulations made with [redacted] met the pre-established acceptance criteria. Neither of the test formulations made with [redacted] met the acceptance criteria. Since a [redacted] tablet is desirable for ease of administration, the tablet formulation with the [redacted] mg, [redacted] was selected for progression into phase 3 studies.

Conclusions:

- The test formulation with [redacted] mg [redacted] was bioequivalent to the reference formulation and was selected for progression into Phase 3 studies.

- Cabotegravir was well tolerated following single dose administration of all four new formulations and the reference formulation.

- There were no deaths or serious AEs. No subjects were withdrawn due to an AE.
- All AEs were mild (Grade 1) in intensity. None of AEs were related to the investigational product.

Effective Date: [redacted]

Synopsis for Study LAI116585

Study Number: LAI116585

Title: A Single-Center, Randomized, Open-Label, Crossover Study to Assess the Relative Bioavailability of New Formulations of GSK1265744 in Healthy Adult Subjects.

Investigators: [redacted] M.D

Study centers: [redacted] ([redacted] United States [redacted]).

Publications: None at the time of this report.

Study period: 29Aug2012 (First subject screen failed), 04 Sept2012 (First subject screened that was enrolled) - 05Nov2012

Phase of development: I

Objectives:

Primary:

To evaluate the relative bioavailability of two new GSK1265744 30 mg free acid capsule formulations compared to a tablet of the current sodium salt formulation in the fasted state.

Secondary:

To assess the safety and tolerability of GSK1265744 administered as a single 30 mg dose of the current sodium salt formulation in the fasted state and two new free acid formulations.

Methodology: This was a single-center, randomized, open-label, balanced, 3 way crossover study in healthy adult subjects to assess the relative bioavailability of two new free acid oral formulations of GSK1265744 30 mg compared to the current GSK1265744 30 mg sodium salt formulation. Subjects had a screening visit within 30 days prior to the first dose of study drug, three treatment periods containing a single dose of study drug, followed by 24 hr of serial PK collection. Subjects checked out of the unit on Day 2 after the 24-hour assessments have been collected and would return to the study unit for the Day 3 (48hr), Day 4 (72hr), Day 6 (120hr), and Day 8 (168hr) pharmacokinetic (PK) collections. Study periods were separated by a washout of at least 14 days between doses.

Number of subjects: Approximately 18 subjects were enrolled and randomized in a cross over fashion to a single dose of the current formulation and the two new formulations in the fasted state.

Diagnosis and main criteria for inclusion: Male or female subjects between 18 and 64 years of age inclusive, at the time of signing the informed consent, body weight ≥50 kg for men and ≥45 kg for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive) were included in the study.

Treatment administration: Subjects were assigned to one of the six sequences in accordance with the randomization schedule.

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

There was a wash out of ≥14 days between doses of study medication
Treatment A = GSK1265744 30 mg sodium salt current formulation fasted
Treatment B = GSK1265744 30 mg free acid [redacted] formulation fasted
Treatment C = GSK1265744 30 mg free acid [redacted] formulation fasted

Criteria for evaluation:

Primary:

- Plasma GSK1265744 AUC(0-∞), AUC(0-t), and Cmax.

Secondary:

- Plasma GSK1265744 C24, t½, tlag, tmax, %AUCex, and CL/F.
- Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, ECG, and vital signs assessments.

Statistical methods: This study was designed to estimate the bioavailability of two new free acid formulations of GSK1265744 30 mg relative to current GSK1265744 30 mg sodium salt formulation. No formal hypothesis was tested. For each primary PK endpoint, point estimates and corresponding 90% confidence intervals were constructed for the ratio of the geometric mean of the test treatment to the geometric mean of the reference treatment, μ(test)/μ(reference).

Plasma GSK1265744 concentration-time data were analyzed by non-compartmental methods with WinNonlin Professional 5.2 or higher. Calculations were based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters were determined, as data permit: maximum observed plasma concentration (Cmax), time to Cmax (tmax), area under the plasma concentration-time curve [AUC(0-t) and AUC(0-∞)], and apparent terminal phase half-life (t1/2), also apparent clearance (CL/F) PK data was presented in graphical and/or tabular form and were summarized descriptively.

2.7.6 Synopses of Individual Studies

Summary:

Demographics:

Number of Subjects	Overall
Number of subjects planned, N:	18
Number of subjects randomized, N:	18
Number of subjects included in All subjects (safety) population, n (%):	18 (100)
Number of subjects included in PK population, n (%):	18 (100)
Number of subjects completed as planned, n (%):	18 (100)
Number of subjects withdrawn (any reason), n (%):	0
Number of subjects withdrawn for SAE, n (%):	0
Number of subjects withdrawn for AE, n (%):	0
Demographics	**Overall**
Age in Years, Mean (SD)	36.7 (12.52)
Sex, n (%)	
Female:	8 (44)
Male:	10 (56)
BMI (kg/m^2), Mean (SD)	25.16 (2.387)
Height (cm), Mean (SD)	167.83 (7.189)
Weight (kg), Mean (SD)	71.06 (9.835)
Ethnicity, n (%)	
Hispanic or Latino:	3 (17)
Not Hispanic or Latino:	15 (83)
Race, n (%)	
African American/African Heritage	6 (33)
American Indian or Alaskan Native	1 (6)
White – White/Caucasian/European Heritage	11 (61)

SAE=Serious Adverse Event, SD = Standard Deviation

PK Summary: The results of the statistical comparison of plasma PK parameters of all analytes are presented in the tables below:

Summary of Selected Plasma GSK1265744 Pharmacokinetic Parameters Following Single Dose Administration [1]

Treatment	AUC(0-∞) (µg.h/mL)	AUC(0-t) (µg.h/mL)	Cmax (µg/mL)	tmax[2] (h)	C24 (µg/mL)	t1/2 (h)	CL/F (L/hr)
Na Salt (n=18)	174 [153, 196] (25)	163 [145, 183] (24)	4.24 [3.86, 4.67] (19)	2.00 (1.0-4.0)	1.98 [1.78, 2.21] (22)	39.9 [36.1, 44.2] (21)	0.17 [0.15, 0.20] (25)
FA [redacted] (n=18)	152 [137, 170] (22)	142 [129, 157] (20)	3.43 [3.08, 3.81] (21)	3.00 (1.0-6.0)	1.72 [1.56,1.90] (20)	41.4 [37.9, 45.2] (18)	0.20 [0.18, 0.22] (22)
FA [redacted] (n=18)	89.4 [77.5, 103] (29)	82.9 [72.7, 94.7] (27)	1.96 [1.71, 2.24] (28)	3.00 (2.0-4.0)	0.99 [0.87, 1.13] (27)	42.8 [38.2, 48.0] (23)	0.34 [0.29, 0.39] (29)

[1] geometric mean [95% CI] (CV%)

[2] median (range)

Plasma GSK1265744 PK Treatment Comparison

Plasma PK Parameter	Ratio of GLS Means (90% CI)	
	FA [redacted] vs Na Salt	FA [redacted] vs Na Salt
AUC(0-∞)	0.877 [0.778, 0.989]	0.515 [0.457, 0.581]
AUC(0-t)	0.872 [0.774, 0.983]	0.509 [0.451, 0.573]
C24	0.867 [0.771, 0.975]	0.498 [0.443, 0.560]
Cmax	0.807 [0.719, 0.906]	0.461 [0.410, 0.517]
t1/2	1.04 [0.997, 1.08]	1.07 [1.03, 1.12]
CL/F	1.14 [1.01, 1.29]	1.94 [1.72, 2.19]

Safety Results:

Overall the study medications were generally well tolerated in healthy subjects in this study. Four subjects reported adverse events (AEs) and all AEs were mild (Grade 1) in intensity. There were no drug related adverse events reported. No other clinically significant changes in clinical laboratory values, or vital signs were observed during the study. Four subjects had electrocardiogram (ECG) values with abnormalities of potential clinical concern, however none of the 12-lead ECG abnormalities were noted by the investigator to be of clinical significance.

Summary of All Adverse Events by Treatment (Safety Population)

Preferred Term	Number (%) of Subjects
	Overall (N=18)
Any event	**4 (22)**
Upper respiratory tract infection	1 (6)
Vaginitis bacterial	1 (6)
Vulvovaginitis trichomonal	1 (6)
Contusion	1 (6)
Headache	1 (6)
Oropharyngeal pain	1 (6)
Alopecia	1 (6)

Conclusions:

- Plasma GSK1265744 AUC and Cmax following the free acid [redacted] formulation administration were approximately 12% and 19% lower than those following the administration of current sodium salt tablet formulation.
- Plasma GSK1265744 AUC and Cmax following the free acid [redacted] formulation administration were approximately 48% and 54% lower than those following the administration of current sodium salt tablet formulation.

- GSK1265744 was well tolerated following single dose administration for all three formulations

Effective Date: [redacted]

Synopsis for Study 205712

Name of company: ViiV Healthcare Group of Companies

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744 (Cabotegravir)

Study Number: 205712

Title: Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifabutin on the pharmacokinetics of oral cabotegravir in healthy subjects

Investigator: [redacted], MD, PhD

Study Center: Clinical Unit Cambridge GlaxoSmithKline, Addenbrookes Centre for Clinical Investigation, Addenbrooke's Hospital, Hill's Road, Cambridge, CB2 0GG, United Kingdom

Publication(s): None at the time of this report

Study Period: 06-JUN-2017 - 07-SEP-2017

Phase of Development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
• To compare steady state Cabotegravir (CAB) exposure following 30 mg oral dose once daily with and without Rifabutin (RBT) 300 mg once daily	• Plasma CAB AUC(0-τ), Cmax
Secondary	
• To describe the pharmacokinetics (PK) of CAB 30 mg oral dose once daily administered alone and with RBT	• Plasma CAB Cτ, tmax, t1/2, CL/F
• To assess the safety and tolerability of CAB 30 mg oral dose administered alone and in combination with RBT 300 mg oral dose once daily	• Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, electrocardiogram (ECG), and vital signs assessments.

AUC(0-τ) = area under the plasma concentration time curve from time zero to the last quantifiable time point
Cmax = maximum observed concentration
Cτ = last quantifiable concentration
tmax = time of maximum observed concentration
t1/2 = the elimination half-life
CL/F = apparent oral clearance

Methodology: This was a phase I, single-center, open-label, fixed-sequence, 2-period crossover study conducted in healthy adults to evaluate the effect of Rifabutin (RBT) on the pharmacokinetics (PK) of oral Cabotegravir (CAB) 30 mg. This study took place in 2

treatment periods and a follow-up period. All subjects underwent a screening visit within 30 days from the first dose of study drug. The overall study duration was planned for approximately 10 weeks (4 weeks screening; 2 weeks for treatment Period 1; 2 weeks for treatment Period 2; and 2 weeks follow-up period).

Period 1: CAB 30 mg once daily × 14 days (Treatment A)

Period 2: RBT 300 mg once daily + CAB 30 mg once daily × 14 days (Treatment B)

Study Design

Subjects	Screening Period	Period 1 Days 1 – 14	Period 2 Days 15 – 28	Follow-up
N=15	Within 30 Days of Day 1	Treatment A	Treatment B	~10-14 days after last dose of CAB

Treatment A = CAB 30 mg once daily × 14 days
Treatment B = RBT 300 mg once daily + CAB 30 mg once daily × 14 days

Number of Subjects: Fifteen healthy adult subjects were enrolled into the study and 12 subjects completed dosing and critical assessments.

Diagnosis and Main Criteria for Inclusion: Healthy males and females aged between 18 to 65 years inclusive, with body weight ≥50 kg and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive) were enrolled in this study.

Treatment Administration:

Product name:	Study Treatment	
	Cabotegravir Tablets, 30 mg	MYCOBUTIN Capsules (rifabutin capsules) sourced in the United Kingdom (UK)
Formulation description:	GSK1265744B ([redacted]) [redacted]	Rifabutin, microcrystalline cellulose, sodium lauryl sulphate, magnesium stearate, and silica gel Rifabutin supplied as hard gelatin capsules having an opaque red-brown cap and body, each containing 150 mg of rifabutin
Dosage form:	Tablet	Capsule
Unit dose strength(s)/Dosage level(s):	Tablet strength = 30 mg Dose level = 30 mg	Capsule strength = 150 mg Dose level = 300 mg
Route of Administration:	Administered orally	Administered orally
Dosing instructions[1]:	Administered 1 tablet with 240 mL of water once daily	Administered 2 capsules with 240 mL of water once daily
Manufacturer/Sou	GlaxoSmithKline	Pfizer Limited

Product name:	Study Treatment	
	Cabotegravir Tablets, 30 mg	MYCOBUTIN Capsules (rifabutin capsules) sourced in the United Kingdom (UK)
rce of Procurement:		Ramsgate Road Sandwich Kent CT139NJ United Kingdom
Method of individualizing dosage:	30 mg = one 30 mg tablet	300 mg = two 150 mg capsules
Batch Number	[redacted]	[redacted]

[1] Dosing of study medication on non-PK days could be with or without food, but dosing on serial PK days (Day 14 in Period 1 and Day 28 in Period 2) was after an overnight fast of at least 6 h, and no food was allowed for 4 h after dosing on the serial PK days.

Statistical Methods:

Sample Size Justification

The sample size of 15 was chosen to obtain 12 evaluable subjects, based on an expected withdrawal rate of approximately 20% and the within-subject variability of CAB, to address the objectives of the study. Based on a within-subject coefficient of variation (CVw) of 11.4% and a sample size of 12 evaluable subjects, it was estimated that the half width of the 90% CI for the treatment difference on log-scale would be within 8.3% of the point estimate for AUC(0-τ) and Cmax.

Analysis population

- Safety Population: All subjects who were enrolled in the study and received at least one dose of the study drug were included in the Safety Population. This population was used for the safety analyses, as well as for summarization of baseline/demographic characteristics.

- Pharmacokinetic Concentration Population: The CAB PK Concentration Population included all subjects in the study who underwent plasma PK sampling and had at least one evaluable PK assay results. CAB assay results from samples collected from a subject with emesis occurring within 4 h of the dose was not considered to be evaluable. This population was used for the concentration listing.

- Pharmacokinetic Parameter Population: The CAB PK Parameter Population included subjects who had valid CAB PK parameter estimates. This population was used for plotting the individual concentration-time data.

- Pharmacokinetic Summary Population: The CAB PK Summary Population included subjects who had valid CAB PK parameter estimates from both periods. This population was used for the concentration and PK parameters summary figures and tables and for the statistical analysis of PK parameter data.

Safety Analyses

No formal hypothesis was tested. Safety data were presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

Pharmacokinetic Analyses

Plasma CAB concentration-time data were analyzed by non-compartmental methods with WinNonlin (Phoenix) 6.3. Calculations were based on the actual sampling times recorded during the study and based on nominal sampling times. From the plasma concentration-time data, the following pharmacokinetic parameters were determined, as data permitted: maximum observed plasma concentration (Cmax), time to Cmax (tmax), concentration at the end of the dosing interval (Cτ), apparent terminal phase half-life (t1/2), area under the concentration-time curve over one dosing interval [AUC(0-τ)], and apparent oral clearance (CL/F).

Summary

Demographics:

Number of Subjects	CAB 30 mg	RBT 300 mg + CAB 30 mg
Number of subjects planned [N]	15	15
Number of subjects enrolled [N][1]	15	14
Number of subjects completed as planned [n (%)]	14 (93)	12 (86)
Number of subjects prematurely discontinued (any reason) [n (%)]	1 (7)	2 (14)
Number of subjects withdrawn for AE [n (%)][1]	0	2 (14%)
Reasons for subject withdrawal [n (%)]		
Subject Reached Protocol-Defined Stopping Criteria[1]	1 (7)	0

[1] One subject discontinued prior to RBT 300 mg + CAB 30 mg co-administration. The subject developed an AE of elevated ALT in the CAB 30 mg only period. The subject reached the protocol-defined stopping criteria of elevated ALT and was withdrawn from the study. However, this subject's withdrawal was not reported under "AEs that led to withdrawal". The reason for the withdrawal was reported as "Subject Reached Protocol-Defined Stopping Criteria".

Demographics	CAB 30 mg (N=15)	RBT 300 mg + CAB 30 mg (N=14)
Age in Years [Mean (SD)]	43.7 (10.51)	44.4 (10.46)
Sex [n (%)]		
Male	15 (100)	14 (100)
BMI (kg/m^2) [Mean (SD)]	26.32 (3.120)	26.60 (3.040)
Height (cm) [Mean (SD)]	178.20 (7.262)	178.57 (7.387)
Weight (kg) [Mean (SD)]	83.78 (12.310)	84.96 (11.850)
Ethnicity [n (%)]		
Not Hispanic or Latino	15 (100)	14 (100)
Race [n (%)]		
Asian - Central/South Asian Heritage	1 (7)	1 (7)
White - White/Caucasian/European	14 (93)	13 (93)

Safety Results

Summary of All Adverse Events (Safety Population)

All Adverse Events by Preferred Term n (%)	In Treatment Phase		Follow-up Phase (N=15)
	CAB 30 mg (N=15)	RBT 300 mg + CAB 30 mg (N=14)	
Subjects with any AE(s), n (%)	1 (7)	7 (50)	6 (40)
Subjects with any drug-related AE(s), n (%)	0	1 (7)	2 (13)
Alanine aminotransferase increased	0	1 (7)	2 (13)
Blood creatine phosphokinase increased	1 (7)	0	1 (7)
Body temperature increased	0	1 (7)	0
Contusion	1 (7)	0	0
Skin abrasion	0	1 (7)	0
Leukopenia	0	1 (7)	0
Neutropenia	0	1 (7)	1 (7)
Pyrexia	0	1 (7)	2 (13)
Viral Infection	0	1 (7)	0
Musculoskeletal stiffness	0	1 (7)	0
Headache	0	1 (7)	0
Hyperkeratosis	0	1 (7)	0
Contact dermatitis	0	0	1 (7)
Food poisoning	0	0	1 (7)
Feeling of body temperature change	0	0	1 (7)
Lethargy	0	0	1 (7)
Cough	0	0	1 (7)
Phosphokinase increase	0	0	1 (7)
Lymphopenia	0	0	1 (7)

CAB 30 mg once daily × 14 days
RBT 300 mg once daily + CAB 30 mg once daily × 14 days

There were no fatal events reported in this study.

There was one non-fatal serious adverse event (SAE) of elevated ALT level reported in the RBT 300 mg + CAB 30 mg co-administration treatment period. ALT levels were elevated to 86 IU/L on Day 21 (on-treatment phase; higher than normal), which fluctuated until 3 weeks after dosing had ceased, when a peak ALT elevation of 417 (Grade 3) was reported. The SAE was considered to be related to the study medication by the investigator. The SAE resolved 65 days after the first dose of study medication.

No clinically significant abnormal changes in vital signs or ECG values were reported in the study.

Pharmacokinetic results:

CAB was readily absorbed with median tmax values of 3 hours when administered alone and 2.5 hours when administered with RBT. Inter-subject variability was low to moderate with %CVb ranging from 24.3% to 36.3%. CAB CL/F was higher following repeat-dose co-administration with RBT, resulting in reductions in CAB AUC(0-τ), Cmax, and Cτ as compared to CAB alone. Plasma t1/2 was not estimated for either period due to limited PK sampling in the terminal phase.

Summary of Derived Plasma Cabotegravir Pharmacokinetic Parameters

Treatment	AUC(0-τ)[1] (h*µg/mL)	Cmax[1] (µg/mL)	tmax[2] (h)	Cτ[1] (µg/mL)	CL/F[1] (L/h)
CAB (n=12)	104 (87.1, 124) [28.3]	6.36 (5.45, 7.42) [24.7]	3.00 (1.00, 4.00)	3.36 (2.72, 4.15) [34.3]	0.289 (0.242, 0.344) [28.3]
RBT + CAB (n=12)	81.7 (67.9, 98.4) [29.9]	5.25 (4.51, 6.11) [24.3]	2.50 (1.00, 4.00)	2.48 (1.98, 3.10) [36.3]	0.367 (0.305, 0.442) [29.9]

[1]Geometric mean (95% CI) [CVb%]
[2]Median (range)
CAB: 30 mg once daily × 14 days
RBT + CAB: RBT 300 mg once daily + CAB 30 mg once daily × 14 days

RBT increased CAB oral clearance by 27% and reduced CAB AUC(0-τ), Cmax, and Cτ by 21%, 17%, and 26%, respectively. The median Cτ observed 24 h following the final dose in Period 1 was the same as the median Day 14 pre-dose concentration, and the median Cτ observed 24 h following the final dose in Period 2 was similar to the median pre-dose concentrations observed on Days 26 and 27.

Summary of Statistical Analysis of Cabotegravir AUC (0-tau) and Cmax (PK Summary Population)

CAB PK Parameter	Treatment Comparison: RBT + CAB vs. CAB (GLSM ratio, 90% CI)
AUC(0-τ)	0.786 (0.743, 0.831)
Cmax	0.825 (0.761, 0.895)
Cτ	0.738 (0.702, 0.776)
CL/F	1.272 (1.204, 1.345)

CAB: 30 mg once daily x 14 days
RBT + CAB: RBT 300 mg once daily + CAB 30 mg once daily × 14 days

Conclusions:

- CAB CL/F was higher by 27% following repeat-dose co-administration with RBT, resulting in reductions in CAB AUC(0-τ), Cmax, and Cτ by 21%, 17%, and 26%, respectively, as compared to CAB alone.

- The moderate reduction in plasma CAB exposure by RBT is not considered clinically relevant following oral CAB administration, as concentrations remained above levels associated with durable suppression of HIV infection in Phase 2 studies.

- No new safety signals were detected during the study. Cabotegravir was generally tolerated when administered alone an in combination with Rifabutin.

Effective Date: [redacted]

Synopsis for Study LAI116181

Study Number: LAI116181

Title: A Phase 1, Open-Label, Crossover Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 and Rilpivirine and Dolutegravir and Rilpivirine in Healthy Adult Subjects

Investigator(s): [redacted], PharmD

Study center(s): [redacted], United States [redacted]

Publication(s): None at the time of this report

Study period: 07Nov2011 – 20Feb2012

Phase of development: I

Objectives:

Primary

To describe and compare steady-state plasma dolutegravir (DTG) pharmacokinetics following administration of DTG 50 mg every 24 hours (q24h) with and without rilpivirine (RPV) 25 mg q24h.

To describe and compare steady-state plasma GSK1265744 pharmacokinetics following administration of GSK1265744 30 mg q24h with and without RPV 25 mg q24h.

To describe and compare steady-state plasma RPV pharmacokinetics following administration of RPV 25 mg q24h with and without GSK1265744 30 mg q24h.

To describe and compare steady-state plasma RPV pharmacokinetics following administration of RPV 25 mg q24h with and without DTG 50 mg q24h.

Secondary

To assess the safety and tolerability of repeat dose DTG 50 mg q24h with or without RPV 25 mg q24h.

To assess the safety and tolerability of repeat dose GSK1265744 30 mg q24h with and without RPV 25 mg q24h.

To assess the safety and tolerability of repeat dose RPV 25 mg q24h.

Methodology:

LAI116181 was a single-center, two-cohort, open-label, three-period, fixed-sequence cross over study in healthy adult subjects.

Subjects (Cohort 1 and Cohort 2) underwent:

A screening visit (30 days prior to the first dose of study drug)

Three treatment periods (There was a washout period of at least 7 days for Cohort 1 and at least 14 days for Cohort 2; between Period 1 and Period 2 but no washout between Period 2 and Period 3. Day 1 of Period 3 started the day after the last day in Period 2).

In Cohort 1, subjects received DTG 50 mg q24h for 5 days (Treatment A) in Period 1 followed by a 7-day washout period. Subjects were then administered RPV 25 mg q24h for 11 days (Treatment B) in Period 2, followed by DTG 50 mg q24h in combination with RPV 25 mg q24h for 5 days (Treatment C) in Period 3.

In Cohort 2, subjects received GSK1265744 30 mg q24h for 12 days (Treatment D) in Period 1, followed by a 14-day washout period. Subjects were then administered RPV 25 mg q24h for 12 days (Treatment B) in Period 2 and then GSK1265744 30 mg q24h in combination with RPV 25 mg q24h for 12 days (Treatment E) in Period 3.

Safety evaluations and serial pharmacokinetic (PK) samples were collected during each treatment period. In Cohort 1, serial blood PK samples were collected on Day 5 of Periods 1 and 3 for DTG PK analysis. Serial blood PK samples were also collected on Day 11 of Period 2 and Day 5 of Period 3 for RPV PK analysis.

In Cohort 2, serial blood samples were collected on Day 12 of Periods 1 and 3 for GSK1265744 PK analysis. Serial blood samples were also collected on Day 12 of Periods 2 and 3 for RPV PK analysis.

A follow-up visit 7 to 14 days after the last dose of study drug.

Number of subjects:

Twenty-eight subjects were enrolled (16 subjects in Cohort 1 and 12 subjects in Cohort 2) and 27 subjects completed the study (16 subjects in Cohort 1 and 11 subjects in Cohort 2).

Diagnosis and main criteria for inclusion:

Healthy male and female subjects as determined by medical evaluation including medical history, physical examination, laboratory tests and cardiac monitoring, between 18 to 55 years of age, with body mass index (BMI) within the range 18.5 to 31.0 kg/m^2 (inclusive) were eligible for inclusion in this study.

Treatment administration:

This was an open-label study.

A description of each oral regimen is provided below:

Cohort 1:
Treatment A = DTG 50 mg q24h x 5 days (Reference Treatment)
Treatment B = RPV 25 mg q24h x 11 days (Reference Treatment)
Treatment C = RPV 25 mg q24h + DTG 50 mg q24h x 5 days (Test Treatment)

Cohort 2:
Treatment D = GSK1265744 30 mg q24h x 12 days (Reference Treatment)
Treatment B = RPV 25 mg q24h x 12 days (Reference Treatment)
Treatment E = RPV 25 mg q24h + GSK1265744 30 mg q24h x 12 days (Test Treatment)

Batch number for GSK1265744 used for the study was [redacted]; DTG was [redacted]; and RPV (batch number [redacted]) was purchased by the site.

Criteria for evaluation:

Primary

Plasma DTG steady state area under the concentration-time curve over the dosing interval (AUC(0-τ)), maximum observed concentration (Cmax), and time of occurrence of Cmax (tmax), pre-dose (trough) concentration at the end of the dosing interval (Cτ), following 50 mg q24h administration with and without RPV 25 mg q24h.

Plasma GSK1265744 steady state AUC(0-τ), Cmax, tmax, and Cτ following GSK1265744 30 mg q24h administration with and without RPV 25 mg q24h.

Plasma RPV steady state AUC(0-τ), Cmax, tmax, and Cτ following RPV 25 mg q24h administration with and without DTG 50 mg q24h or GSK1265744 30 mg q24h.

Secondary

Safety and tolerability parameters, including adverse event (AE), concurrent medication, clinical laboratory, electrocardiogram (ECG), and vital signs assessments.

Statistical methods:

No formal hypothesis was tested in this study. An estimation approach was used to evaluate the effect of drug-interaction. The sample size of 16 and 12 subjects in Cohort 1 and Cohort 2 respectively was chosen based on expected withdrawal rate of approximately 10% and the within-subject variability to address the objectives of the study.

The DTG, GSK1265744 and RPV PK Concentration Populations (all subjects who underwent plasma PK sampling and had evaluable PK assay results) were used for the concentration listing, plotting and PK parameter listing. The PK DTG, GSK1265744, and RPV Summary Populations (all subjects who underwent plasma PK sampling and had evaluable DTG, GSK1265744 or RPV PK parameters estimated from dosing alone and in combination) were used for PK parameter plotting, PK parameter summary and for analysis of PK parameters data.

Plasma concentrations of DTG, GSK1265744, and RPV were determined using a validated high-performance liquid chromatography-tandem mass spectrometry (HPLC/MS/MS) method. Plasma DTG, GSK1265744, and RPV concentration-time data were analyzed by non-compartmental methods with WinNonlin Professional Edition version 5.3.

Individual subject PK parameter values and descriptive summaries of each parameter were reported by treatment. The focus of the statistical analysis was to estimate the two-way drug-interaction effect of RPV on DTG and GSK1265744 PK parameters and effect of DTG and GSK1265744 on RPV PK parameters. Analysis of variance (ANOVA) was performed using SAS mixed effect models procedure to assess the relative effect of RPV on DTG and GSK1265744, and the effect of DTG and GSK1265744 on RPV (AUC(0-τ), Cmax, and Cτ, separately for each cohort). The point estimates and corresponding 90% confidence intervals for the parameters of interest were provided for the between treatment comparisons. Plasma tmax, pre-dose plasma concentration (C0), minimum observed concentration (Cmin) and terminal phase half-life (t½) for all analytes were summarized with the descriptive statistics. All of the PK parameters were log-transferred, except tmax.

All subjects who were randomized in the study and received at least one dose of study drug were included in the Safety Population. This was the population for the safety analyses, and for summarization of baseline/demographic characteristics.

2.7.6 Synopses of Individual Studies

Summary:

Demographics:

Number of Subjects	Cohort 1	Cohort 2	Overall
Planned, N:	16	12	28
Enrolled, N:	16	12	28
All subjects (Safety) Population, n (%):	16 (100)	12 (100)	28 (100)
DTG PK Concentration Population, n (%):	16 (100)	0	16 (57)
DTG PK Summary Population, n (%):	16 (100)	0	16 (57)
RPV PK Concentration Population, n (%):	16 (100)	12 (100)	28 (100)
RPV PK Summary Population, n (%):	16 (100)	11 (92)	27 (96)
GSK1265744 PK Concentration Population, n (%):	0	12 (100)	12 (43)
GSK1265744 PK Summary Population, n (%):	0	11 (92)	11 (39)
Subjects Completed, n (%):	16 (100)	11 (92)	27 (96)
Subjects withdrawn (any reason), n (%):	0	1 (8)	1 (4)
Subjects withdrawn for SAE, n (%):	0	0	0
Subjects withdrawn for AE, n (%):	0	0	0
Reasons for subject withdrawal			
Investigator Discretion, n (%)	0	1 (8)	1 (4)
Demographics	**Cohort 1**	**Cohort 2**	**Overall**
Age in Years, Mean (SD)	34.4 (11.33)	27.4 (10.57)	31.4 (11.37)
Sex, n (%)			
Female:	2 (13)	2 (17)	4 (14)
Male:	14 (88)	10 (83)	24 (86)
BMI (kg/m^2), Mean (SD)	26.51 (2.58)	27.03 (3.24)	26.73 (2.83)
Height (cm), Mean (SD)	178.5 (10)	175.75 (12.71)	177.32 (11.11)
Weight (kg), Mean (SD)	84.46 (10.56)	83.74 (15.23)	84.15 (12.51)
Ethnicity, n (%)			
Hispanic or Latino:	4 (25)	1 (8)	5 (18)
Not Hispanic or Latino:	12 (75)	11 (92)	23 (82)
Race, n (%)			
African American/African Heritage	4 (25)	7 (58)	11 (39)
American Indian or Alaskan Native	1 (6)	0	1 (4)
Native Hawaiian or Other Pacific Islander	1 (6)	0	1 (4)
White – White/Caucasian/European Heritage	10 (63)	5 (42)	15 (54)

SAE=Serious Adverse Event, SD = Standard Deviation

PK Summary: The results of the statistical comparison of plasma PK parameters of all analytes are presented in the tables below:

Plasma Pharmacokinetic Parameters of DTG with and without RPV (DTG PK Summary Population)

Plasma DTG PK Parameter	DTG[1] (n=16)	DTG + RPV[1] (n=16)
AUC(0-τ) (μg.h/mL)	48.8 [40.8, 58.4] (35)	54.7 [46.1, 64.9] (33)
Cmax (μg/mL)	3.46 [2.96, 4.04] (30)	3.90 [3.43, 4.44] (25)
Cτ (μg/mL)	1.07 [0.850, 1.34] (45)	1.31 [1.04, 1.65] (46)
Tmax[2] (h)	3.50 (1.0-4.0)	3.50 (1.0-4.0)

1. Geometric mean [95% Confidence Interval (CI)] (Between subject variability CVb%)
2. Median (range)

Treatments:
DTG = DTG 50 mg once daily (QD) x 5 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days

Plasma Pharmacokinetic Parameters of GSK1265744 with and without RPV (GSK1265744 PK Summary Population)

Plasma GSK1265744 PK Parameter	GSK1265744[1] (n=11)	GSK1265744 + RPV[1] (n=11)
AUC(0-τ) (μg.h/mL)	142 [118, 171] (28)	159 [138, 183] (21)
Cmax (μg/mL)	8.22 [6.83, 9.89] (28)	8.65 [7.69, 9.72] (18)
Cτ (μg/mL)	4.65 [3.73, 5.78] (33)	5.29 [4.49, 6.23] (25)
Tmax[2] (h)	4.00 (2.0-4.0)	4.00 (1.0-4.0)

1. Geometric mean [95% CI] (CVb%)
2. Median (range)

Treatments:
GSK1265744 = GSK1265744 30 mg QD x 12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD x 12 days

Plasma RPV Pharmacokinetic Parameters (RPV PK Summary Population)

Plasma RPV PK Parameter	Cohort 1: RPV with or without DTG	
	RPV[1] (n=16)	DTG + RPV[1] (n=16)
AUC(0-τ) (ng.h/mL)	2227 [1872, 2649] (33)	2368 [1985, 2825] (34)
Cmax (ng/mL)	148 [128, 173] (29)	164 [136, 197] (36)
Cτ (ng/mL)	74.5 [60.3, 92.2] (41)	90.5 [70.9, 115] (48)
Tmax[2] (h)	4.00 (4.0-6.0)	4.00 (2.0-5.0)
Plasma RPV PK Parameter	**Cohort 2: RPV with or without GSK1265744**	
	RPV[1] (n=11)	GSK1265744 + RPV[1] (n=11)
AUC(0-τ) (ng.h/mL)	2473 [2034, 3008] (30)	2441 [1916, 3110] (37)
Cmax (ng/mL)	171 [137, 213] (34)	165 [120, 226] (50)
Cτ (ng/mL)	87.4 [66.8, 114] (42)	80.3 [58.6, 110] (50)
Tmax[2] (h)	4.00 (3.0-6.0)	4.00 (3.0-5.0)

1. Geometric mean [95% CI] (CVb%)
2. Median (range)

Treatments:
Cohort 1 RPV = RPV 25 mg QD x 11 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days
Cohort 2 RPV = RPV 25 mg QD x 12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD x 12 days

Plasma DTG PK Treatment Comparison (DTG PK Summary Population)

PK Parameter	Geometric least square (GLS) Mean Ratio [90% CI]
	DTG + RPV vs DTG
AUC(0-τ)	1.12 [1.05, 1.19]
Cmax	1.13 [1.06, 1.21]
Cτ	1.22 [1.15, 1.30]

Treatments:
DTG = DTG 50 mg QD x 5 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days

Plasma GSK1265744 PK Treatment Comparison (GSK1265744 PK Summary Population)

PK Parameter	GLS Mean Ratio [90% CI]
	GSK1265744 + RPV vs GSK1265744
AUC(0-τ)	1.12 [1.05, 1.19]
Cmax	1.05 [0.963, 1.15]
Cτ	1.14 [1.04, 1.24]

Treatments:
GSK1265744 = GSK1265744 30 mg QD x 12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD x 12 days

Plasma RPV PK Treatment Comparison (RPV PK Summary Population)

PK Parameter	GLS Mean Ratio [90% CI]	
	Cohort 1 DTG + RPV vs RPV	Cohort 2 GSK1265744 + RPV vs RPV
AUC(0-τ)	1.06 [0.976, 1.16]	0.987 [0.890, 1.09]
Cmax	1.10 [0.992, 1.22]	0.963 [0.849, 1.09]
Cτ	1.21 [1.07, 1.38]	0.919 [0.789, 1.07]

Treatments:
Cohort 1 RPV = RPV 25 mg QD x 11 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days
Cohort 2 RPV = RPV 25 mg QD x 12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD x 12 days

Safety Results:

DTG at 50 mg, RPV at 25 mg and GSK1265744 at 30mg q24h (QD) were generally well tolerated in healthy subjects in this study. All AEs were Grade 1, with the exception of three AEs (insomnia, catheter site inflammation and toothache) which were Grade 2. No subject became pregnant, died, or experienced a serious adverse event (SAE), Grade 3/4 AE, or AE leading to premature discontinuation of investigational product during the study. One subject on GSK1265744 and RPV developed a Grade 4 creatinine kinase (CK) elevation that was attributed to strenuous exercise. No other clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed during the study.

Summary of All Adverse Events by Treatment (Safety Population)

Preferred Term	Cohort 1			Cohort 2		
	DTG (N=16)	RPV (N=16)	DTG + RPV (N=16)	GSK1265744 (N=12)	RPV (N=12)	GSK1265744 + RPV (N=12)
Subject with Any AE, n (%)	2 (13)	3 (19)	8 (50)	3 (25)	2 (17)	5 (42)
Headache	2 (13)	1 (6)	3 (19)	0	1 (8)	2 (17)
Dizziness	0	0	1 (6)	0	0	1 (8)
Somnolence	0	0	0	0	0	1 (8)
Toothache	0	0	0	0	0	1 (8)
Oral herpes	0	0	0	0	0	1 (8)
Decreased appetite	0	0	0	1 (8)	0	1 (8)
Catheter site related reaction	0	0	2 (13)	0	0	0
Catheter site inflammation	0	0	1 (6)	0	0	0
Dyspepsia	0	0	1 (6)	0	0	0
Pharyngitis	0	0	1 (6)	0	0	0
Abnormal dreams	0	1 (6)	0	0	0	0
Insomnia	0	1 (6)	0	0	0	0
Cough	0	0	0	2 (17)	0	0
Arthralgia	0	0	0	0	1 (8)	0
Dermatitis contact	0	1 (6)	0	0	0	0

Treatments:
Cohort 1: DTG = DTG 50 mg QD x 5 days
RPV = RPV 25 mg QD x 11 days
DTG + RPV = DTG 50 mg QD + RPV 25 mg QD x 5 days
Cohort 2: GSK1265744 = GSK1265744 30 mg QD x 12 days
RPV = RPV 25 mg QD x 12 days
GSK1265744 + RPV = GSK1265744 30 mg QD + RPV 25 mg QD x 12 days

Conclusions:

Pharmacokinetic parameters of each drug alone were similar to those when given in combination demonstrating a lack of interaction between RPV and DTG or GSK1265744.

Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ), and Cmax, and a 22% increase in Cτ.

Co-administration of GSK1265744 with RPV resulted in no change in GSK1265744 AUC(0-τ), Cmax, and Cτ.

Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in Cτ.

Co-administration of GSK1265744 with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and an 8% decrease in Cτ.

DTG, RPV and GSK1265744 given alone or in combination as DGT + RPV or GSK1265744 were well tolerated in this study. No deaths, serious AEs, Grade 3/4 AEs, or withdrawals due to AEs.

Effective Date: [redacted] 20[redacted]

Synopsis for Study LAI117010

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available at the time of this report **Name of active substance:** Cabotegravir

Study Number: LAI117010

Title: Phase I, single-center, open label, fixed-sequence cross-over study to evaluate the effect of rifampin on the pharmacokinetics of oral cabotegravir in healthy subjects

Investigator: [redacted], MD

Study Center: [redacted] in the United States

Publication(s): None at the time of this report

Study Period: 01-JUL-2015 to 11-SEP-2015

Phase of development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
To compare the single dose (SD) pharmacokinetics (PK) of cabotegravir (CAB) oral 30 mg when co-administered with rifampin (RIF) 600 mg once daily (QD) at steady-state to those of CAB oral 30 mg administered alone.	• Plasma CAB maximum observed concentration (Cmax), area under the concentration-time curve over infinite time (AUC[0-inf]).
Secondary	
To describe PK of CAB oral 30 mg once daily administered alone and co-administered with RIF.	Plasma CAB concentration at 24 hours (C24), area under the concentration-time curve up to the last measurable concentration (AUC [0-t]), time of occurrence of Cmax (tmax), half-life (t1/2), apparent clearance (CL/F)
To assess the safety and tolerability of CAB 30 mg oral administered alone and in combination with RIF 600 mg once daily.	Safety and tolerability parameters, including adverse events (AEs), concurrent medication, clinical laboratory screens, electrocardiogram (ECG) and vital signs assessments.

Methodology:

This was a phase I, single-center, open label, fixed-sequence crossover study in healthy adults to evaluate the effect of RIF on the PK and safety of oral CAB 30 mg.

Study Design

Subjects	Screening Period	Period 1 Day 1 – Day 7	Period 2 Days 8 - 20	Period 3 Days 21 - 28	
N=15	Within 30 Days of Day 1	Single dose CAB 30 mg (Day 1)	RIF 600 mg once daily for 13 days (Days 8 – 20)	Single dose CAB 30 mg on Day 21 + RIF 600 mg QD for 8 days (Days 21-28)	Follow-up Day 38 –42

Treatment A: Single dose CAB 30 mg (Day 1)
Treatment B: RIF 600 mg QD for 13 days (Days 8 – 20)
Treatment C: CAB 30 mg on Day 21 (single dose) + RIF 600 mg QD for 8 days (Days 21-28)

Subjects enrolled in the study received a single dose (SD) of CAB 30 mg on day 1, followed by collection of serial PK samples over 8 days. Subjects then received RIF 600 mg daily on days 8-28 with co-administration of a single dose of CAB 30 mg on day 21 and collection of serial PK samples from days 21 to 28. Safety and tolerability were assessed throughout the study through assessment of AEs and clinical laboratory tests.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were healthy males and females between 18 and 65 years of age, body weight ≥50 kg and body mass index (BMI) within the range 18.5 – 31.0 kg/m^2 (inclusive); and alanine aminotransferase (ALT), alkaline phosphatase and bilirubin ≤1xULN. Subjects were excluded if they had a current or chronic history of liver disease, or known hepatic or biliary abnormalities and history of clinically significant cardiovascular disease.

Number of Subjects:

Approximately 15 subjects were enrolled in the study and all subjects completed the study.

Treatment Administration:

Treatment	Drug	Dose/Form/Route	Frequency/Duration	Batch Number
Treatment A	Cabotegravir sodium	30 mg/Tablet/Oral	Single dose	[redacted]
Treatment B	Rifadin (rifampin)	600 mg/Capsule/Oral	QD/13 days	[redacted]
Treatment C	Cabotegravir sodium	30 mg/Tablet/Oral	Single dose	[redacted]
	Rifadin (rifampin)	600 mg/Capsule/Oral	QD/8 days	[redacted]

Statistical Methods:

Sample size justification

Based on a within-subject coefficient of variation (CVw) of 11.4% and a sample size of 12 evaluable subjects, it was estimated that the half width of the 90% confidence interval for the treatment difference on log-scale is within 8.3% of the point estimate for AUC(0-t)/AUC(0-∞) and Cmax. If the point estimate of the ratio of geometric means was 1, then 90% confidence interval is approximately (0.92, 1.09).

Analysis Populations

The following populations were used for the analysis and reporting of data:

Screening Population: All subjects who had signed the consent form were included in this population.

Safety Population: All subjects who enrolled into the study and received at least one dose of study drug were included in the Safety Population.

Pharmacokinetic Concentration Population: The CAB PK Concentration Population included all subjects who underwent plasma PK sampling and had evaluable PK assay results.

Pharmacokinetic Parameter Population: The CAB PK Parameter Population for this study included all subjects with CAB PK parameters estimated.

Pharmacokinetic Summary Population: The CAB PK Summary Population for this study included subjects who had CAB PK parameter estimates from both serial PK sampling time periods.

PK Analyses

Plasma CAB concentration-time data were analyzed by non-compartmental methods with WinNonlin (Phoenix) 6.3. Calculations were based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following PK parameters were determined: AUC(0-∞), AUC(0-t), C24, Cmax, tmax, t1/2, and CL/F.

Statistical Analyses

Descriptive summaries presented for PK data included n, mean, standard deviation (SD), coefficient of variation for the mean (%CV), median, minimum, and maximum, geometric mean with associated 95% confidence interval (CI), and the between-subject CV (%CVb) for the geometric mean.

The point estimates of the geometric least squares mean (GLSM) ratio for the selected PK parameters and the associated 90% CIs were provided for treatment comparisons (test:reference).

Safety data were presented in tabular and/or graphical format and summarized descriptively according to GlaxoSmithKline's (GSK's) Integrated Data Standards Library (IDSL) standards whereas, n and percent were used as summary statistics for categorical variables.

Summary

A total of 15 subjects entered the study and received all study treatments. All the subjects completed the study.

Demographics:

Number of Subjects	**Overall**
Number of subjects planned [N]	15
Number of subjects entered [N]	15
Number of subjects completed as planned [n (%)]	15 (100)
Number of subjects withdrawn (any reason) [n (%)]	0
Age in Years [Mean (SD)]	48.5 (14.11)
Sex [n (%)]	
Female:	5 (33)
Male:	10 (67)
BMI (kg/m^2) [Mean (SD)]	26.71 (3.578)
Height (cm) [Mean (SD)]	172.41 (6.979)
Weight (kg) [Mean (SD)]	79.63 (12.788)
Ethnicity [n (%)]	
Hispanic or Latino:	1 (7)
Not Hispanic or Latino:	14 (93)
Race [n (%)]	
African American/African Heritage	3 (20)
White – White/Caucasian/European Heritage	12 (80)

Safety Results

Most Frequent Adverse Events	CAB 30 mg SD	RIF 600 mg QD	CAB 30 mg SD + RIF 600 mg QD	Overall
	n (%)	n (%)	n (%)	n
Any AE	3 (20)	15 (100)	1 (7)	15 (100)
Any AE related to investigational product	1 (7)	15 (100)	0	15 (100)
Most Common AEs: (≥ 10% overall):				
Chromaturia	0	15 (100)	0	15 (100)
Decreased appetite	0	2 (13)	0	2 (13)
Headache	1 (7)	1 (7)	0	2 (13)

Treatment A: Single dose CAB 30 mg (Day 1)
Treatment B: RIF 600 mg QD for 13 days (Days 8 – 20)
Treatment C: CAB 30 mg on Day 21 (single dose) + RIF 600 mg QD for 8 days (Days 21-28)

There were no deaths, no serious AEs (SAEs), and no significant AEs reported in this study. No clinically significant changes in laboratory values over time in hematology, chemistry, or urinalysis results were observed during this study. No clinically significant changes over time were noted in any ECG and vital sign evaluations. There were no pregnancies reported in the study.

Pharmacokinetics

Summary of Plasma CAB Pharmacokinetic Parameters in LAI117010

Treatment	AUC(0-∞)[1] (h*μg/mL)	Cmax[1] (μg/mL)	tmax[2] (h)	C24[1] (μg/mL)	t1/2[1] (h)	CL/F[1] (L/h)
CAB (n=15)	146 (128, 167) [23.9]	3.61 (3.28, 3.96) [16.9]	2.00 (1.00-6.00)	1.72 (1.49, 1.97) [25.5]	38.5 (35.7, 41.6) [13.9]	0.205 (0.180, 0.234) [23.9]
CAB + RIF (n=15)	59.7 (52.8, 67.5) [22.4]	3.39 (3.05, 3.76) [19.1]	1.00 (1.00-4.00)	0.860 (0.749, 0.988) [25.5]	16.4 (14.7, 18.2) [19.5])	0.502 (0.444, 0.568) [(22.4]

1 Geometric mean (95% CI) [CVb%]
2 Median (range)
CAB: Single dose CAB 30 mg (Day 1)
CAB+RIF: CAB 30 mg on Day 21 (single dose) + steady state RIF 600 mg QD (Days 8-28)

When CAB 30 mg was coadministered with RIF 600 mg, CAB AUC(0-∞) was decreased by 59%; no effect was observed in CAB Cmax; CAB CL/F was increased by 140%; and t1/2 decreased by 57%.

Summary of Plasma CAB PK Parameters Treatment Comparisons

CAB PK Parameter	Treatment Comparison: CAB + RIF vs CAB (GLSM ratio, 90% CI)
AUC(0-∞)	0.41 (0.36, 0.46)
Cmax	0.94 (0.87, 1.02)
CL/F	2.4 (2.2, 2.8)
t1/2	0.43 (0.39, 0.46)

CAB: Single dose CAB 30 mg (Day 1)
CAB+RIF: CAB 30 mg on Day 21 (single dose) + steady state RIF 600 mg QD (Days 8-28)

Conclusions:

- Co-administration of steady-state RIF 600 mg with single dose oral CAB 30mg decreased CAB AUC(0-∞) by 59% and had no impact on CAB Cmax.
- CAB administered alone or in combination with steady state RIF was well tolerated in the study with no deaths, no serious or significant AEs, no vital signs or ECG abnormalities, and no Grade 3 or Grade 4 laboratory abnormalities reported in the study.
- Co-administration of RIF with oral CAB 30 mg once daily is not recommended.

Effective Date: [redacted]

Synopsis for Study LAI117011

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available/known at the time of this report

Name of active substance: Cabotegravir/GSK1265744

Study Number: LAI117011

Title: An Open-label Study to Evaluate the Pharmacokinetics of an Oral Contraceptive Containing Levonorgestrel and Ethinyl Estradiol when Co-administered with GSK1265744 in Healthy Adult Female Subjects

Investigator(s): [redacted], BM BCh, DPhil, BA

Study Center(s): The study was conducted at one center at [redacted], United Kingdom [redacted]

Publication(s): None at the time of this report.

Study Period: 14-AUG-2014 - 01-DEC-2014

Phase of development: I

Objectives and Endpoints (criteria for evaluation):

Objective	Endpoint
Primary	
To demonstrate the lack of an effect of cabotegravir (GSK1265744; CAB) 30mg on the exposure of levonorgestrel (LNG) and ethinyl estradiol (EE) in healthy female subjects.	Plasma area under the concentration-time curve over the dosing interval (AUC[0-τ]) of LNG and EE following Microgynon with and without CAB.
Secondary	
To evaluate the safety and tolerability of oral CAB 30 mg q24h when given in combination with Microgynon.	Safety and tolerability parameters, including adverse events (AEs), clinical laboratory tests, electrocardiogram (ECG), and vital signs assessments.
To investigate the effect of CAB on other pharmacokinetic (PK) parameters of LNG and EE.	Maximum observed plasma concentration (Cmax), plasma concentration at the end of the dosing interval (Cτ), time to maximum drug concentration (tmax), and oral clearance (CL/F) of LNG and EE after Microgynon alone and after Microgynon with CAB.
To assess the impact of CAB on the pharmacodynamic (PD) effects of Microgynon on endogenous luteinizing hormone (LH), follicle stimulating hormone (FSH), and progesterone levels when given in combination compared with these parameters when Microgynon is administered alone.	Predose serum levels of LH and FSH on Days 1, 10, 11, 21 and 22. Predose serum levels of progesterone on Days 1, 10, 11, 21 and 22.
To evaluate the PK of CAB when co-administered with LNG and EE.	CAB PK parameters: AUC(0-τ), Cmax, tmax, Cτ and CL/F

Methodology:

This study was an open-label, fixed-sequence crossover study in healthy adult female subjects. Subjects who were not already on a stable regimen of Microgynon were switched to Microgynon for a minimum of one cycle of 21 days to evaluate tolerability, followed by a washout period of 7 days (when no active treatment was received), before continuing to Treatment Period 1. During Treatment Period 1, subjects received Microgynon once daily (QD) on Days 1-10. Subjects were asked to come to the research unit the morning of Day 1. Following completion of the required measurements on Day 1, subjects received a dose of Microgynon and were dispensed one package of Microgynon for Days 2-8 dosing (at home). Subjects returned to the study center on Day 8 and remained through the morning of Day 11 (of Treatment Period 2). On the morning of Day 9, blood draws were collected to assess the predose concentration of LNG and EE. Authorized study center personnel administered the subject's dose of Microgynon after the predose blood draws were collected and recorded the date and time of dosing. On the morning of Day 10, predose PD blood samples for LH, FSH,

progesterone, and predose PK samples for LNG, and EE were collected. Subjects were dosed with Microgynon followed by 24-hour serial PK blood collection for LNG and EE. On the morning of Day 11, a 24-hour LNG and EE PK sample and a predose blood sample for LH, FSH and progesterone were collected. Subjects were dosed with a morning dose of Microgynon and their first dose of oral CAB 30mg. After Day 11, subjects were discharged from the research unit with the remaining Microgynon and CAB tablets for Days 12-19 dosing (at home). The duration of Period 1 was 10 days (Day 1-10 Microgynon only).

During Treatment Period 2, subjects were instructed to take their study drugs (Microgynon + CAB) at the same time each day on Days 12-19. Subjects returned to the study center on Day 19 and remained in the unit through the morning of Day 22. On the morning of Day 20, blood draws were collected to assess the predose concentration of CAB, LNG and EE. On the morning of Day 21, predose PD blood samples for LH, FSH, progesterone, and predose PK samples for LNG, EE, and CAB were collected. Subjects then received a dose of Microgynon and CAB, and underwent 24-hour serial PK blood collection for LNG, EE, and CAB. On the morning of Day 22, a 24-hour LNG, EE, and CAB PK sample and a predose blood sample for LH, FSH and progesterone were collected. After Day 22 assessments were completed, subjects were discharged from the research unit. Subjects who chose to continue to use Microgynon as their oral contraceptive (OC) were instructed to have 7 Microgynon-free days (Days 22-28) during which withdrawal menses was expected. Subjects who switched to Microgynon to participate in the study and who wished to return to their original (or to a different) OC did not have a 7 day contraceptive free period. Instead, they were instructed to start the next cycle of the original (or a different) OC on Day 22. The duration of Period 2 was 11 days (Days 11-21 Microgynon + CAB). Subjects returned to the study center 7-14 days after their last dose of study drug (Days 28-35) for follow-up evaluations.

Diagnosis and Main Criteria for Inclusion:

Healthy female subjects between 18 and 45 years of age inclusive, with body mass index (BMI) within the range 18 to 30 kg/m^2 (inclusive) and body weight ≥50 kg (110 lbs) and <114 kg (<250 lbs) were included in this study.

Number of Subjects:

Twenty subjects were enrolled into the study and 19 subjects completed dosing and critical assessments.

Treatment Administration:

	Study Treatment	
Product name:	GSK1265744	Microgynon (ethinyl estradiol and levonorgestrel)
Formulation description:	GSK1265744B ([redacted])	Microgynon tablets contain the following inactive ingredients: Lactose monohydrate, maize starch, povidone, talc, magnesium stearate, sucrose, polyethylene glycol, calcium carbonate, glycerol, titanium dioxide, yellow ferric oxide pigment, montab glycol wax, purified water.
Dosage form:	Tablet, [redacted] mg	Tablet
Unit dose strength(s)/Dosage level(s):	30 mg = 1 tablet Dose = 30 mg	Strength = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg
Route/ Administration/ Duration:	Administered orally once daily	Administered orally once daily
Dosing instructions:	Dosed with 240mL of water	Dosed with 240mL of water
Manufacturer/ source of procurement:	GlaxoSmithKline	Bayer (site to purchase)
Batch Number	Lot No: [redacted] Batch No: N/A Input Batch No: [redacted]	Batch No: [redacted] Expiry date: 30 Oct 2016

Statistical Methods:

The primary objective of this study was to demonstrate lack of effect of multiple doses of CAB on the PK [AUC(0-τ)] of LNG and EE. To assess this, a bioequivalence (BE) approach was employed using Schuirmann's two one-sided t-test procedure with α=0.05 for each test. Lack of effect was to be demonstrated if the 90% confidence interval (CI) for both LNG and EE ratios of geometric least-squares means for AUC(0-τ) lie within 0.8 and 1.25.

All of the PK parameters were log-transformed, except tmax. Following $\log_e$-transformation, AUC(0-τ), Cmax, and Cτ of EE and LNG were separately analyzed using a mixed effects model with treatment as fixed effect and subject as a random effect. The ratios of the geometric least square (GLS) means and associated 90% CIs were estimated for the differences between test treatment (Microgynon +CAB) and reference treatment (Microgynon). LH, FSH, and progesterone concentrations from both periods were listed and summarized by treatment.

Summary

A total of 20 female subjects were enrolled and received at least one dose of Microgynon and CAB. Of the 20 subjects, 19 completed dosing and all critical assessments. One subject (Subject [redacted]) discontinued treatment on Day 18 and was withdrawn from the study on Day 28 due to an AE (urinary tract infection [UTI]) which was considered unrelated to study drug.

Demographics:

Subject Disposition and Demography (Safety Population)			
Number of Subjects	**Microgynon QD (N=20)**	**Microgynon QD+ CAB 30 mg QD (N=20)**	**Overall (N=20)**
Number of subjects randomized, n (%)	20	20	20
Number of subjects completed, n (%)	20	19	19
Number of subjects included in safety population, n (%)	20 (100)	20 (100)	20 (100)
Number of subjects included in PK concentration population, n (%)	20 (100)	19 (95)	20 (100)
Number of subjects included in PK Parameter population, n (%)	20 (100)	19 (95)	20 (100)
Number of subjects included in PK Summary population, n (%)	19 (95)	19 (95)	19 (95)
Number of subjects included in PD population, n (%)	20 (100)	20 (100)[a]	20 (100)
Number of subjects withdrawn (any reason), n (%)	0	1 (5)	1 (5)
Reasons for subject withdrawal, n (%)			
Adverse events	0	1 (5)	1 (5)
Demographics	**Microgynon QD (N=20)**	**Microgynon QD+ CAB 30 mg QD (N=20)**	**Overall (N=20)**
Age in Years, Mean (SD)	26.5 (5.64)	26.5 (5.64)	26.5 (5.64)
Sex, n (%)			
Female:	20 (100)	20 (100)	20 (100)
Male:	0	0	0
BMI (kg/m^2), Mean (SD)	24.48 (3.196)	24.48 (3.196)	24.48 (3.196)
Height (cm), Mean (SD)	163.13 (6.347)	163.13 (6.347)	163.13 (6.347)
Weight (kg), Mean (SD)	65.09 (8.992)	65.09 (8.992)	65.09 (8.992)
Ethnicity, n (%)			
Not Hispanic or Latino:	20 (100)	20 (100)	20 (100)
Race, n (%)			
African American/African Heritage	2 (10)	2 (10)	2 (10)
White – White/Caucasian/European Heritage	18 (90)	18 (90)	18 (90)

a. Subject [redacted] provided Period 2 Day 11 pre-dose PD samples but was withdrawn prior to the collection of Period 2 Day 21/Day 22 PD samples.
Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily

Safety Results:

Thirteen subjects reported at least 1 AE. All AEs were of mild to moderate intensity. There were no Grade 3/4 treatment emergent laboratory abnormalities reported in the study. No serious adverse events (SAEs), deaths or other significant AEs were reported in the study. The most commonly reported AEs overall were headache (n=6 [30%]), and nausea (n=5 [25%]) with no clear association with CAB dosing.

One subject (Subject [redacted]) was withdrawn from the study due to an AE. Subject [redacted] was diagnosed with a UTI and required treatment with trimethoprim. The UTI was not attributed to study drug. The subject ceased CAB dosing and was withdrawn from the study. She was advised to continue Microgynon as her preferred contraceptive and returned to the unit for follow-up procedures.

Summary of All Adverse Events by Treatment (Safety Population)			
System Organ Class Preferred Term	**Microgynon QD (N=20)**	**Microgynon QD+ CAB 30 mg QD (N=20)**	**Overall (N=20)**
Any Event, n (%)	**8 (40)**	**9 (45)**	**13 (65)**
Nervous system disorders, n (%)			
Headache	3 (15)	4 (20)	6 (30)
Dizziness	2 (10)	0	2 (10)
Migraine	0	1 (5)	1 (5)
Gastrointestinal disorders, n (%)			
Nausea	4 (20)	1 (5)	5 (25)
Vomiting	0	1 (5)	1 (5)
Infections and infestations, n (%)			
Nasopharyngitis	1 (5)	1 (5)	2 (10)
Upper respiratory tract infection	1 (5)	0	1 (5)
Urinary tract infection	0	1 (5)	1 (5)
General disorders and administration site conditions, n (%)			
Asthenia	0	1 (5)	1 (5)
Influenza like illness	0	1 (5)	1 (5)
Skin and subcutaneous tissue disorders, n (%)			
Eczema	1 (5)	0	1 (5)
Rash	0	1 (5)	1 (5)
Blood and lymphatic system disorders, n (%)			
Lymphadenopathy	0	1 (5)	1 (5)

Summary of All Adverse Events by Treatment (Safety Population)			
System Organ Class Preferred Term	**Microgynon QD (N=20)**	**Microgynon QD+ CAB 30 mg QD (N=20)**	**Overall (N=20)**
Any Event, n (%)	**8 (40)**	**9 (45)**	**13 (65)**
Musculoskeletal and connective tissue disorders, n (%)			
Musculoskeletal chest pain	1 (5)	0	1 (5)

Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily

One subject (Subject [redacted]) reported a Grade 2 migraine 5 days after the last dose of CAB. The migraine resolved in approximately 28 hours. The AE was considered to be related to study drug.

Drug-Related Adverse Events by Treatment (Safety Population)			
System Organ Class Preferred Term	**Microgynon QD (N=20)**	**Microgynon QD+ CAB 30 mg QD (N=20)**	**Overall (N=20)**
Any Event, n (%)	**0**	**1 (5)**	**1 (5)**
Nervous system disorders, n (%)			
Migraine	0	1 (5)	1 (5)

Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily

Pharmacokinetic Results:

Levonorgestrel AUC(0-τ), Cmax and Cτ following administration of Microgynon + CAB 30 mg were comparable to values observed following Microgynon alone.

Summary of Steady-state Plasma Levonorgestrel Pharmacokinetic Parameters and Treatment Comparisons			
	Geometric Mean [95% CI] (CVb%)		**GLS Mean Ratio (90% CI)**
Levonorgestrel Parameter	**Microgynon QD (n=19)**	**Microgynon QD + CAB 30mg QD (n=19)**	**Microgynon + CAB 30mg vs. Microgynon**
AUC(0-τ) (h*ng/mL)	77.4 [64.5, 92.9] (39)	87.0 [72.1, 105] (40)	1.12 (1.07, 1.18)
Cmax (ng/mL)	6.86 [5.84, 8.06] (34)	7.20 [6.28, 8.26] (29)	1.05 (0.959, 1.15)

2.7.6 Synopses of Individual Studies

Summary of Steady-state Plasma Levonorgestrel Pharmacokinetic Parameters and Treatment Comparisons			
	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
Levonorgestrel Parameter	Microgynon QD (n=19)	Microgynon QD + CAB 30mg QD (n=19)	Microgynon + CAB 30mg vs. Microgynon
Cτ (ng/mL)	2.41 [1.98, 2.95] (43)	2.59 [2.09, 3.22] (47)	1.07 (1.01, 1.15)
tmax[1] (h)	1.00 (0.5 –2.5)	1.00 (0.5 – 3.0)	------

1. Median (range)

Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily

Ethinyl estradiol AUC(0-τ), Cmax and Cτ following administration of Microgynon + CAB 30 mg were comparable to values observed following Microgynon alone

Summary of Steady-state Plasma Ethinyl Estradiol Pharmacokinetic Parameters and Treatment Comparisons			
	Geometric Mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI)
Ethinyl Estradiol Parameter	Microgynon QD (n=19)	Microgynon QD + CAB 30mg QD (n=19)	Microgynon + CAB 30mg vs. Microgynon
AUC(0-τ)[1] (h*pg/mL)	773 [656, 911] (33)	800 [698, 916] (28)	1.02 (0.968, 1.08)
Cmax (pg/mL)	86.2 [72.4, 103] (38)	79.5 [68.0, 92.8] (33)	0.922 (0.827, 1.03)
Cτ[1] (pg/mL)	16.0 [12.5, 20.4] (51)	15.7 [12.9, 19.0] (40)	1.00 (0.919, 1.10)
tmax[2] (h)	1.00 (0.5 – 2.5)	1.50 (0.5 – 2.6)	-----

1. n= 17 for Microgynon and n=18 for Microgynon + CAB
2. Median (range)

Microgynon QD = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg once daily; Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily

Summary of Steady State Plasma CAB Pharmacokinetic Parameters following Coadministration with Microgynon	
	Geometric Mean [95% CI] (CVb%)
CAB Parameter	Microgynon QD + CAB 30mg QD (n=19)
AUC(0-τ) (h*μg/mL)	133 [121, 148] (21)
Cmax (μg/mL)	7.81 [7.13, 8.56] (19)
Cτ (μg/mL)	4.33 [3.87, 4.86] (24)
tmax (h)[1]	3.00 (1.0 – 4.2)

1. Median (range)

Microgynon QD + CAB 30 mg = levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg + oral cabotegravir/GSK1265744 30 mg coadministered once daily

Pharmacodynamic and Biomarker Results:

There was no apparent difference in mean LH, FSH and progesterone concentrations between Microgynon alone and Microgynon co-administered with CAB.

Conclusions:

- Co-administration of repeat dose cabotegravir (CAB) and the oral contraceptive Microgynon had no effect on the pharmacokinetic profile of levonorgestrel (LNG) and ethinyl estradiol (EE).
- The combination of CAB and LNG/EE was well tolerated in healthy volunteers. Specifically there were no deaths, SAEs, or clinically significant trends in post-dose laboratory abnormalities, vital signs or ECG values observed. All adverse events were mild to moderate in intensity.
- Steady-state CAB plasma PK parameters in this study were comparable to historical values.
- Co-administration of CAB with Microgynon had no pharmacodynamic effect on LH, FSH and progesterone compared to when Microgynon was administered alone.

Effective Date: [redacted]

Synopsis for Study ITZ111839

Identifier: RM2009/00483/00 **Study Number:** ITZ111839

Title: A Phase I, open label crossover study to evaluate the effect of etravirine on GSK1265744 pharmacokinetics in healthy adult subjects (ITZ111839)

Investigator: [redacted], MD

Study center: [redacted]

Publications: None at the time of this report.

Study period:

Initiation Date:	29 July 2009
Completion Date:	28 September 2009

Phase of development: I

Objectives:

The primary objective was:

To compare steady-state plasma GSK1265744 pharmacokinetics (PK) following administration of GSK1265744 30mg every 24 hours (q24h) with and without etravirine (ETV) 200mg every 12 hours (q12h).

The secondary objectives were:

To assess the safety and tolerability of repeat dose co-administration of GSK1265744 30mg q24h with and without ETV 200mg q12h.

To assess the steady state plasma ETV PK following co-administration of GSK1265744 30mg q24h and ETV 200mg q12h.

Methodology: This was a single-center, open-label, two-period, single-sequence cross over study in healthy adult subjects. A total of approximately 12 healthy subjects were enrolled to provide data from at least 10 evaluable subjects. Subjects had a screening visit within 30 days prior to the first dose of study drug, two treatment periods, and a follow-up visit 7-14 days after the last dose of study drug. There was no washout between treatment periods.

Cohort	Sample Size	Period 1; Days 1-10	Period 2; Days 1-14
1	12	Treatment A[1]	Treatment B[2]

1. Treatment A = GSK1265744 30mg q24h x 10 days
2. Treatment B = ETV 200mg q12h + GSK1265744 30mg q24h x 14 days

Period 1. Subjects received GSK1265744 30mg q24h (Treatment A) from Day 1 to Day 10. All doses were administered following a moderate fat meal. Subjects were housed in the unit for the entire duration of the period. Serial PK sampling was performed on Day 10.

Period 2. Day 1 of Period 2 was the day after Day 10 of Period 1. Subjects received GSK1265744 30mg q24h and ETV 200mg q12h (Treatment B) from Day 1 to Day 14. GSK1265744 was dosed in the morning. The morning ETV dose was given together with the GSK1265744 dose while the evening ETV dose was given 12 hours later. All doses were administered following a moderate fat meal. The first dose of Treatment B was given after Period 1 Day 10 24h PK sample had been collected. Subjects were housed in the unit for the entire duration of the period. Pre-dose PK concentrations were drawn in the morning on Days 8, 11, 12 and 13 and serial PK sampling on Day 14. On Day 14, the evening ETV dose was given immediately after the 12h PK sample was collected. Subjects were discharged on the morning of Day 15 and instructed to return for the follow-up visit.

Follow-up. A follow-up visit was conducted within 7-14 days after the last dose of study drug.

Number of subjects: A total of approximately 12 healthy subjects were planned to be enrolled to provide data from at least 10 evaluable subjects.

Subject Disposition and Demographics:

Number of Subjects	Overall
Number of subjects planned, N:	12
Number of subjects enrolled, N:	12
Number of subjects included in Safety Population, n (%):	12 (100%)
Number of subjects included in PK population, n (%):	12 (100%)
Number of subjects completed as planned, n (%):	12 (100%)
Number of subjects withdrawn (any reason), n (%):	0
Demographics	
Age in Years, Mean (standard deviation [SD]) Median (Range)	30.7 (6.57) 29.0 (23, 48)
Sex, n (%)	
Male:	12 (100%)
BMI (kg/m^2), Mean (SD)	26.1 (2.50)
Height (cm), Mean (SD)	176.6 (5.52)
Weight (kg), Mean (SD)	81.18 (8.161)
Ethnicity, n (%)	
Hispanic or Latino:	7 (58%)
Not Hispanic or Latino:	5 (42%)
Race, n (%)	
African American/African Heritage	3 (25%)
Native Hawaiian or Other Pacific Islander	1 (8%)
White – White/Caucasian/European Heritage	8 (67%)

Diagnosis and main criteria for inclusion: Healthy male or female subjects between 18 and 50 years of age, with body weight ≥50kg for men and ≥45kg for women, and body mass index (BMI) within the range 18.5-31.0kg/m^2 (inclusive).

Treatment administration: Subjects were assigned to a single treatment sequence as follows:

Treatment A = GSK1265744 30mg q24h x 10 days (Reference Treatment)

Treatment B = ETV 200mg q12h + GSK1265744 30mg q24h x 14 days (Test Treatment).

The batch number for GSK1265744 was [redacted]. Commercially available ETV was obtained by the site.

Criteria for evaluation: The primary endpoint of the study was plasma GSK1265744 steady-state AUC(0-τ), Cmax, Cτ, Cmin, t½, and tmax following administration of GSK1265744 30mg q24h for 10 days and following co-administration of GSK1265744 30mg q24h with ETV 200mg q12h for 14 days.

The secondary endpoints of the study were safety and tolerability parameters, including adverse events (AEs), concurrent medication, clinical laboratory, electrocardiograms

(ECGs), and vital signs assessments, and plasma ETV steady state PK parameters, including AUC(0-τ), Cmax, and Cmin following co-administration of GSK1265744 30mg q24h and ETV 200mg q12h.

Statistical methods:

GSK1265744 PK. The statistical analysis was performed on the log-transformed PK parameters, AUC(0-τ), C0, Cτ, Cmax, and Cmin.

Analysis of variance (ANOVA) was performed using SAS Mixed Linear Models procedure to assess the effect of ETV on GSK1265744. Subject was fitted as a random effect and treatment was fitted as a fixed effect in the model. The ratio of GLS means and associated 90% confidence intervals (CIs) were estimated for the PK parameters of interest.

GSK1265744 given alone in Period 1 was considered as reference treatment and GSK1265744 co-administered with ETV in Period 2 was considered as test treatment.

Steady State Assessment. Plasma GSK1265744 pre-morning dose concentration values (C0) obtained in the morning on Days 8, 11, 12, 13, and 14 of Period 2 were plotted versus day by treatment. An ANOVA with terms for subject as a random effect and day as a fixed effect was performed on the $\log_e$-transformed C0. Day was treated as a continuous variable in the model. Achievement of plasma GSK1265744 steady state was assessed calculating the point estimate and 90% CI of the slope of the linear regression of Days 8 to 14 C0 versus Day by treatment. To claim that steady state was reached, the pre-dose concentration slope estimate was close to zero or the 90% CI for the slope estimate included zero. The same analysis was performed with the Days 11 to 14, and Days 12 to 14 C0 data.

Summary:

Safety: GSK1265744 30mg q24h for 10 days, alone or in combination with ETV 200mg q12h for 14 days, was well tolerated in healthy subjects. No deaths, SAEs, or withdrawals due to AEs occurred during this study. No Grade 3 or 4 AEs were reported. The most commonly reported AEs were insomnia, nausea, and headache.

Summary of Adverse Events Reported in At Least 2 Subjects Overall in ITZ111839		
Preferred Term	**GSK1265744 (N=12)**	**GSK1265744 + ETV (N=12)**
Subjects with Any AE, n (%)	8 (67%)	9 (75%)
Insomnia	0	4 (33%)
Nausea	2 (17%)	1 (8%)
Headache	0	2 (17%)

GSK1265744 = GSK1265744 30mg q24h x 10 days
GSK1265744 + ETV = GSK1265744 30mg q24h x 14 days + ETV 200mg q12h

Similar to the overall AEs regardless of causality, the most commonly reported drug related AEs were insomnia (4 subjects receiving GSK1265744 + ETV), nausea (2

subjects receiving GSK1265744 and 1 subject receiving GSK1265744 + ETV), and headache (2 subjects receiving GSK1265744 + ETV).

One abnormal laboratory value was reported as a drug-related AE: Subject [redacted] had Grade 2 increased blood amylase while receiving GSK1265744 + ETV during Period 2. Subject [redacted] had two Grade 4, one Grade 3, and three Grade 2 clinical laboratory abnormalities during the study: Grade 4 increased AST and CPK attributed to intensive exercise at follow-up, Grade 3 increased sodium (prior to first dose in the study), and Grade 2 increased lipase (at follow-up), increased ALT (at follow-up), and increased total bilirubin (at Period 1, Day 10 and at Period 2, Days 4 and 7).

No clinically significant vital signs or ECG values were observed.

Pharmacokinetics: A summary of plasma GSK1265744 PK parameters following repeat dose administration is provided below.

Summary of Plasma GSK1265744 Pharmacokinetic Parameters Following Repeat Dose Administration[1]

Treatment	AUC(0-τ) (μg.h/mL)	Cmax (μg/mL)	Cmin (μg/mL)	Cτ (μg/mL)	tmax[2] (h)
GSK1265744	183 (13)	9.47 (11)	6.40 (14)	6.50 (14)	3.04 (2.00-12.00)
GSK1265744 + ETV	184 (9)	9.83 (11)	5.52 (12)	6.49 (12)	4.00 (2.00-8.00)

GSK1265744 = GSK1265744 30mg q24h x 10 days
GSK1265744 + ETV = GSK1265744 30mg q24h x 14 days + ETV 200mg q12h
1. geometric mean (CVb%)
2. median (range)

The results of the statistical comparison of GSK1265744 plasma PK parameters are presented in the table below.

Plasma GSK1265744 PK Treatment Comparison	
Plasma GSK1265744 PK Parameter	**Geometric Least Square Mean Ratio [90% CI]**
	ETV +GSK1265744 vs GSK1265744
AUC(0-τ)	1.01 [0.956, 1.06]
Cmax	1.04 [0.987, 1.09]
C0	0.854 [0.792, 0.921]
Cτ	0.999 [0.942, 1.06]
Cmin	0.861 [0.801, 0.926]

GSK1265744 = GSK1265744 30mg q24h x 10 days
GSK1265744 + ETV = GSK1265744 30mg q24h x 14 days + ETV 200mg q12h

The results of the statistical comparison showed that co-administration of GSK1265744 with ETV had no effect on pharmacokinetics of GSK1265744.

The results of the plasma ETV PK parameters are summarized and presented in the table below:

Summary of Plasma Etravirine Pharmacokinetic Parameters Following Repeat Dose Administration[1]				
Treatment	AUC(0-τ) (ng.h/mL)	Cmax (ng/mL)	Cmin (ng/mL)	Cτ (ng/mL)
GSK1265744 + ETV	9176 (25)	975 (24)	557 (26)	597 (28)

GSK1265744 + ETV = GSK1265744 30mg q24h x 14 days + ETV 200mg q12h
1. geometric mean (percent coefficient of variation [CVb%])

The results of the steady state assessment showed that GSK1265744 steady state was not confirmed during 14 days of dosing when co-administered with ETV since 90% CI does not include zero. Even though it was not confirmed statistically, putative steady state can be assumed based on the nearly flat slope between Days 13 and 14 in the graphical evaluation of GSK1265744 trough values.

The results of the steady state assessment showed that ETV reached steady-state after 11 days of dosing when co-administered with GSK1265744.

Conclusions:

GSK1265744 30mg q24h for 10 days, alone or in combination with ETV 200mg q12h for 14 days, was well tolerated in healthy subjects. No deaths, SAEs, or withdrawals due to AEs occurred during this study.

Co-administration of GSK1265744 and ETV had no effect on pharmacokinetics of GSK1265744.

Date of Report: [redacted] 20[redacted]

Synopsis for Study 201479

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744

Study Number: 201479

Title: A Phase I Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 in Subjects with Hepatic Impairment and Healthy Matched Control Subjects

Investigators: [redacted]; [redacted]; [redacted]

Study Centers: Three centers in the United States

Publications: None at the time of this report

Study Period: 22-Jun-2015 to 16-Sep-2016

Phase of Development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
• To compare plasma PK parameters of CAB in subjects with hepatic impairment to healthy controls matched in gender, age, and body mass index (BMI)	• Plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC(0-∞)] and maximum observed concentration (Cmax) following a single oral dose of CAB
Secondary	
• To evaluate the impact of hepatic impairment on the plasma protein binding and unbound concentration of CAB	• Unbound concentration and unbound fraction in plasma of CAB at 2 and 24 hours post dose
• To investigate the effect of hepatic impairment on other CAB PK parameters	• Plasma area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration [AUC(0-t)], percentage of AUC(0-∞) obtained by extrapolation (%AUCex), concentration observed at 24-hours post dose (C24), apparent terminal phase half-life (t½), apparent clearance (CL/F), lag time before observation of drug concentrations (tlag), time of occurrence of Cmax (tmax) and apparent terminal phase volume of distribution (Vz/F) following a single oral dose of CAB
• To assess the safety and tolerability of a single 30 mg oral dose of CAB	• Safety and tolerability parameters, including adverse events, clinical laboratory tests, electrocardiogram (ECG), and vital signs assessments

Methodology: This was a Phase 1, open-label, parallel group, single-dose adaptive study in adults with moderate hepatic impairment and matched, healthy control subjects with normal hepatic function. In Part 1, healthy control subjects (n=8) were matched in gender, age (±10 years), and BMI (±25%) to subjects with moderate (n=8) hepatic impairment. All subjects received cabotegravir (CAB) 30 mg as a single oral dose in the fasted state followed by pharmacokinetic sampling for total concentrations of CAB in plasma. The unbound CAB concentrations were assessed at sparse sampling times. Since the AUC(0-∞) of CAB did not increase by >2-fold in moderately impaired subjects relative to matched controls, the originally planned Part 2 of the study in adults with mild hepatic impairment was not conducted.

Number of Subjects: Eight healthy control subjects were matched in gender, age, and BMI to 8 subjects with moderate hepatic impairment.

Diagnosis and Main Criteria for Inclusion:

Healthy and Hepatic Impairment Subjects: Male and female subjects, between 18 and 70 years of age inclusive, with body weight ≥50 kg and BMI within the range 19 to 41 kg/m2 were eligible for the study.

Specific inclusion criteria for subjects with hepatic impairment: Child-Pugh score of 7-9 AND previous confirmation of liver cirrhosis by liver biopsy or other medical imaging technique associated with an unambiguous medical history (such as evidence of portal hypertension). Subjects with chronic (>6 months), stable hepatic impairment due to any etiology with no acute episodes of illness with previous 1 month prior to screening were also considered. Subjects with pre-existing condition (except hepatic impairment) or with presence of Grade 3 or 4 elevations in aspartate aminotransferase, alanine aminotransferase (ALT), or bilirubin were not allowed to participate in the study.

Treatment Administration: All subjects received a single oral dose of CAB 30 mg tablet (Batch No. [redacted]) with 240 mL of water in the fasted state.

Statistical Methods:

Sample Size Assumption: The target sample size of 8 evaluable subjects per cohort was chosen based on feasibility, to address the objectives of the study.

For a between-subject coefficient of variation (CVb) of 24% (based on previous CAB studies) and a sample size of 8 subjects per cohort, it was estimated that the half width of the 90% confidence interval (CI) for the cohort difference on log-scale would be within 20.8% of the point estimate for AUC(0-t)/AUC(0-∞) and Cmax. If the point estimate of the ratio of geometric means was 1, then 90% CI was considered to be approximately (0.81, 1.23).

Sensitivity analysis assuming a higher between-subject CVb of 36% and a sample size of 8 evaluable subjects per cohort was conducted. It was estimated that the lower and upper bounds of the 90% CI for the cohort difference on log-scale would be within 30.7% of the point estimate for AUC(0-t)/AUC(0-∞) and Cmax.

Analysis Populations

Screening Population: Included all subjects who had signed the consent form.

Safety Population: Included all subjects who enrolled in the study and received at least one dose of study drug. This was the population for the safety analyses, as well as for presentation/ summarization of baseline/demographic characteristics.

Pharmacokinetic Concentration Population: Included all subjects who underwent plasma pharmacokinetic (PK) sampling and had evaluable CAB assays. PK assay results from samples collected from a subject with emesis occurring within 4 hours of the dose were not to be considered as evaluable. This population was used for listing, summarization and plotting of concentration-time data.

Pharmacokinetic Summary Population: Included subjects who had CAB PK parameter estimates. This population was used for summary and plotting of PK parameters and statistical comparisons between cohorts. PK assay results from samples collected from a subject with emesis occurring within 4 hours of the dose were not to be considered as evaluable.

Interim Analyses: There was no formal interim analysis planned for the study, however, the preliminary PK and safety from Part 1 was reviewed internally at GlaxoSmithKline (GSK) to determine if Part 2 of the study was required prior to the start of Part 2. If the geometric mean total plasma AUC (0-∞) of CAB increased by >2-fold in moderately impaired subjects compared to matched controls, Part 2 was to be conducted to evaluate CAB pharmacokinetics in another group of subjects with mild impairment.

Pharmacokinetic Analyses:

Plasma CAB concentration-time data was analyzed by non-compartmental methods with WinNonlin 6.3 or higher and the following pharmacokinetic parameters were determined, as data permitted: AUC(0-∞), AUC(0-t), %AUCex, Cmax, tmax, C24, tlag, CL/F, Vz/F, and t½. Unbound fraction (fu) was calculated using the total and unbound plasma concentration of CAB data generated at 2 and 24 hours post dose for both normal and hepatic impairment subjects. Log-transformed PK parameters (except %AUCex, tmax and tlag) were analyzed by analysis of covariance (ANCOVA) with gender and cohort as fixed effects and age and BMI as continuous covariates.

The relationship between plasma CAB PK parameters, including AUC(0-t), AUC(0-∞), Cmax, C24, t½, CL/F, Vz/F, fu2 and fu24, and liver function measurements, including Child-Pugh score (overall score and liver synthetic ability [albumin, bilirubin, and prothrombin time (PT)]) was assessed by Pearson correlation and linear and/or nonlinear regression methods. For the analysis of relationship between PK and Child-Pugh score as continuous variable, subjects with normal hepatic function were considered to have a score = 0.

Safety Analyses: Safety data was presented in tabular and/or graphical format and summarized descriptively. No formal statistical analysis of the safety data was conducted.

Summary

Subject Disposition and Demographics: The subject disposition and demographics for the overall study is presented in the tables below

Number of Subjects	**Moderate Hepatic Impaired (n=8)**	**Healthy Matched (n=8)**	**Overall (N=16)**
Number of subjects planned [N]	8	8	16
Number of subjects entered [N]	8	8	16
Number of subjects included in safety population [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects included in PK Concentration population [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects included in PK Summary Population [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects completed as planned [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects withdrawn (any reason) [n (%)]	0	0	0
Demographics (Safety Population)	**Moderate Hepatic Impaired**	**Healthy Matched**	**Overall**
n	8	8	16
Age in Years [Mean (SD)]	60.3 (3.20)	56.9 (6.17)	58.6 (5.06)
Sex [n (%)]			
Female:	2 (25)	2 (25)	4 (25%)
Male:	6 (75)	6 (75)	12 (75%)
BMI (kg/m^2) [Mean (SD)]	29.3 (3.78)	29.2 (4.17)	29.2 (3.85)
Height (cm) [Mean (SD)]	176 (11.6)	171 (11.2)	173 (11.3)
Weight (kg) [Mean (SD)]	91.1 (18.4)	86.1 (18.9)	88.6 (18.2)
Ethnicity [n (%)]			
Hispanic or Latino	1 (13)	2 (25)	3 (19%)
Not Hispanic or Latino	7 (88)	6 (75)	13 (81%)
Race [n (%)]			
African American/African Heritage	2 (25)	2 (25)	4 (25)
White – White/Caucasian/European Heritage	6 (75)	6 (75)	12 (75)
Child Pugh total score [n (%)]			
7	3 (37.5%)	NA	
8	3 (37.5%)	NA	
9	2 (25.0%)	NA	

Safety Results:

All the reported adverse events (AEs) were Grade 1, except for the AEs of increased blood pressure (BP) and upper respiratory infection in 1 subject from the healthy matched control cohort, which were Grade 2 in severity.

Summary of All Adverse Events by Cohort (Safety Population)

Preferred Term	Moderate Hepatic Impaired (n=8)	Healthy Matched (n=8)	Overall (N=16)
Subjects with any AE(s), n (%)	2 (25)	3 (38)	5 (31)
Folliculitis[a]	1 (13)	0	1 (6)
Gastroenteritis	1 (13)	0	1 (6)
Upper respiratory tract infection*	0	1 (13)	1 (6)
Constipation*	1 (13)	0	1 (6)
Blood pressure increased*	0	1 (13)	1 (6)
Back pain	0	1 (13)	1 (6)
Headache*	0	1 (13)	1 (6)
Papule	1 (13)	0	1 (6)

*Drug-related AEs
Post-SAC, after further evaluation by the investigator, the folliculitis AE was determined to be not related to study drug, and instead was a pre-existing condition triggered by sweating and hot weather.

There were no deaths or serious adverse events (SAEs) reported during the study. None of the adverse events led to discontinuation of the study drug or withdrawal of any subject from the study.

Pharmacokinetic Results:
Unbound plasma CAB concentration:
The unbound plasma CAB concentrations in moderate hepatic impaired subjects were 40% and 55% higher than those in healthy subjects at 2h and 24h post dose, respectively.

Summary and Comparison of Unbound Plasma CAB Concentrations 2h and 24h following Single Dose Oral CAB 30mg (PK Concentration and PK Summary Population)

Unbound CAB Conc	Statistic	Moderate Hepatic Impaired (n=7)*	Healthy Matched[1] (n=7)*	Hepatic Impaired versus Healthy GLSM Ratio (90% CI)
2h Post Dose (µg/mL)	Median (range)	0.00831 (0.00289, 0.0234)	0.00591 (0.00364, 0.00958)	----
	Mean (SD)	0.0094 (0.00661)	0.0058 (0.00227)	----
	GLS Mean	0.0074	0.0053	1.401 (0.798, 2.459)

Unbound CAB Conc	Statistic	Moderate Hepatic Impaired (n=7)*	Healthy Matched[1] (n=7)*	Hepatic Impaired versus Healthy GLSM Ratio (90% CI)
24h Post Dose (µg/mL)	Median (range)	0.00432 (0.00163, 0.0105)	0.00260 (0.00136, 0.00441)	----
	Mean (SD)	0.0050 (0.00317)	0.0026 (0.00107)	----
	GLS Mean	0.0041	0.0026	1.552 (0.820, 2.938)

* For Subject [redacted] with hepatic impairment and healthy Subject [redacted], protein binding samples were collected, but due to shipment issues, not received and thus not processed.
1. Healthy control subjects are matched to the moderate hepatic impairment subjects in gender, age (±10 years), and BMI (±25%)

Summary of Select Plasma CAB Pharmacokinetic Parameters Following Single Dose Oral CAB 30 mg (PK Summary Population)

CAB PK Parameter (Units)	Moderate Hepatic Impaired (n=8) Geometric mean [95% CI] (%CVb)	Healthy Matched[1] (n=8) Geometric mean [95% CI] (%CVb)
AUC(0-∞) (h*µg/mL)	102 [75.2, 138] (37.3)	127 [94.7, 170] (36.2)
AUC(0-t) (h*µg/mL)	98.2 [73.3, 132] (36.2)	121 [91.0, 162] (35.4)
Cmax (µg/mL)	2.70 [1.94, 3.76] (41.1)	3.55 [2.90, 4.33] (24.3)
C24 (µg/mL)	1.23 [0.956, 1.58] (30.8)	1.50 [1.13, 2.01] (35.6)
CL/F (L/h)	0.295 [0.218, 0.399] (37.3)	0.236 [0.176, 0.317] (36.2)
Vz/F (L)	13.1 [10.1, 17.0] (31.6)	12.7 [9.79, 16.4] (31.7)
t½ (h)	30.8 [23.7, 40.1] (32.2)	37.2 [33.4 ,41.5] (13.1)
tmax (h)[2]	2.0 (1.0 –4.0)	2.0 (1.0 – 3.0)
Fraction unbound at 2h (%)[3]	0.307 [0.202, 0.467] (47.6)	0.157 [0.119, 0.207] (30.5)

CAB PK Parameter (Units)	Moderate Hepatic Impaired (n=8) Geometric mean [95% CI] (%CVb)	Healthy Matched[1] (n=8) Geometric mean [95% CI] (%CVb)
Fraction unbound at 24h (%)[3]	0.322 [0.184, 0.564] (66.6)	0.166 [0.134, 0.207] (23.9)

1. Healthy control subjects are matched to the hepatic impairment subjects in gender, age (±10 years), and BMI (±25%)
2. Data are represented as median (range)
3. n=7 for both moderate hepatic impaired and healthy matched groups

Unbound CAB fractions were statistically higher in subjects with higher albumin score (lower serum albumin concentration) and higher Child-Pugh score. There was no apparent relationship between CAB unbound fraction and total protein concentration.

Statistical Comparison of Plasma CAB Pharmacokinetic Parameters After Single CAB 30 mg Oral Dose (PK Summary Population)

Plasma CAB PK Parameter	Ratio of GLS Means (90% CI) Moderate Hepatic Impaired (n=8) vs Healthy Matched (n=8)
AUC(0-∞)	0.725 (0.497, 1.058)
AUC(0-t)	0.731 (0.508, 1.053)
Cmax	0.685 (0.505, 0.929)
C24	0.732 (0.526, 1.018)
CL/F	1.379 (0.945, 2.012)
Vz/F	1.134 (0.834, 1.541)
t½	0.822 (0.648, 1.042)
Fraction unbound at 2h*	2.137 (1.574, 2.902)
Fraction unbound at 24h*	1.902 (1.139, 3.175)

* n=7 for both moderate hepatic impaired and healthy matched groups.

Conclusions:

- Moderate hepatic impairment had minimal impact on total plasma CAB PK. The fraction unbound (%) of cabotegravir in moderate hepatic impairment subjects was ~90% – 114% higher than those in healthy subjects likely due to lower albumin concentrations.
- CAB may be taken without dose adjustment in subjects with mild to moderate hepatic impairment.
- No new safety signal was detected during the study.

Effective Date: [redacted]

Synopsis for Study 201480

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744 (cabotegravir, CAB)

Study Number: 201480

Title: A Phase I, Open-Label, Parallel-Group Study to Evaluate the Pharmacokinetics and Safety of GSK1265744 in Subjects with Severe Renal Impairment and Healthy Matched Control Subjects

Investigators: [redacted], MD, ; [redacted], MD

Study Centers: 2 centers in the United States

Publication: None at the time of this report

Study Period: 13-Jul-2015 – 01-Nov-2016

Phase of Development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
• To compare plasma PK parameters of CAB in subjects with severe renal impairment to healthy controls matched for gender, age, and body mass index (BMI) following a single oral dose	• Plasma area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-∞]) and maximum observed concentration (Cmax) following a single oral dose of CAB
Secondary	
• To evaluate the impact of severe renal impairment on the plasma protein binding and unbound concentration of CAB	• Unbound concentration and unbound fraction in plasma of CAB at 2 and 24 h post dose
• To investigate the effect of severe renal impairment on other PK parameters of CAB	• Plasma AUC from time zero (pre-dose) to the time of the last quantifiable concentration (AUC[0-t]), percentage of AUC(0-∞) obtained by extrapolation (%AUCex), Concentration observed 24 hours post dose (C24), apparent terminal phase half-life (t1/2), apparent oral clearance (CL/F), lag time before observation of drug concentrations in

Objectives	Endpoints
	sampled matrix (tlag), time of occurrence of Cmax (tmax), and apparent terminal phase volume of distribution (Vz/F) following a single oral dose of CAB
• To assess the safety and tolerability of a 30 mg single dose administration of CAB	• Safety and tolerability parameters, including adverse events, clinical laboratory tests, electrocardiogram (ECG), and vital signs assessments

Methodology:

This was a Phase 1, open label, multiple center, single-dose study to assess the impact of renal impairment on CAB disposition following a single oral dose. The study compared the PK in human subjects with severely impaired renal function (creatinine clearance [CL_{CR}] <30 mL/minutes (min) based on 24-h urine collection), who did not require renal replacement therapy, with matched healthy subjects with normal renal function (CL_{CR} ≥90 mL/min).

Each subject participated in the study for approximately 2 to 6 weeks.

The study comprised of two cohorts:

Cohort	Sample size	Renal function	CL_{CR}[1]	Treatment[2]
1	8	Severe renal impairment[3]	<30 mL/min	Oral CAB 30 mg
2	8	Normal renal function	≥90 mL/min	Oral CAB 30 mg

1. CL_{CR} was determined at screening by 24-h urine collection
2. All subjects received a single 30 mg oral dose of CAB
3. Subjects were not on any form of renal replacement therapy

Number of Subjects:

A sufficient number of adult subjects were enrolled to obtain 8 evaluable subjects per cohort.

Diagnosis and Main Criteria for Inclusion:

Renally Impaired Subjects (Cohort 1): Male or females, aged between 18 and 70 years (inclusive) with body weight of ≥50 kg, body mass index (BMI) within the range 19-38 kg/m^2 and with severe renal impairment, defined as subjects with a creatinine clearance of <30 mL/min as determined by a 24-hour urine creatinine clearance done at screening were included in the study.

Healthy Subjects (Cohort 2): Healthy Male or females, matched for age ±10 years to renally impaired subjects and between 18 and 70 years (inclusive) with body weight of ≥50 kg; BMI matched with ±25% of renally impaired subjects and within the range 19-38 kg/m^2, and with a creatinine clearance ≥90 mL/min as determined by a 24-hour urine creatinine clearance done at screening were included in the study.

Treatment Administration:

All subjects received the same treatment: a single oral dose of CAB 30 mg and there were no dose adjustments allowed in this study.

Product Name	Dose/Form/Route	Frequency/Duration	Batch number
GSK1265744 (Cabotegravir, CAB)	30 mg/tablet/oral	Administered 1 tablet orally as a single dose with 240 mL of water	[redacted]

Statistical Methods:

A sample size of 8 subjects was a feasible and reasonable sample size to provide sufficient PK data. Based on the CAB formulation comparisons (LAI117008 and LAI116585), the within subject coefficients were in the range of 21-24% and 19-21% for the CAB PK parameters. For a between-subject coefficient of variation (CVb) of 24% and a sample size of 8 subjects per cohort, it was estimated that the half width of the 90% confidence interval (CI) for the treatment difference on log-scale was within 22.4% of the point estimate for AUC(0-t)/AUC(0-∞) and Cmax. If the point estimate of the ratio of geometric means is 1, then the 90% CI is approximately (0.80, 1.25).

The following populations were used for the analysis and reporting of data:

Screening Population included all subjects who signed the consent form were included in this population.

Safety Population included all subjects who enrolled in the study and received at least one dose of study drug were included in the Safety Population. This was the population for the safety analyses, as well as for presentation and summarization of baseline/demographic characteristics.

The PK Concentration Population included all subjects in the study who underwent plasma PK sampling and have evaluable CAB assay results. This population was used for listing, summarization and plotting of concentration-time data.

The PK Summary Population included subjects who had valid CAB PK parameter estimates. This population was used for summarization and statistical analysis of PK parameters data

The following analyses were performed:

Pharmacokinetic analyses:

Plasma CAB concentration-time data were analyzed by non-compartmental methods with WinNonlin 6.3. Calculations were based on the actual sampling times recorded during the study. From the plasma concentration-time data, the following pharmacokinetic parameters were determined, as data permitted: area under the plasma concentration time curve from time zero to infinity AUC(0-∞), area under the plasma concentration time curve from time zero to the time of the last quantifiable concentration (AUC(0-t)), percentage of AUC(0-∞) obtained by extrapolation (%AUCex), maximum observed plasma concentration (Cmax), time to Cmax (tmax), concentration observed at 24-h post dose (C24), absorption lag time (tlag), apparent oral clearance (CL/F), apparent terminal phase volume of distribution (Vz/F), and terminal phase elimination half-life (t1/2).

Following $\log_e$-transformation, parameters (except %AUCex, tmax and tlag) were analyzed by analysis of covariance (ANCOVA), where cohort and gender were considered as fixed effect with age and BMI as continuous covariates. This analysis was performed using the mixed linear models procedure within the SAS/STAT module of the SAS system (Version 9.4). Point estimates and their associated 90% CIs were constructed for the cohort difference (renal impaired cohort vs normal cohort). The ratio of geometric least-squares (GLS) means and associated 90% CIs were estimated for the PK parameters of interest.

For tmax, tlag and %AUCex, descriptive summary statistics were provided.

Safety analyses:

Safety data were presented in tabular and/or graphical format and summarized descriptively according to GlaxoSmithKline's (GSK's) Integrated Data Standards Library (IDSL) standards.

Other analyses:

The relationship between plasma CAB PK parameters, including AUC(0-t), AUC(0-∞), Cmax, t1/2, CL/F, Vz/F, and FU2H, FU24H, and renal function measurement (creatinine clearance determined by 24-hour urine collection and glomerular filtration rate [GFR]) were assessed by Pearson correlation and linear regression methods.

2.7.6 Synopses of Individual Studies

Summary

Demographics:

Number of Subjects	Severe Renally Impaired (n=8)	Healthy Matched Controls (n=8)	Overall (N=16)
Number of subjects planned [N]	8	8	16
Number of subjects enrolled [N]	8	8	16
Number of subjects included in All subjects (safety) population [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects included in PK concentration population [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects included in PK summary population [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects completed as planned [n (%)]	8 (100)	8 (100)	16 (100)
Number of subjects withdrawn (any reason) [n (%)]	0	0	0
Demographics	**Severe Renally Impaired (n=8)**	**Healthy Matched Controls (n=8)**	**Overall (n=16)**
Age in Years [Mean (SD)]	55.6 (11.12)	52.3 (11.27)	53.9 (10.96)
Sex [n (%)]			
Female:	2 (25)	2 (25)	4 (25)
Male:	6 (75)	6 (75)	12 (75)
BMI (kg/m^2) [Mean (SD)]	28.51 (3.424)	28.13 (3.804)	28.32 (3.502)
Height (cm) [Mean (SD)]	171.90 (6.996)	174.18 (10.933)	173.04 (8.944)
Weight (kg) [Mean (SD)]	84.24 (10.674)	85.78 (16.561)	85.01 (13.483)
Ethnicity [n (%)]			
Hispanic or Latino:	1 (13)	0	1 (6)
Not Hispanic or Latino:	7 (88)	8 (100)	15 (94)
Race [n (%)]			
American Indian or Alaska Native	0	1 (13)	1 (6)
Black or African American	3 (38)	1 (13)	4 (25)
White - White/Caucasian/European Heritage	5 (63)	6 (75)	11 (69)
Creatinine Clearance (mL/min) [Mean (SD)]	22.1 (3.83)	121.3 (21.66)	-

Safety Results

All Adverse Events	Severe Renally Impaired (n=8) n (%)	Healthy Matched Controls (n=8) n (%)	Overall (N=16) n (%)
Subjects with any AE(s), n (%)	3 (38)	2 (25)	5 (31)
Subjects with any Drug-related AE(s), n (%)	2 (25)	0	2 (13)
Change of bowel habit	0	1 (13)	1 (6)
Diarrhoea	0	1 (13)	1 (6)
Gastrointestinal pain	1 (13)	0	1 (6)
Nausea	1 (13)	0	1 (6)
Vomiting	1 (13)	0	1 (6)
Conjunctival haemorrhage	0	1 (13)	1 (6)
Infusion site pain[1]	1 (13)	0	1 (6)
Lipase increased	1 (13)	0	1 (6)
Somnolence	1 (13)	0	1 (6)

1. Pain around an IV catheter that was inserted for phlebotomy.

There were no deaths, serious AEs or other significant AEs reported in the study. No clinically significant abnormal changes in clinical laboratory, vital signs, or ECG values were reported in the study.

Pharmacokinetic results:

Summary and Comparison of Unbound Plasma CAB Concentration-Time Data by Cohort

Concentration of unbound plasma CAB (μg/mL)	Severe Renal Impairment (n=8)[2]	Healthy Matched Controls[1] (n=8)[2]	GLS Mean Ratio (90% CI) Severe Renal Impairment vs Healthy Match
2 hours	0.0056 (0.0034, 0.0129)	0.0047 (0.0022, 0.0162)	1.32 (0.807, 2.153)
24 hours	0.0030 (0.0022, 0.0050)	0.0020 (0.0013 0.0025)	1.67 (1.33, 2.09)

1. Healthy control subjects are matched to the severe renal impairment subjects in gender, age (±10 years), and BMI (±25%)
2. Median (range)

Summary and Comparison of Selected CAB Pharmacokinetic Parameters Following Single Dose Administration to Severe Renally Impaired Subjects and Healthy Matched Control Subjects (PK Summary Population)

PK Parameter	Geometric mean [95% CI] (CVb%)		GLS Mean Ratio (90% CI) (Severe renal impairment versus healthy match)
	Severe Renal Impairment (n=8)	Healthy Matched Controls (n=8)	
AUC (0-∞) (µg*h/mL)	143[1] [115, 177] (23)	140 [116, 170] (23)	0.973 (0.835, 1.14)
AUC (0-t) (µg*h/mL)	143 [115, 178] (27)	133 [110, 160] (23)	1.08 (0.885, 1.32)
Cmax (µg/mL)	3.34 [2.67, 4.17] (27)	3.37 [2.96, 3.83] (15)	1.01 (0.865, 1.17)
C24 µg/mL)	1.65 [1.34, 2.02] (25)	1.62 [1.34, 1.96] (23)	1.02 (0.868, 1.20)
tmax (h)	2.00 (1.0 – 4.2)	2.00 (1.0- 4.0)	NA
t1/2 (h)	39.2[1] [33.9, 45.4] (16)	40.5 [36.9, 44.5] (11)	0.930 (0.831, 1.04)
FU2H (%)	0.18 [0.14, 0.23] (29)	0.14 [0.08, 0.22] (63)	1.31 (0.843, 2.03)
FU24H (%)	0.17 [0.15, 0.19] (17)	0.11 [0.09, 0.14] (30)	1.51 (1.19, 1.92)
CL/F (L/h)	0.21[1] [0.17, 0.26] (23)	0.21 [0.18, 0.26] 23	1.03 (0.881, 1.20)
Vz/F (L)	11.90[1] [10.3, 13.7] (16)	12.50 [10.4, 15] (22)	0.955 (0.839, 1.09)

1. N=7; for subject [redacted], parameters associated with terminal phase such as AUC(0-∞), t1/2, CL/F and Vz/F, were excluded from PK summary population as the coefficient of determination (R2) was <0.85 and percentage of AUC(0-∞) extrapolated was>20%"

Conclusions:

CAB AUC(0-∞) and Cmax were similar in subjects with severe renal impairment (creatinine clearance <30 mL/min) compared to healthy, matched control subjects.

The unbound fraction was 31% to 51% higher in subjects with severe renal impairment at 2 h and 24 h post dose, respectively, and was considered not clinically significant.

CAB can be administered without dose adjustment in subjects with mild to severe renal impairment (not on renal replacement therapy).

No new safety signal was detected during the study.

Effective Date: [redacted]

Synopsis for Study ITZ111451

Identifier: RM2008/00633/00 **Study Number:** ITZ111451

Title: A Double-Blind, Parallel, Randomized, Placebo-Controlled, Single and Repeat Dose Escalation First Time in Human Study to Investigate the Safety, Tolerability and Pharmacokinetics of GSK1265744 in Healthy Male and Female Subjects and Subjects Infected with HIV

Investigators: This was a multicenter study.

Study centers: This study was conducted at one site for Parts A and B and four sites for Part C in the United States.

Publications: None at the time of this report.

Study period:

Initiation Date:	Part A: 13 February 2008 Part B: 25 February 2008 Part C: 23 September 2008
Completion Date:	Part A: 14 April 2008 Part B: 13 July 2008 Part C: 18 November 2008

Phase of development: I/IIa

Objectives:

Primary

To investigate the safety, tolerability, and pharmacokinetics of GSK1265744 following single and repeat oral administration in healthy subjects.

To investigate the safety, tolerability, pharmacokinetics, antiviral activity of GSK1265744 during 10-day monotherapy in HIV-infected adults at the highest tolerated exposure in healthy subjects.

Secondary

To estimate GSK1265744 accumulation and time invariance and assess attainment of steady state following repeat administration.

To examine dose proportionality of GSK1265744 pharmacokinetic parameters following single and repeat administration.

To explore concentration-effect relationships for various safety parameters, if appropriate.

To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.

To assess the immunologic effect of GSK1256744 vs. placebo administered orally over 10 days in HIV-1 infected subjects.

Methodology: This was a Phase I, double-blind, randomized, placebo-controlled, single and repeat dose escalation study of GSK1265744 in healthy subjects and a single repeat dose cohort in HIV-1 infected subjects.

Subjects and all site personnel, with the exception of the study pharmacist or designee, were blinded to subject randomization throughout the study. For Parts A and B, the GSK study team was assessing data on a real-time basis while making dosing escalation decisions, the team was unblinded to accurately review the safety, tolerability and PK data after each dosing period. The GSK study team did not reveal the treatment assignments to the site personnel or subjects. For Part C, the treatment for subjects was unblinded on Day 11 so that subjects receiving placebo had the option to decline OT.

Decisions regarding replacement of subjects prematurely discontinued from study drug in any cohort were made by the Investigator and the GSK medical monitor on a case-by-case basis. Study design is provided in the following table.

GSK1265744 FTIH Study Design									
	Part A: Single Dose Healthy subjects			Part B: QD x 14 Day Repeat Dose Healthy subjects			Part C: QD x 10 Day Repeat Dose HIV-1 infected subjects		
Week[1]	Cohort	N Active/ Placebo	Dose[2] (mg)	Cohort	N[3] Active/ Placebo	Dose[2] (mg)	Cohort	N Active/ Placebo	Dose[2] (mg)
1	A	7/2	50						
2	B	7/2	5						
3	A	7/2	10						
4	B	7/2	25						
5									
6									
7									
8									
9				C	8/2	5			
10									
11									
12				D	8/2	10			
13									
14									
15				E	8/2	25			
16									
17									
18									
19									
20									
21							F	6/2	30[4]

1. Dose escalations were planned to run in successive weeks; however, each subsequent dose escalation commenced only when plasma GSK1265744 PK and safety data from at least five active subjects had been reviewed.
2. Illustration of projected doses. The planned doses may have been changed, switched, or cancelled based upon PK and safety from the preceding cohorts. Escalations did not exceed 2-3-fold, except in the case of undetectable concentrations following the first dose (dose levels may have been skipped if C24 < 30ng/mL), up to 100mg. At 100mg or above, dose escalations did not exceed 2-fold.
3. Sample size may have been increased after examination of data from the first 9 subjects.
4. Optimized therapy (OT) was administered for 14 days starting on Day 14 (± 1 day).

Part A: Single Dose. Part A of the study investigated single escalating doses of GSK1265744. Approximately 18 healthy subjects were planned to be enrolled using an alternating panel of 2 cohorts (9 subjects per cohort). In each of the 2 single dose cohorts, 7 out of the 9 subjects were randomized to active dose and 2 out of the 9 subjects were randomized to placebo. Subjects randomized to placebo received placebo on all dosing occasions.

The projected single escalating doses of GSK1265744 ranged from a starting dose of 50mg to a maximum dose of 800mg. Doses were escalated in a sequential fashion, contingent on the safety and pharmacokinetics profile of previous doses. Dose escalations progressed with modifications based on the actual human PK and safety data from the preceding cohorts. Safety, tolerability, and PK data from a minimum of five subjects receiving active GSK1265744 in the preceding cohort were evaluated prior to dose escalation. Data acquired following dosing in the first dose (50mg) revealed higher

than expected exposures of GSK1265744, thus planned doses were modified to allow for lower doses after the 50mg dose. The next dose that was administered was 5mg, followed by 10mg and 25mg.

Part B: Repeat Dose with Healthy Subjects. The repeat dose escalation component (Part B) was initiated based on the evaluation of preliminary safety, tolerability and PK profile in at least four single dose levels in Part A. Approximately 30 healthy subjects were planned to be enrolled using a sequential panel of 3 cohorts (10 subjects per cohort). Cohorts were comprised of 8 active/2placebo.

Part C: Repeat Dose with HIV-1 Infected Subjects. The repeat dose HIV-1 infected cohort (Part C) was initiated based on the evaluation of preliminary safety, tolerability and PK profile in all single dose levels in Part A and all repeat dose levels in Part B. Up to 12 HIV-1 infected subjects were planned to be enrolled to achieve approximately 8 evaluable subjects (6 active/2placebo) in one cohort. Based on Investigator site facilities, Part C may have been conducted on an in-patient or an out-patient basis.

After completion of dosing with GSK1265744, optimized therapy (OT), 3 active, marketed antiretroviral medications were administered to subjects receiving GSK1265744 for a minimum of 14 days. The treatment for subjects was unblinded on Day 11 so that subjects receiving placebo had the option to decline OT.

Number of subjects: For Part A, approximately 18 subjects were planned to be enrolled using an alternating panel of 2 cohorts (9 subjects per cohort). For Part B, approximately 30 healthy subjects were planned to be enrolled using a sequential panel of 3 cohorts (10 subjects per cohort). For Part C, up to 12 HIV-1 infected subjects were planned to be enrolled to achieve approximately 8 evaluable subjects (6 active/2 placebo) in one cohort. Additional subjects/cohorts may have been enrolled to allow for evaluation of additional dose levels. For both Parts A and B, a minimum of 6 active subjects must have completed dosing and critical assessments at each dose level.

Subject Disposition and Demographics:

Summary of Subject Disposition and Demographic Characteristics for Part A for ITZ111451						
Part A Number of Subjects	**SD 5mg (N=7)**	**SD 10mg (N=7)**	**SD 25mg (N=7)**	**SD 50 mg (N=7)**	**Placebo (N=4)**	**Overall (N=18)**
Number of subjects planned, N:	7	7	7	7	4	18
Number of subjects randomized, N:	7	7	7	7	4	18
Number of subjects included in Safety Population, n (%):	7 (100%)	7 (100%)	7 (100%)	7 (100%)	4 (100%)	18 (100%)
Number of subjects included in PK Population, n (%):	7 (100%)	7 (100%)	7 (100%)	7 (100%)	0	14 (100%)
Number of subjects completed as planned, n (%):	7 (100%)	7 (100%)	7 (100%)	7 (100%)	3 (75%)	17 (94%)
Number of subjects withdrawn (any reason), n (%):	0	0	0	0	1 (25%)	1 (6%)
Number of subjects withdrawn for AE, n (%):	0	0	0	0	1 (25%)	1 (6%)
Demographics	**SD 5mg (N=7)**	**SD 10mg (N=7)**	**SD 25mg (N=7)**	**SD 50 mg (N=7)**	**Placebo (N=4)**	**Overall (N=18)**
Age in Years, Median (Min, Max)	25.0 (19, 40)	42.0 (18, 54)	25.0 (19, 40)	42.0 (18, 54)	26.0 (22, 29)	28.0 (18, 54)
Sex, n (%)						
Female:	0	2 (29%)	0	2 (29%)	0	2 (11%)
Male:	7 (100%)	5 (71%)	7 (100%)	5 (71%)	4 (100%)	16 (89%)
BMI (kg/m^2), Median (Min, Max)	23.60 (21.3, 28.7)	23.09 (21.6, 28.2)	23.60 (21.3, 28.7)	23.09 (21.6, 28.2)	25.20 (22.8, 27.9)	23.61 (21.3, 28.7)
Height (cm), Median (Min, Max)	179.00 (176.0, 192.0)	174.00 (164.0, 179.0)	179.00 (176.0, 192.0)	174.00 (164.0, 179.0)	179.00 (176.0, 183.0)	177.50 (164.0, 192.0)
Weight (kg), Median (Min, Max)	78.30 (67.9, 101.2)	69.90 (64.5, 81.4)	78.30 (67.9, 101.2)	69.90 (64.5, 81.4)	82.75 (70.7, 88.7)	76.75 (64.5, 101.2)
Ethnicity, n (%)						
Hispanic or Latino:	0	0	0	0	0	0
Not Hispanic or Latino:	7 (100%)	7 (100%)	7 (100%)	7 (100%)	4 (100%)	18 (100%)
Race, n (%)						
African American/African Heritage	1 (14%)	0	1 (14%)	0	1 (25%)	2 (11%)
Asian – South East Asian Heritage	0	1 (14%)	0	1 (14%)	0	1 (6%)
White – White/Caucasian/European Heritage	6 (86%)	6 (86%)	6 (86%)	6 (86%)	3 (75%)	15 (83%)

SD 5mg=5mg Suspension QD X 1 Day
SD 10mg=10mg Suspension QD X 1 Day
SD 25mg=25mg Suspension QD X 1 Day
SD 50mg=50mg Suspension QD X 1 Day

One subject receiving placebo during Part A was withdrawn due to AEs (gingival swelling and toothache).

Summary of Subject Disposition and Demographic Characteristics for Part B (Healthy Subjects) for ITZ111451

Part B Number of Subjects	**GSK1265744 RD 5mg (N=8)**	**GSK1265744 RD 10mg (N=8)**	**GSK1265744 RD 25mg (N=8)**	**Placebo (N=6)**	**Overall Part B (N=30)**
Number of subjects planned, N:	8	8	8	6	30
Number of subjects randomized, N:	8	8	8	6	30
Number of subjects included in Safety Population, n (%):	8 (100%)	8 (100%)	8 (100%)	6 (100%)	30 (100%)
Number of subjects included in PK Population, n (%):	8 (100%)	8 (100%)	8 (100%)	0	24 (100%)
Number of subjects completed as planned, n (%):	8 (100%)	8 (100%)	8 (100%)	6 (100%)	30 (100%)
Number of subjects withdrawn (any reason), n (%):	0	0	0	0	0
Demographics	**GSK1265744 RD 5mg (N=8)**	**GSK1265744 RD 10mg (N=8)**	**GSK1265744 RD 25mg (N=8)**	**Placebo (N=6)**	**Overall Part B (N=30)**
Age in Years, Median (Min, Max)	28.0 (21, 48)	25.5 (19, 46)	25.0 (21, 38)	28.0 (19, 43)	25.5 (19, 48)
Sex, n (%)					
Female:	1 (13%)	0	0	0	1 (3%)
Male:	7 (88%)	8 (100%)	8 (100%)	6 (100%)	29 (97%)
BMI (kg/m^2), Median (Min, Max)	23.65 (19.9, 29.1)	23.32 (20.5, 28.3)	23.83 (21.5, 26.9)	24.10 (22.8, 28.6	23.97 (19.9, 29.1)
Height (cm), Median (Min, Max)	177.50 (166.0, 182.0)	182.50 (166.0, 189.0)	175.50 (171.0, 192.0)	178.00 (170.0, 183.0)	177.50 (166.0, 192.0)
Weight (kg), Median (Min, Max)	75.85 (63.5, 93.3)	71.65 (61.0, 97.8)	75.45 (65.9, 98.6)	77.35 (71.7, 91.6)	75.50 (61.0, 98.6)
Ethnicity, n (%)					
Hispanic or Latino:	1 (13%)	0	0	1 (17%)	2 (7%)
Not Hispanic or Latino:	7 (88%)	8 (100%)	8 (100%)	5 (83%)	28 (93%)
Race, n (%)					
African American/African Heritage	0	2 (25%)	3 (38%)	0	5 (17%)
White – White/Caucasian/ European Heritage	7 (88%)	6 (75%)	5 (63%)	6 (100%)	24 (80%)
Mixed Race	1 (13%)	0	0	0	1 (3%)

RD 5mg=5mg Suspension QD X 14 Day
RD 10mg=10mg Suspension QD X 14 Day
RD 25mg=25mg Suspension QD X 14 Day

Summary of Subject Disposition and Demographic and Baseline Characteristics for Part C (HIV-Infected Subjects) for ITZ111451			
Part C Number of Subjects	**GSK1265744 30mg (N=8)**	**Placebo (N=3)**	**Overall Part C (N=11)**
Number of subjects planned, N:	8	3	11
Number of subjects randomized, N:	8	3	11
Number of subjects included in Safety Population, n (%):	8 (100%)	3 (100%)	11 (100%)
Number of subjects included in PK Population, n (%):	8 (100%)	0	8 (73%)
Number of subjects completed as planned, n (%):	7 (87.5%)	3 (100%)	10 (91%)
Number of subjects withdrawn due to AEs, n (%):	1 (12.5%)	0	1 (9%)
Number of subjects withdrawn (any reason), n (%):	1 (12.5%)	0	1 (9%)
Demographics	**GSK1265744 30mg (N=8)**	**Placebo (N=3)**	**Overall Part C (N=11)**
Age in Years, Median (Min, Max)	41.5 (27, 51)	48.0 (30, 49)	42.0 (27, 51)
Sex, n (%)			
Female:	0	0	0
Male:	8 (100%)	3 (100%)	11 (100%)
BMI (kg/m^2), Median (Min, Max)	25.83 (23.7, 29.4)	28.43 (26.4, 30.7)	26.36 (23.7, 30.7)
Height (cm), Median (Min, Max)	176.00 (161.0, 185.0)	180.00 (173.0, 185.0)	177.00 (161.0, 185.0)
Weight (kg), Median (Min, Max)	80.15 (75.0, 92.1)	97.30 (78.9, 99.5)	82.30 (75.0, 99.5)
Ethnicity, n (%)			
Hispanic or Latino:	3 (38%)	0	3 (27%)
Not Hispanic or Latino:	5 (63%)	3 (100%)	8 (73%)
Race, n (%)			
African American/African Heritage	0	0	0
White – White/Caucasian/ European Heritage	8 (100%)	3 (100%)	11 (100%)
Mixed Race	0	0	0
Baseline HIV-1 PCR RNA (log_{10} copies/mL) Mean (SD) Median (Range)	 4.140 (0.2672) 4.132 (3.73, 4.61)	 5.093 (0.4250) 4.869 (4.83, 5.58)	Not calculated
CD4+ cells (per cm^3) Mean (SD) Median (Range)	 437.5 (128.92) 395.0 (330, 740)	 373.3 (68.07) 350.0 (320, 450)	Not calculated

One subject in Part C was withdrawn from the study due to an AE (jaundice), which was observed during OT with atazanavir and ritonavir.

Diagnosis and main criteria for inclusion: *Parts A and B*: Healthy male and female subjects between 18 and 55 years of age, with a body weight ≥ 50 kg (110 lbs.) for men and ≥ 45 kg (99 lbs) for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive). *Part C*: HIV-infected cohort only: CD4+ cell count ≥ 200 $cells/mm^3$ and plasma HIV-1 RNA ≥ 5,000 copies/mL, no current antiretroviral therapy and had not received any antiretroviral therapy in the 12 weeks prior to first dose, and adequate treatment options to construct highly active antiretroviral therapy (HAART) with at least 3 active antiretrovirals for future treatment, based on review and agreement by the Investigator and the GSK Medical Monitor.

Treatment administration: The following treatments were administered during the study:

Drug	Dose/Form/Route	Frequency/Duration	Batch Number
GSK1265744	5, 10, 25, 50mg/ suspension/ oral 5, 10, 25mg/ suspension/oral	Single Dose Repeat Doses, QD, for 14 days	[redacted]
Placebo	5, 10, 25, 50mg/ suspension/ oral 5, 10, 25mg/suspension/oral	Single Dose Repeat Doses, QD, for 14 days	[redacted]
GSK1265744	6 x 5mg / tablet / oral	Repeat Doses, QD, for 10 days	[redacted]
Placebo	6 x 5mg / tablet / oral	Repeat Doses, QD, for 10 days	[redacted]

Criteria for evaluation: The primary endpoints of this study were GSK1265744 safety parameters, adverse events (AEs), absolute values and changes over time of hematology, clinical chemistry, urinalysis, vital signs (blood pressure (BP) and heart rate), electrocardiogram (ECG) intervals, ECG rhythm and telemetry, GSK1265744 pharmacokinetic parameters following single dose administration: area under the plasma concentration curve (AUC(0-∞), AUC(0-t)), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), observed concentration at 24h post-dose (C24), terminal half-life (t1/2), and following repeat administration: AUC(0-τ), concentration at end of dosing interval (Cτ), Cmax, minimum observed concentration (Cmin), tmax, t1/2 on Day 14 (healthy subjects) or Day 10 (HIV-infected subjects), and in HIV-infected subjects, change from baseline in plasma HIV-1 ribonucleic acid (RNA) on Day 11.

The secondary endpoints of this study were Day 14 GSK1265744 AUC(0-τ) compared to AUC(0-24) on Day 1 to estimate accumulation ratio (R) and GSK1265744 AUC(0-τ) on Day 14 compared to AUC(0-∞) on Day 1 to evaluate time invariance following repeat administration of GSK1265744, pre-morning dose concentrations (Cτ) on Day 2 through 13 to assess the achievement of steady state of GSK1265744 following repeat administration in healthy subjects, GSK1265744 PK parameters: AUC(0-∞), AUC(0-t), Cmax, and C24 (concentration at 24h post-dose) following single dose administration and AUC(0-τ), Cτ, Cmin, and Cmax following repeat administration at different doses for the assessment of dose proportionality, plasma HIV-1 RNA change from baseline in HIV cohort, plasma HIV-1 RNA change from baseline to nadir (maximum change) in HIV cohort, plasma HIV-1 RNA rate of decline (slope) over 11 days in HIV cohort, and to assess the development of genotypic viral resistance, if appropriate, in HIV cohort.

Statistical methods: For subjects in each active treatment group the following pharmacokinetic parameters were determined from the plasma concentration-time data for GSK1265744.

Part/Day	Plasma GSK1265744 PK Parameters Calculated
Part A	AUC(0-∞), AUC(0-t), Cmax, tmax, Ct, C24, t1/2, tlag, and CL/F
Part B/Day 1 Part C/Day 1	AUC(0-t), AUC(0-24), Cmax, tmax,C24, t1/2, tlag, and CL/F
Part B/Day 14 Part C/Day 10	AUC(0-τ), Cτ, Cmax, Cmin, tmax, tlag, t1/2, and CL/F

Dose Proportionality: Part A and Part B: Dose proportionality of GSK1265744 PK parameters was assessed following single dose administration (AUC(0-t), AUC(0-∞), AUC(0-24), Cmax and C24) and repeat dose administration (AUC(0-τ) Cmax, Cτ, and Cmin) using the power model. The power model was fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. For Part A of the study, both the intercept and slope were fitted as random effects first. For Part B of the study, only a fixed effects power model was considered. The mean slope was estimated from the power model and the corresponding 90% confidence interval calculated. Intra-subject CV% calculated from the model was presented in the table.

Accumulation Ratio Analysis: Parts B and C: An analysis of variance (ANOVA) with a random effect term for subject and fixed effect terms for day was performed by dose on the $\log_e$-transformed AUC. Day was treated as a class variable in the model. The accumulation ratio of GSK1265744 was estimated by calculating the ratio of the geometric least squares (GLS) means of PK parameters on Day 14 of Part B or Day 10 of Part C to those on Day 1 and the corresponding 90% CI for each dose.

Time Invariance: Parts B and C: An ANOVA with terms for subject as a random effect and day as a fixed effect was performed by dose on the $\log_e$-transformed AUC. Day was treated as a class variable in the model. The time invariance of GSK1265744 was assessed by calculating the ratio of the GLS means of AUC(0-τ) on Day 14 of Part B or Day 10 of Part C to AUC(0-∞) on Day 1 and the corresponding 90% CI for each dose. AUC(0-∞) on Day 1 were considered as the reference phase in the analysis and AUC(0-τ) on Day 14 or Day 10 as test phase.

Steady State Assessment: Parts B and C: Plasma GSK1265744 pre-dose Cτ values obtained on Days 10-14 of Part B or Days 7-11 of Part C of the study were plotted versus day by treatment (dose). An ANOVA with terms for subject as a random effect and day as a fixed effect was performed by dose on the $\log_e$-transformed Cτ. Day was treated as a continuous variable in the model. Achievement of plasma GSK1265744steady state was assessed by visual inspection of plots and calculating the point estimate and 90% CI of the slope of the linear regression of Days 10 to 14 of Part B or Days 7-11of Part C of pre-dose Cτ versus Day by dose group. To claim that steady state was reached, the pre-dose concentration slope estimate was close to zero and the 90% CI for the slope estimate included zero.

Pharmacogenetic, Viral Genotyping and Phenotyping Analyses. The viral genotypic/phenotypic data were listed and descriptive summaries provided.

Efficacy Analyses. The primary efficacy analysis was plasma HIV-1 RNA change from baseline to Day 11, which was summarized by treatment. Change from baseline of plasma HIV-1 RNA to Day 11 was compared between active treatment and placebo using analysis of covariance (ANCOVA), with treatment fitted as a fixed effect, and baseline plasma HIV-1 RNA as a covariate. The corresponding point estimates and two-sided 95% CIs of the differences and p-values were presented.

The secondary efficacy analysis was plasma HIV-1 RNA change from baseline, which was calculated for each subject on each post-baseline visit, where data were non-missing. Plasma HIV-1 RNA change from baseline to the on treatment (between Day 1-14) nadir (maximum change) was calculated for each subject and summarized by treatment. Change from baseline of plasma HIV-1 RNA to the on-treatment nadir was compared between active treatment and placebo using ANCOVA, with treatment fitted as a fixed effect, and baseline plasma HIV-1 RNA as a covariate. The corresponding point and two-sided 95% CI estimates of the differences and t-test p-values were presented.

Plasma HIV-1 RNA change from baseline between Day 1 and Day 11 was fitted in a mixed-effects linear model by treatment, with baseline plasma HIV-1 RNA and day fitted as fixed effects and subject fitted as a random effect. Estimated mean rate of decline (i.e., slope of day) with corresponding 90% CI was provided for each treatment.

The proportion of subjects with plasma HIV-1 RNA < 50 copies/mL and proportion of subjects with plasma HIV-1 RNA change from baseline >1.7 $\log_{10}$ copies/mL decrease were summarized by treatment and visit.

Lymphocyte subsets data (total lymphocyte counts, percentage, CD4+ cell counts, and CD8+ cell counts) were listed by treatment, subject, and visit and summarized by treatment and visit along with change from baseline.

Summary:

Safety: GSK1265744, administered as a solution at doses of 5mg, 10mg, 25mg, and 50 mg in single doses, and in repeat doses of 5mg, 10mg, and 25mg, was well tolerated in healthy subjects. GSK1265744 30mg was also well tolerated in HIV-infected subjects. No deaths or SAEs were reported during this study. No Grade 3 or 4 AEs were reported during Parts A, B, or C.

The most frequently reported AE during Part A was application site erythema (related to ECG patches), reported by one subject receiving GSK1265744 25mg, and three subjects receiving GSK1265744 50 mg. No drug-related AEs were reported during Part A.

Summary of All Adverse Events in Part A of ITZ111451					
Adverse Events	**SD 5mg (N=7)**	**SD 10mg (N=7)**	**SD 25mg (N=7)**	**SD 50 mg (N=7)**	**Placebo (N=4)**
Any AE, n (%)	**1 (14%)**	**0**	**3 (43%)**	**5 (71%)**	**1 (25%)**
Application site erythema	0	0	1 (14%)	3 (43%)	0
Injection site discharge	1 (14%)	0	0	0	0
Gastroenteritis	0	0	1 (14%)	0	0
Upper respiratory tract infection	0	0	1 (14%)	0	0
Arthralgia	0	0	1 (14%)	0	0
Erythema	0	0	0	1 (14%)	0
Rash	0	0	0	1 (14%)	0
Ecchymosis	0	0	0	1 (14%)	0
Mouth injury	0	0	0	1 (14%)	0
Cough	0	0	0	1 (14%)	0
Nasal congestion	0	0	0	1 (14%)	0
Swelling face	0	0	0	0	1 (25%)
Gingival swelling	0	0	0	0	1 (25%)
Toothache	0	0	0	0	1 (25%)

SD 5mg=5mg Suspension QD X 1 Day
SD 10mg=10mg Suspension QD X 1 Day
SD 25mg=25mg Suspension QD X 1 Day
SD 50 mg=50 mg Suspension QD X 1 Day

The most commonly reported AEs during Part B were headache (4 subjects; 13%), application site erythema at ECG patch sites (4 subjects; 13%), erythema [at an antecubital site] (2 subjects; 7%), and pain in extremity (2 subjects; 7%). The most commonly reported drug-related AE during Part B was headache (4 subjects; 13%).

Summary of All Adverse Events and Drug-Related Adverse Events in Part B of ITZ111451					
	GSK1265744				
Most Frequent Adverse Events	**RD 5mg (N=8)**	**RD 10mg (N=8)**	**RD 25mg (N=8)**	**Placebo (N=6)**	**Overall Part B (N=30)**
Any AE, n (%)	5 (63%)	3 (38%)	2 (25%)	3 (50%)	13 (43%)
Headache	1 (13%)	0	1 (13%)	2 (33%)	4 (13%)
Application site erythema	2 (25%)	2 (25%)	0	0	4 (13%)
Erythema	0	2 (25%)	0	0	2 (7%)
Pain in extremity	1 (13%)	1 (13%)	0	0	2 (7%)
Application site pruritus	1 (13%)	0	0	0	1 (3%)
Fatigue	1 (13%)	0	0	0	1 (3%)
Somnolence	1 (13%)	0	0	0	1 (3%)
Rash papular	1 (13%)	0	0	0	1 (3%)
Excoriation	1 (13%)	0	0	0	1 (3%)
Abnormal dreams	1 (13%)	0	0	0	1 (3%)
Cough	1 (13%)	0	0	0	1 (3%)
Respiratory tract congestion	1 (13%)	0	0	0	1 (3%)
Thrombophlebitis	1 (13%)	0	0	0	1 (3%)
Dry mouth	0	0	1 (13%)	0	1 (3%)
Oral mucosal exfoliation	0	0	1 (13%)	0	1 (3%)
Ventricular extrasystoles	0	0	1 (13%)	0	1 (3%)
Streptococcal pharyngitis	0	0	1 (13%)	0	1 (3%)
Abdominal discomfort	0	0	0	1 (17%)	1 (3%)
Sunburn	0	0	0	1 (17%)	1 (3%)
Drug-Related Adverse Events	**RD 5mg (N=8)**	**RD 10mg (N=8)**	**RD 25mg (N=8)**	**Placebo (N=6)**	**Overall Part B (N=30)**
Any Drug-Related AE, n (%)	3 (38%)	0	1 (13%)	2 (33%)	6 (20%)
Headache	1 (13%)	0	1 (13%)	2 (33%)	4 (13%)
Somnolence	1 (13%)	0	0	0	1 (3%)
Fatigue	1 (13%)	0	0	0	1 (3%)
Pain in extremity	1 (13%)	0	0	0	1 (3%)
Abnormal dreams	1 (13%)	0	0	0	1 (3%)
Ventricular extrasystoles	0	0	1 (13%)	0	1 (3%)
Abdominal discomfort	0	0	0	1 (17%)	1 (3%)

RD 5mg=5mg Suspension QD X 14 Days
RD 10mg=10mg Suspension QD X 14 Days
RD 25mg=25mg Suspension QD X 14 Days

The most commonly reported AEs during Part C were dizziness (3 subjects; 27%), headache (2 subjects; 18%), and dyspepsia (2 subjects; 18%). The most commonly reported drug-related AEs during Part C were dizziness (2 subjects; 18%) and dyspepsia (2 subjects; 18%). The AEs shown in Part C included those in subjects who were also received OT.

Summary of All Adverse Events and Drug-Related Adverse Events in Part C of ITZ111451				
Most Frequent Adverse Events	**GSK1265744 30mg (N=8)**	**Placebo (N=3)**	**OT (N=8)**	**Overall Part C (N=11)**
Any AE, n (%)	2 (25%)	2 (67%)	4 (50%)	6 (55%)
Dizziness	1 (13%)	0	2 (25%)	3 (27%)
Headache	1 (13%)	0	1 (13%)	2 (18%)
Dyspepsia	1 (13%)	0	1 (13%)	2 (18%)
Fatigue	1 (13%)	0	0	1 (9%)
Somnolence	0	0	1 (13%)	1 (9%)
Abnormal dreams	0	0	1 (13%)	1 (9%)
Hot flush	0	0	1 (13%)	1 (9%)
Jaundice	0	0	1 (13%)	1 (9%)
Diarrhea	0	1 (33%)	0	1 (9%)
Neck pain	0	1 (33%)	0	1 (9%)
Drug-Related Adverse Events	**GSK1265744 30mg (N=8)**	**Placebo (N=3)**	**OT (N=8)**	**Overall Part C (N=11)**
Any Drug-Related AE, n (%)	2 (25%)	1 (33%)	1 (13%)	3 (27%)
Dizziness	1 (13%)	0	1 (13%)	2 (18%)
Dyspepsia	1 (13%)	0	1 (13%)	2 (18%)
Headache	1 (13%)	0	0	1 (9%)
Fatigue	1 (13%)	0	0	1 (9%)
Diarrhea	0	1 (33%)	0	1 (9%)

When AEs were combined for all parts of the study, the most frequently reported AEs were application site erythema (8 subjects; 14%), headache (6 subjects; 10%), dizziness (3 subjects 5%), and erythema [due to razor burn and at antecubital sites] (3 subjects; 5%). When drug-related AEs were combined for all parts of the study, the most frequently reported drug-related AE was headache (5 subjects; 8%). The AEs shown in Part C included those in subjects who also received OT.

Summary of Most Frequently Reported Adverse Events and Drug-Related Adverse Events (At Least Two Subjects Overall) in Parts A, B, and C Combined in ITZ111451								
Adverse Events	**SD Active (N=14)**	**SD Placebo (N=4)**	**RD Active (N=24)**	**RD Placebo (N=6)**	**HIV Active (N=8)**	**HIV Placebo (N=3)**	**OT (N=8)**	**Overall (N=59)**
Any AE, n (%)	9 (64%)	1 (25%)	10 (42%)	3 (50%)	2 (25%)	2 (67%)	4 (50%)	29 (49%)
Application site erythema	4 (29%)	0	4 (17%)	0	0	0	0	8 (14%)
Headache	0	0	2 (8%)	2 (33%)	1 (13%)	0	1 (13%)	6 (10%)
Dizziness	0	0	0	0	1 (13%)	0	2 (25%)	3 (5%)
Erythema	1 (7%)	0	2 (8%)	0	0	0	0	3 (5%)
Fatigue	0	0	1 (4%)	0	1 (13%)	0	0	2 (3%)
Somnolence	0	0	1 (4%)	0	0	0	1 (13%)	2 (3%)
Dyspepsia	0	0	0	0	1 (13%)	0	1 (13%)	2 (3%)
Pain in extremity	0	0	2 (8%)	0	0	0	0	2 (3%)
Abnormal dreams	0	0	1 (4%)	0	0	0	1 (13%)	2 (3%)
Cough	1 (7%)	0	1 (4%)	0	0	0	0	2 (3%)
Drug-Related Adverse Events	**SD Active (N=14)**	**SD Placebo (N=4)**	**RD Active (N=24)**	**RD Placebo (N=6)**	**HIV Active (N=8)**	**HIV Placebo (N=3)**	**OT (N=8)**	**Overall (N=59)**
Any AE, n (%)	0	0	4 (17%)	2 (33%)	2 (25%)	1 (33%)	1 (13%)	9 (15%)
Headache	0	0	2 (8%)	2 (33%)	1 (13%)	0	0	5 (8%)
Dizziness	0	0	0	0	1 (13%)	0	1 (13%)	2 (3%)
Dyspepsia	0	0	0	0	1 (13%)	0	1 (13%)	2 (3%)
Fatigue	0	0	1 (4%)	0	1 (13%)	0	0	2 (3%)

OT = optimized therapy

During all three Parts of the study, no clinical laboratory values were reported as AEs. During Part A, there were no Grade 3 or 4 laboratory abnormalities. During Part B, one asymptomatic Grade 3 elevated lipase and two asymptomatic Grade 2 increased lipase values were reported. Subject [redacted] (RD 25mg) had a Grade 3 increased lipase (258U/L) at pre-dose on Day 4, which returned to normal (25 U/L) on the following day. This subject also had a grade 3 increased lipase (242 U/L) at Follow-up, which had resolved (27 U/L) at a subsequent visit scheduled 9 days later. All other lipase values for this subject were within the normal range. During Part C, one Grade 4 increased total bilirubin, two Grade 3 increased total bilirubin, and two Grade 2 increased total bilirubin values were reported. The bilirubin increases were primarily due to indirect hyperbilirubinemia. All of these subjects experienced these bilirubin elevations during OT, and all were receiving atazanavir and ritonavir as components of the OT.

No clinically significant vital signs or ECG values were reported during the study.

Pharmacokinetics: GSK1265744 plasma PK parameters following single and repeat dose administration are summarized in the tables below. Half-life was not estimated for Part A.

Summary of Selected Plasma GSK1265744 Pharmacokinetic Parameters Following Single Dose Administration (Part A, Solution)[1]

Treatment	AUC(0-t) (μg.h/mL)	Cmax (μg/mL)	C24 (μg/mL)	tmax[2] (h)	Clast[3] (μg/mL)
5mg (n=7)	26.6 [23.4, 30.1] (14)	1.15 [0.99, 1.33] (16)	0.42 [0.37, 0.48] (13)	0.50 (0.50-1.00)	0.16 [0.13, 0.18] (18)
10mg (n=7)	51.7 [42.4, 63.0] (22)	2.15 [1.84, 2.51] (17)	0.83 [0.68, 1.02] (22)	1.00 (0.50-1.50)	0.32 [0.23, 0.45] (38)
25mg (n=7)	117 [104, 132] (13)	4.38 [3.54, 5.41] (23)	1.93 [1.67, 2.23] (16)	1.50 (0.50-3.00)	0.74 [0.61, 0.90] (21)
50mg (n=7)	231 [170, 313] (34)	8.57 [6.89, 10.7] (24)	3.82 [2.81, 5.18] (34)	1.50 (0.50-3.00)	1.48 [0.94, 2.35] (53)

1. geometric mean [95%CI] (CVb%)
2. median (range)
3. Clast occurred at 72 hours post dose for all subjects at all doses.

Summary of Selected Day 14 Plasma GSK1265744 Pharmacokinetic Parameters Following Repeat Dose Administration to Healthy Subjects (Part B, Solution)[1]

Treatment	AUC(0-24) (μg.h/mL)	Cmax (μg/mL)	Cτ (μg/mL)	Cmin (μg/mL)	tmax[2] (h)	Accum Ratio (AUC)[3]
5mg (n=8)	32.5 [28.6, 37.0] (16)	2.08 [1.78, 2.42] (19)	1.06 [0.90, 1.25] (20)	0.99 [0.83, 1.18] (21)	0.63 (0.25-1.50)	2.38 [2.21, 2.57] (9)
10mg (n=8)	69.2 [59.6, 80.3] (18)	4.29 [3.80, 4.84] (15)	2.39 [1.98, 2.88] (23)	2.04 [1.71, 2.45] (22)	0.88 (0.50-1.50)	2.52 [2.28, 2.78] (12)
25mg (n=8)	160 [136, 188] (20)	9.47 [8.12, 11.1] (19)	5.40 [4.51, 6.47] (22)	5.22 [4.36, 6.24] (22)	1.25 (0.50-4.00)	2.51 [2.17, 2.92] (18)

1. geometric mean [95%CI](CVb%)
2. median (range)
3. Accumulation ratio= Day 14 AUC(0-24)/Day 1 AUC(0-24)

Summary of Selected Plasma GSK1265744 Pharmacokinetic Parameters Following Single and Repeat Dose Administration to HIV-infected Subjects (Part C, Tablet formulation)[1]							
Treatment Day	**AUC(0-24) (μg.h/mL)**	**Cmax (μg/mL)**	**C24 (μg/mL)**	**tmax[1] (h)**	**Cmin (μg/mL)**	**t1/2 (h)**	**Accum Ratio[3]**
Day 1 (n=8)	41.5 [31.2, 55.0] (35)	2.84 [2.18, 3.70] (32)	1.25 [0.91, 1.72] (39)	1.50 (1.00-3.00)	---	---	---
Day 10 (n=8)	104 [82.9, 131] (28)	6.37 [5.26, 7.72] (23)	3.28 [2.46, 4.38] (36)	2.50 (1.00-4.00)	2.85 [2.15, 3.78] (35)	31.5 [26.3, 37.7] (22)	2.51 [2.21, 2.86] (15)

1. geometric mean [95%CI](CVb%)
2. median (range)
3. Accumulation ratio= Day 10 AUC(0-24)/Day 1 AUC(0-24)

Summary of Dose Proportionality of GSK1265744 Steady State PK Parameters Following Single and Repeat Dose Administration (Parts A and B, Solution)			
Plasma GSK1265744 PK Parameter	**Slope [90% CI]**		
	SD, Part A[1]	**Day 1, Part B[1]**	**Day 14, Part B[2]**
AUC(0-t) or AUC(0-τ)	0.926 [0.885, 0.968]	0.954 [0.898, 1.010]	0.986 [0.892, 1.080]
Cmax	0.847 [0.801, 0.894]	0.864 [0.795, 0.932]	0.938 [0.847, 1.030]
C24 or Cτ	0.944 [0.901, 0.988]	0.989 [0.932, 1.046]	1.006 [0.892, 1.120]
Cmin	NA	NA	1.033 [0.923, 1.143]

1. AUC(0-t) and C24
2. AUC(0-tau) and Ctau

GSK1265744 PK exposure increased less than proportionally to dose following single dose (5 to 50mg) administration in Part A and increased proportionally to dose following repeat dose (5 to 25mg) administration in Part B.

GSK1265744 plasma concentrations reached steady state by 12 days of repeat administration. The accumulation ratio based on AUC(0-τ) ranged from 2.38 to 2.52 across dose levels. Assuming time-invariant PK, the effective half-life is estimated to be 30.5-33h.

Summary of GSK1265744 Accumulation Assessments following Repeat Dose Administration in Healthy Subjects (Part B, Solution) and HIV infected Subjects (Part C, Tablet formulation)				
Plasma GSK1265744 PK Parameter	**GLS Mean Ratio [90% CI]**			
	Part B			Part C
	5mg	10mg	25mg	30mg
AUC(0-24)	2.38 [2.24, 2.53]	2.52 [2.32, 2.73]	2.52 [2.23, 2.83]	2.51 [2.27, 2.78]
Cmax	1.78 [1.64, 1.92]	1.86 [1.71, 2.04]	2.00 [1.78, 2.25]	2.24 [1.99, 2.53]
$C\tau$	2.58 [2.35, 2.83]	2.84 [2.58, 3.13]	2.67 [2.33, 3.07]	2.62 [2.35, 2.93]

Following 14-day repeat dose administration of GSK1265744 in healthy subjects, the mean accumulation ratios for AUC(0-τ), Cmax, and $C\tau$ were estimated to be 2.38-2.52, 1.78-2.00, and 2.41-2.63, respectively, across dose levels. GSK1265744 accumulation ratios following administration of GSK1265744 tablet formulation for 10 days to HIV infected subjects were similar to those determined following 14-days repeat administration of solution formulation to healthy subjects. Since Day 1 AUC(0-∞) could not be estimated in either Part B or C, time invariance was not evaluated. However, assuming time invariant PK, the accumulation ratio for AUC(0-24) should equal $1/(1-e^{-k\tau})$, where k is the elimination rate constant and τ is the dosing interval. For accumulation ratios of 2.38-2.52 and a dosing interval of 24h, the elimination rate constant is estimated to be 0.0211-0.0227 h^{-1}, and the corresponding effective half-life is estimated to be 30.5-33h.

GSK1265744 steady state was reached by Day 12 for all doses in Part B. GSK1265744 steady state was achieved by Day 7 following repeat administration of 30mg (6x 5mg tablets) in HIV infected subjects in Part C.

Viral Genotyping and Phenotyping: Six of the eleven subjects had genotype and phenotype available for both Day 1 and Day 11. While differences were observed between Day 1 and Day 11 genotypes in four of the six subjects, the variation in phenotype was remarkably small. The lack of a substantial increase in GSK1265744 or raltegravir IC_{50} between Day 1 and Day 11 is reflective of the mutations observed. In no case was a mutation associated with clinical resistance to raltegravir or elvitegravir selected in subjects receiving GSK1265744. In addition, none of the treatment emergent mutations were associated with *in vitro* resistance to GSK1265744. Raltegravir IC_{50}s were approximately 10-fold higher than GSK1265744 IC_{50}s.

Efficacy: Virology and Immunology: There was a statistically significant difference in plasma HIV-1 RNA (log_{10} copies/mL) from baseline to Day 11 for subjects treated with GSK1265744 30mg compared to subjects who received placebo ($p<0.001$). Median decrease in plasma HIV-1 RNA from baseline to Day 11 for the GSK1265744 30mg group was 2.548 log_{10} copies/mL compared to 0.273 log_{10} copies/mL for the placebo group.

Summary of Plasma HIV-1 RNA Change from Baseline for Part C of ITZ111451						
Parameter	Treatment	Mean (SD)	Median (Range)	Treatment versus Placebo[1]		
				LS Mean	Difference (95% CI)	p-value
Plasma HIV-1 RNA Change from Baseline to Day 11 (log_{10} copies/mL)	GSK1265744 30mg (N=8)	-2.344 (0.6491)	-2.548 (-2.97, -0.99)	-2.549	-2.865 (-3.249, -2.480)	<0.001
	Placebo (N=3)	-0.232 (0.2247)	-0.273 (-0.43, 0.01)	0.315	--	--
Plasma HIV-1 RNA Change from Baseline to Nadir (log_{10} copies/mL)	GSK1265744 30mg (N=8)	-2.449 (0.6739)	-2.727 (-2.97 -0.99)	-2.675	-2.852 (-2.925, -2.779)	<0.001
	Placebo (N=3)	-0.427 (0.2600)	-0.397 (-0.70, -0.18)	0.177	--	--

1. ANCOVA with treatment as fixed effect and baseline HIV-1 RNA as covariate.

The proportion of subjects with plasma HIV-1 RNA less than 50 copies /mL was 75% at Day 14 for subjects receiving GSK1265744 30mg. It should be noted that subjects received antiretroviral therapy with at least three active agents out to Day 28. This response was maintained for 5 of 8 subjects (63%) at follow-up. No subjects in the placebo group achieved plasma HIV-1 RNA less than 50 copies/mL.

The proportion of subjects receiving GSK1265744 with plasma HIV-1 RNA decreases greater than 1.7 log_{10} copies/mL was 7 of 8 subjects (88%) on Days 9 through 14 on GSK1265744 alone and on optimized therapy through follow-up. No subjects in the placebo group achieved plasma HIV-1 RNA decreases greater than 1.7 log_{10} copies/mL.

Changes in lymphocyte subsets (CD4+ and CD8+ cells and CD4+/CD8+ ratios) were variable with no consistent trends.

Conclusions:

GSK1265744, administered as a solution at doses of 5mg, 10mg, 25mg, and 50 mg in single doses, and in repeat doses of 5mg, 10mg, and 25mg, was well tolerated in healthy subjects. Repeat doses of GSK1265744 30mg (administered as 6-5mg tablets) were also well tolerated in HIV-infected subjects. No deaths or SAEs were reported during this study. No Grade 3 or 4 AEs were reported during Parts A, B, or C. No clinically significant trends in laboratory, vital sign or ECG changes were noted.

GSK1265744 PK exposure increased less than proportionally to dose following single dose (5 to 50mg) administration in Part A and increased proportionally to dose following repeat dose (5 to 25mg) administration in Part B.

Following repeat dose administration, plasma concentrations of GSK1265744 reached steady state after 12 days of dosing of solution in healthy subjects and by Day 7 following repeat administration of tablets in HIV infected subjects.

The accumulation ratio for AUC ranged from 2.38 to 2.52 across dose levels and populations.

Following repeat administration of the solution formulation in healthy subjects in Part B, Day 14 geometric mean Cτ values were 6.4-, 14-, and 33-fold above the in vitro PA-IC_{90} (0.166µg/mL) for the 5mg, 10mg, and 25mg QD doses, respectively, supporting evaluation of QD doses in HIV infected subjects.

In Part C, HIV-infected subjects (integrase inhibitor naïve) received repeat administration of GSK1265744 30mg for 10 days followed by an optimized background regimen of 3 active antiretrovirals for 14 days. Day 10 geometric mean Cτ for GSK1265744 was 20-fold above the in vitro PA-IC_{90}, lower than predicted based on solution data. However, all subjects achieved a Day 11 HIV RNA change from baseline of -1.9 log_{10} or better regardless of Day 10 Cτ or inhibitory quotient (Cτ/PA-IC_{90}).

No PK/PD relationships were elucidated based on graphical evaluation of the data. .

No mutations associated with in vitro resistance to GSK1265744 were selected in this 10-day monotherapy trial.

No phenotypic resistance to GSK1265744 was observed at Day 1 or at Day 11 in any subjects.

There was no association between genotypic changes in the integrase enzyme and changes in GSK1265744 IC_{50}.

There was a statistically significant difference in plasma HIV-1 RNA (log_{10} copies/mL) from baseline to Day 11 for subjects treated with GSK1265744 30mg compared to subjects who received placebo ($p<0.001$).

The proportion of subjects with plasma HIV-1 RNA less than 50 copies/mL was 75% at Day 14 for subjects receiving GSK1265744 30mg.

Date of Report: [redacted] 20[redacted]

Synopsis for Study LAI114433

Title: An Observer- and Subject-Blinded, Randomized, Placebo-Controlled, Single Dose Escalation Study to Investigate the Safety, Tolerability and Pharmacokinetics of Intramuscular and Subcutaneous Long Acting GSK1265744 in Healthy Subjects.

Investigator: [redacted] MD.
Study center: [redacted] United States [redacted].

Publications: None at the time of this report.

Study period: 29 Sep 2010 – 20 Nov 2012

Phase of development: I

Objectives:

Primary

To investigate the safety, tolerability, and pharmacokinetics of GSK1265744 LAP following single dose intramuscular (IM) or subcutaneous (SC) administration in healthy subjects.

Secondary

To examine dose proportionality of GSK1265744 LAP pharmacokinetic parameters following single dose IM or SC administration.

To explore concentration-effect relationships for various safety parameters, if appropriate.

To investigate GSK1265744 pharmacokinetic (PK) in cervicovaginal fluid (CVF), vaginal tissue (VT), cervical tissue (CT) and rectal tissue (RT) and relate to GSK1265744 PK in plasma.

Methodology: LAI114433 was a Phase I, observer- and subject-blind, randomized, placebo-controlled, single dose escalation study to determine the safety, tolerability, and PK profile of IM and SC injections of GSK1265744 LAP in healthy subjects. This study consists of a screening visit, a single injection, and follow-up evaluations for a minimum of 12 weeks following the injection.

On Day 1 subjects in Cohorts 1 to 7, were randomized to receive either GSK1265744 injectable suspension IM, GSK1265744 injectable suspension SC, or placebo injections. Subjects in Cohorts 8 and 9 were randomized to receive 400mg GSK1265744 IM in a single 400mg injection (Cohort 8) or divided into two 200mg injections (Cohort 9). Subjects returned to the clinical research unit (CRU) for assessments on Days 3, 4, 5, 6, 7, 10, and 14, Week 3, Week 4, Week 5, Week 6, Week 8, Week 10, and Week 12.

Dosing between cohorts were separated by a minimum of 3 weeks to allow review of individual safety data and PK prior to dosing the next cohort. In the absence of safety and tolerability issues, subsequent cohorts were dosed a minimum of 3 weeks after the last subject in the previous cohort was dosed. No subject received the next higher dose until the preceding lower active dose had been safely administered to at least 5 subjects.

Subjects remained in the study for a minimum of 12 weeks after administration of study drug (Day 1). After 12 weeks, subjects were continue to followed for safety and PK assessments once every four weeks or more often until the GSK1265744 plasma concentration was below 0.10 μg/mL or until the subject completes Week 24 and all adverse events (AE) were resolved or stabilized according to the Investigator and the Sponsor.

Number of subjects: Approximately 72 adult subjects were randomized to receive active treatment or placebo.

Diagnosis and main criteria for inclusion:

Male or female subjects between 18 and 55 years of age inclusive, at the time of signing the informed consent with a body weight ≥50 kg for men and ≥45 kg for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive). For Cohorts 3 and 7 body weight ≥60 kg for men and women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive).

Treatment administration: Subjects were assigned to active or placebo treatment in accordance with the randomization schedule generated by Discovery Biometrics (DB), prior to the start of the study, using validated internal software.

Criteria for evaluation:

Primary

GSK1265744 LAP safety and tolerability parameters including AEs, clinical laboratory, Electrocardiogram (ECG), and vital sign assessments.

GSK1265744 LAP pharmacokinetic parameters following single dose IM or SC administration: area under the plasma concentration time curve from time zero to the last quantifiable time points (AUC(0-τ)), area under the plasma concentration time curve from time zero to infinity (AUC(0-∞)), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 1 month post-dose (C720 hours), apparent terminal phase half-life for LAP administration (t½), lambda z as a measure of absorption rate constant (λz).

Secondary

GSK1265744 LAP PK parameters: absorption lag time (tlag), and apparent clearance (CL/F,LAP) following single dose administration, AUC%ex.

AUC(0-∞), AUC(0-τ), Cmax, and C720 hours following single dose administration at different doses for the assessment of dose proportionality.

GSK1265744 concentrations in CVF, CT, VT, RT, and blood plasma and ratio of CVF, CT, VT, and RT concentration to blood plasma.

Statistical methods:

The primary objectives of this study were to investigate the safety, tolerability, and pharmacokinetics of single doses of GSK1265744 LAP. No formal statistical hypotheses was tested. Where appropriate, an estimation approach was taken, and point estimates and confidence intervals (CI) were constructed. Plasma GSK1265744 concentration-time data were analyzed by non-compartmental methods with WinNonlin 5.2 or higher and the following pharmacokinetic parameters were assessed following single dose IM or SC administration: area under the plasma concentration time curve from time zero to the last quantifiable time points (AUC(0-t)), area under the plasma concentration time curve from time zero to infinity (AUC(0-∞)), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at 1 month post-dose (C720 hours), apparent terminal phase half-life.

Summary:

Adverse events and serious adverse events (SAEs) were collected from the start of IP and until the final follow-up visit. In addition, SAEs assessed as related to study participation were collected from the time of consent to participation in the study, up to and including any follow-up contact. The most frequent AEs reported in this study are presented below.

Most Frequent (≥2 Subjects in any arm) Adverse Events – On-Therapy	GSK1265744 LAP									
	IM						SC			
	100mg	200mg	400mg	800mg	400mg (200x2)	Pbo	100mg	200mg	400mg (200x2)	Pbo
Safety Population, N	6	6	14	6	8	8	6	6	6	6
Any event n(%)	5 (83)	5 (83)	12 (86)	5 (83)	6 (75)	5 (63)	5 (83)	6 (100)	6 (100)	5 (83)
Injection site pain	3 (50)	5 (83)	9 (64)	5 (83)	5 (63)	2 (25)	3 (50)	6 (100)	5 (83)	2 (33)
Injection site nodule	1 (17)	0	3 (21)	1 (17)	1 (13)	0	3 (50)	5 (83)	6 (100)	0
Injection site erythema	2 (33)	0	2 (14)	1 (17)	0	0	2 (33)	5 (83)	4 (67)	1 (17)
Headache	1 (17)	2 (33)	4 (29)	1 (17)	4 (50)	3 (38)	3 (50)	5 (83)	0	1 (17)
Cough	2 (33)	1 (17)	0	0	0	2 (25)	0	0	1 (17)	2 (33)
Back pain	0	0	3 (21)	1 (17)	0	0	1 (17)	0	0	0
Nausea	0	0	2 (14)	0	2 (25)	0	1 (17)	0	0	0
Oropharyngeal pain	0	0	1 (7)	1 (17)	0	1 (13)	0	0	0	2 (33)
Vomiting	0	0	2 (14)	0	1 (13)	1 (13)	1 (17)	0	0	0
Sneezing	0	0	1 (7)	0	0	0	0	0	2 (33)	1 (17)
Pain	0	0	2 (14)	0	0	1 (13)	0	0	0	0
Erythema	0	0	0	0	1 (13)	0	0	2 (33)	0	0
Rhinorrhoea	0	0	0	0	0	0	0	0	2 (33)	1 (17)
Blood creatine phosphokinase increased	2 (33)	0	0	0	0	0	0	0	0	0

A total of 72 subjects were enrolled and dosed in the study. Fifty-eight subjects completed the study and 14 subjects discontinued the study (7 [10%] subjects lost to follow-up and 7 [10%] subjects withdrew consent). The majority of subjects in the study were White (81%), not Hispanic/Latino (79%), and male (54%). The mean age was 35.1 years (range: 18 to 55 years)

2.7.6 Synopses of Individual Studies

	GSK1265744 LAP									
	IM						SC			
	100mg	200mg	400mg	800mg	400mg (200x2)	Pbo	100mg	200mg	400mg (200x2)	Pbo
Number of subjects planned, N:	6	6	14	6	8	8	6	6	6	6
Number of subjects randomized, N:	6	6	14	6	8	8	6	6	6	6
Number of subjects included in All subjects (safety) population, n (%):	6 (100)	6 (100)	14 (100)	6(100)	8 (100)	8 (100)	6 (100)	6 (100)	6 (100)	6 (100)
Number of subjects included in PK population, n (%):	6 (100)	6 (100)	14 (100)	6 (100)	8 (100)	8 (100)	6 (100)	6 (100)	6 (100)	6 (100)
Number of subjects completed as planned, n (%):	5 (83)	6 (100)	10 (71)	6(100)	6 (75)	8 (100)	5 (83)	4 (67)	4 (67)	6 (100)
Number of subjects withdrawn (any reason), n (%):	1 (17)	0	4 (29)	1(17)	2 (25)	1(17)	1 (17)	2 (33)	2 (33)	0
Number of subjects withdrawn for SAE, n (%):	0	0	0	0	0	0	0	0	0	0
Number of subjects withdrawn for AE, n (%):	0	0	0	0	0	0	0	0	0	0
Reasons for subject withdrawal, n (%)	IM						SC			
Lost to follow-up	1 (17)	0	3 (21)	0	1 (13)	0	0	1 (17)	1 (17)	0
Withdrew Consent	0	0	1 (7)	1(17)	1 (13)	1(17)	1 (17)	1 (17)	1 (17)	0
Demographics	IM						SC			
Age in Years, Mean (SD)	34.3 (9.65)	34.2 (11.91)	36.1 (9.56)	39.7 (13.28)	30.4 (7.91)	35.5 (10.73)	34.5 (13.34)	30.0 (6.63)	41.2 (7.60)	34.8 (14.27)
Sex, n (%)	IM						SC			
Female:	4 (67)	2 (33)	7 (50)	2 (33)	4 (50)	5 (63)	1 (17)	2 (33)	2 (33)	4 (67)
Male:	2 (33)	4 (67)	7 (50)	4 (67)	4 (50)	3 (38)	5 (83)	4 (67)	4 (67)	2 (33)
BMI (kg/m^2), Mean (SD)	23.90 (2.89)	25.51 (3.15)	26.68 (2.88)	26.64 (2.58)	24.48 (3.86)	27.01 (2.68)	26.16 (3.10)	24.40 (2.89)	28.41 (1.56)	25.07 (3.50)
Height (cm), Mean (SD)	166.2 (9.7)	175.8 (7.7)	168.4 (5.2)	171.0 (8.6)	168.9 (6.3)	168.5 (10.2)	176.3 (5.6)	170.5 (6.2)	174.5 (4.7)	173.2 (7.4)
Weight (kg), Mean (SD)	65.9 (8.8)	78.6 (7.8)	75.9 (10.8)	77.9 (10.0)	30.4 (7.9)	76.5 (8.6)	81.7 (12.6)	71.4 (12.4)	86.4 (4.1)	74.62 (5.8)

2.7.6 Synopses of Individual Studies

	GSK1265744 LAP									
	IM						SC			
	100mg	200mg	400mg	800mg	400mg (200x2)	Pbo	100mg	200mg	400mg (200x2)	Pbo
Ethnicity, n (%)										
Hispanic or Latino:	3 (50)	0	2 (14)	1 (17)	4 (50)	1 (13)	2 (33)	1 (17)	2 (33)	1 (17)
Not Hispanic or Latino:	3 (50)	6 (100)	12 (86)	5 (83)	4 (50)	7 (88)	4 (67)	5 (83)	4 (67)	5 (83)
Race, n (%)	6	6	14	6	8	8	6	6	6	6
African American/African Heritage	0	2 (33)	2 (14)	0	1 (13)	3 (38)	2 (33)	1 (17)	2 (33)	1 (17)
White – White/Caucasian/European Heritage	6 (100)	4 (67)	12 (86)	6 (100)	7 (88)	5 (63)	4 (67)	5 (83)	4 (67)	7 (88)

Individual plasma GSK1265744 PK parameters following IM and SC dose administration are listed in the Table below. Absorption of GSK1265744 from depot injection sites began within 4h, the first sampling time, following LAP administration as no lagtime was observed in any subject. Plasma concentration-time profiles were consistent with long-acting administration, with low Cmax values, prolonged median tmax values ranging from 6 to 69 days, and measureable concentrations in some subjects to ~1year post dose. In addition, the apparent terminal phase t1/2, which reflects rate limiting step of absorption from the depot site rather than elimination from plasma, is prolonged, with geometric mean values ranging from 25 to 54 days. Split LAP administered dosing – 400mg (200mg x 2) IM and SC as well as 800mg (400mg x 2) IM – achieved geometric mean C648h (4Wks) above 4*PA-IC90.

Summary of Selected Plasma GSK1265744 Pharmacokinetic Parameters Following Single Dose IM and SC Administration[1]

PK parameter	Treatment							
	IM					SC		
	100mg	200mg	400mg	400mg (200x2)	800mg (400x2)	100mg	200mg	400mg (200x2)
n	6	6	14	8	6	6	6	6
AUC(0-648) (µg.h/mL)	118 (74.9)	136 (26.0)	290 (46.2)	644 (61.7)	1497 (79.2)	90.7 (36.7)	265 (41.1)	368 (54.3)
AUC(0-1992) (µg.h/mL)	320 (75.4)	502 (30.4)	9533 (54.3)	1798 (50.6)	3851 (50.8)	3294 (45.5)	8524 (35.8)	1292 (61.8)
AUC(0-t) (µg.h/mL)	607 (43.3)	1068 (37.4)	1921 (60.9)	2445 (52.7)	5651 (17.5)	433 (102)	1005 (85.7)	2402 (16.1)
AUC(0-∞) (µg.h/mL)	9205 (12.3)	1234 (34.6)	26526 (29.8)	2687 (53.0)	5872 (12.6)	6894 (24.0)	17065 (2.6)	2734 (22.3)
Cmax (µg/mL)	0.2 (58.6)	0.3 (28.9)	0.7 (55.2)	1.4 (53.4)	3.3 (75.1)	0.2 (62.1)	0.5 (48.6)	0.9 (83.4)
tmax2 (day)	9.00 (4.0-83.0)	44.50 (27.0-170.1)	69.00 (2.0-213.0)	13.00 (4.0-84.2)	7.58 (5.0-147.0)	16.50 (4.0-55.0)	6.00 (3.0-27.0)	27.00 (3.0-83.0)
C648h µg/mL)	0.1 (82.7)	0.2 (37.0)	0.4 (54.6)	1.1 (49.3)	2.0 (76.9)	0.1 (60.8)	0.4 (69.1)	0.7 (96.6)
CL/F (L/hr)	0.15 (12.3)	0.1 (34.6)	0.16 (29.8)	0.1 (53.0)	0.1 (12.5)	0.14 (24.0)	0.15 (2.6)	0.1 (22.3)
t1/2 (day)	33.37 (66.8)	53.9 (32.2)	38.36 (57.3)	31.78 (61.8)	25.4 (51.7)	50.44 (76.9)	42.75 (53.1)	42.8 (52.0)

[1] geometric mean (CV%)
[2] median (range)
[3]n=13; [4]n=5; [5]n=4; [6]n=10; [7]n=3; [8]n=7

The results of the dose proportionality assessment by Power model showed that plasma GSK1265744 exposures following single IM injection increased less than dose proportional in the dose range of 100mg to 400mg. Plasma GSK1265744 exposures following split IM injections (400mg and 800mg IM) increased slightly more than dose proportional except C648. Plasma exposures of GSK1265744 following SC injection increased approximately dose proportional in the dose range of 100mg to 400mg.

Summary of Dose Proportionality of Single Dose GSK1265744 PK Using Power Model

Route of Administration	Parameter	Slope	90% Confidence Interval
IM Single Injection	AUC(0-648)	0.696	[0.415, 0.978]
	AUC(0-∞)	0.814	[0.601, 1.03]
	C648	0.794	[0.482, 1.11]
	Cmax	0.722	[0.437, 1.01]
IM Two Injection	AUC(0-648)	1.22	[0.347, 2.08]
	AUC(0-∞)	1.13	[0.588, 1.67]
	C648	0.891	[0.105, 1.68]
	Cmax	1.26	[0.456, 2.06]
SC	AUC(0-648)	1.01	[0.681, 1.34]
	AUC(0-∞)	0.987	[0.820, 1.15]
	C648	1.11	[0.627, 1.59]
	Cmax	1.02	0.586, 1.44]

The results of the dose proportionality assessment by ANOVA showed that plasma exposures of GSK1265744 following single IM injection increased less than dose proportional as dose increased from 100mg to 200mg and 100mg to 400mg. Plasma exposures of GSK1265744 increased more than dose proportional as dose increased from 100mg to 800mg except AUC(0-∞). Two IM injections also resulted in more than dose proportional increase in GSK1265744 plasma exposures except AUC(0-∞). Plasma exposures of GSK1265744 following single SC injection increased more than dose proportional as dose increased from 100mg to 200mg. Plasma exposures of GSK1265744 following single SC injection increased approximately dose proportional as dose increased from 100mg to 400mg.

Summary of Dose Proportionality of Single Dose GSK1265744 PK Using ANOVA

Plasma GSK1265744 PK Parameter	GLS Mean Ratio [90% CI]			
IM	IM200 vs IM100	IM400 vs IM100	IM800 vs IM100	IM400 (200x2) vs IM100
AUC(0-∞)	1.34 [0.932, 1.93]	2.88 [2.07, 4.03]	6.39 [4.44, 9.19]	2.92 [2.07, 4.13]
AUC(0-648)	1.16 [0.690, 1.93]	2.46 [1.59, 3.81]	12.7 [7.60, 21.3]	5.47 [3.38, 8.86]
Cmax	1.25 [0.752, 2.06]	2.58 [1.69, 3.95]	12.5 [7.55, 20.7]	5.23 [3.27, 8.38]
C648	1.51 [0.883, 2.57]	2.93 [1.86, 4.60]	12.7 [7.45, 21.7]	6.85 [4.16, 11.3]
SC	SC200 vs SC100		SC400 vs SC100	
AUC(0-∞)	2.48 [1.96, 3.14]		3.97 [3.21, 4.91]	
AUC(0-648)	2.92 [1.90, 4.49]		4.05 [2.64, 6.23]	
Cmax	2.58 [1.41, 4.72]		4.08 [2.23, 7.46]	
C648	2.63 [1.33, 5.21]		4.64 [2.35, 9.19]	

The results of the analysis showed that GSK1265744 plasma exposures were similar following 400mg IM injections of Cohort 3 and Cohort 8 where different clinical batches were administered. Splitting 400mg IM into 2-IM injection resulted in a >2-fold increase

in plasma GSK1265744 AUC(0-648h), Cmax and C648h. Dose splitting did not affect GSK1265744 AUC(0-∞).

Summary of Formulation Changes and Splitting Injections on GSK1265744 PK Parameters

Plasma PK Parameter	Ratio of GLS Means (90% CI)	
	IM 400mg Cohort 3 vs Cohort 8	IM 400mg (200x2) vs IM 400mg
AUC(0-∞)	1.10 [0.759, 1.58]	1.01 [0.730, 1.41]
AUC(0-648)	0.930 [0.599, 1.44]	2.22 [1.53, 3.23]
Cmax	1.11 [0.666, 1.86]	2.03 [1.37, 3.00]
C648	1.04 [0.626, 1.74]	2.34 [1.60, 3.42]

GSK1265744 tissue concentrations were low. Assuming a density of 1g/mL, median cervical and vaginal tissue concentrations were approximately equivalent to the in vitro PA-IC90 (0.166μg/mL) at some visits.

Summary of GSK1265744 Tissue Concentrations by Visit[1]

Tissue Type	Tissue Concentration (μg/g) (n=4/visit)			
	400mg IM unsplit (Cohort 8)		400mg IM split (2x 200mg IM, Cohort 9)	
	Week 2	Week 8	Week 4	Week 12
Cervical	0.081 (NQ- 0.17)	0.096 (0.06 - 0.19)	0.177 (0.07- 0.50)	0.133 (NQ - 0.21)3
Vaginal2	0.121 (NQ - 0.18)	0.184 (0.09 - 0.44)	0.155 (NQ - 0.90)	0.181 (NQ - 0.35)
Rectal2	NQ (NQ - 0.10)	NQ (NQ - 0.05)	0.079 (NQ - 0.20)	0.063 (NQ - 0.08)

[1] median (range)

[2]n=8 samples

[3]n=3 samples

NQ-Non-quantifiable concentration measured as below LLQ

Across visits, median cervical and vaginal tissue:plasma ratios ranged from 0.16 to 0.28. Median rectal tissue:plasma ratios were ≤0.08. Linear regression showed good correlation between cervicovaginal tissue concentrations and plasma concentrations.

Summary of GSK1265744 Tissue:Plasma Ratios by Tissue Type[1]

	400mg IM unsplit (Cohort 8)	400mg IM split (2x 200mg IM, Cohort 9)
Cervical[2]	0.20 (0.0 - 0.40)	0.16(0.0 - 0.4)
Vaginal[3]	0.28 (0.0 - 0.7)	0.19 (0.0 - 0.7)
Rectal[3]	0.00 (0.0 - 0.1)	0.08 (0.0 - 0.2)

[1] median (range)
[2]n=8 unsplit; n=7 split
[3]n=24

Conclusions:

GSK1265744 was well tolerated as a single injection of 100, 200 and 400 mg IM or 100 and 200mg SC and as a split injection of 800 mg IM and 400mg SC . There were no deaths, drug related SAEs, or withdrawals due to AEs. The most frequent non-injection related AEs were Headache, Nausea and Back pain. Graded lab abnormalities were infrequent, with no laboratory trends identified relative to placebo identified. There were no clinically significant trends in vital signs or ECGs. IM and SC injection related AEs were mild, with injection site pain occurring most frequently followed by erythema and nodule formation.

LAP administration of GSK1265744 produced prolonged low plasma concentrations in healthy subjects for up to ~1 year in some subjects.

GSK1265744 apparent terminal half-lives following LAP administration ranged from 25 -54 days, reflecting rate limiting absorption rather than the the terminal phase elimination t1/2 of ~40h observed following oral administration.

Splitting injections increased the rate but not the extent of absorption, and achieved geometric mean C648h (4Wks) above 4*PA-IC90 (0.664µg/mL) in the range of concentrations which produced antiviral response following oral administration in Human Immunodeficiency Virus (HIV) infected subjects. This will also enable loading dose strategy in repeat dose LAP administration.

Tissue concentrations were low with median tissue:plasma ratios ranging from 16-28% in cervicovaginal tissue and ≤8% in rectal tissue following GSK1265744 400mg IM. As this dose produced subtherapeutic plasma concentrations based on available oral data, higher LAP doses should provide higher tissue concentrations and may be evaluated in GSK1265744 prevention studies.

Effective Date: [redacted]

Synopsis for Study LAI117008

Title: An Open Label, Non-Randomized, Mass Balance Study to Investigate the Recovery, Excretion, and Pharmacokinetics of 14C-GSK1265744 Administered as a Single Oral Dose and a Placebo-Controlled, Randomized Study to Describe the Pharmacokinetics of a Supratherapeutic Dose of GSK1265744 in Healthy Adult Subjects.

Investigator: [redacted] MD

Study center:

The study was conducted at one center at [redacted] United States [redacted].

Publications:

None at the time of this report.

Study period: 08 May 2013-10 Jul 2013

Phase of development: I

Objectives:

Primary Objectives

Part A

- To determine the total recovery and relative excretion of total radioactivity in urine and feces after a single, oral solution dose of [14C]-GSK1265744.
- To describe the pharmacokinetics of plasma GSK1265744 and total radioactivity in blood and plasma after a single, oral solution dose of [14C]- GSK1265744.

Part B

- To assess the safety and tolerability of single, supratherapeutic dose administration of GSK1265744 150 mg when compared to placebo.
- To evaluate the plasma GSK1265744 PK following administration of a single supratherapeutic dose of GSK1265744 150 mg

Secondary Objectives

Part A

- To evaluate the safety and tolerability of GSK1265744 following single-dose, oral administration in healthy subjects.

- To determine the blood:plasma ratio of [14C]-GSK1265744-related material and the amount of total radioactivity associated with blood cellular components.

- To define the metabolic profile of GSK1265744 in plasma, urine, bile, and feces and to identify and quantify (where possible) major metabolites in these matrices following administration of a single oral solution dose of [14C]-GSK1265744.

Methodology:

This was a two-part study in healthy adults. Part A was a phase 1, non-randomized, open label, single-dose, single-centre mass balance study utilizing a radiolabeled dose to investigate the recovery, excretion, and pharmacokinetics of oral GSK1265744 in a cohort of 6 healthy adult male subjects.

Study Design: Part A

Part	Sample Size (active)	Day 1
A	6	Treatment A: 30 mg

Treatment A: 30 mg 14C-GSK1265744 of approximately 70 µCi (0.96 MBq) of radioactivity x 1 dose (fasted)

Part A consisted of a screening period, a treatment phase, and follow-up evaluations. Subjects underwent a pre-study screening visit within 30 days of the first dose and those who successfully passed pre-study assessments and met eligibility criteria were enrolled into the study. Subjects in Part A received the equivalent of a 30 mg (26.7 mg mean) dose of GSK1265744 as an oral solution, containing approximately 70 µCi (0.96 MBq) of radioactivity under fasted conditions. Blood, urine and fecal samples were collected for a minimum of 336 hours (14 days) to a maximum of 504 hours (21 days) following study drug administration. Measurement of total radioactivity present in individual samples (plasma, urine, and feces) was performed. Subjects could have been discharged from the unit as early as the morning of day 16 if total radioactivity in 2 consecutive 24-hour collections (288-312 hours post dose [day 13- 14] and 312-336 hours [day 14-15] post dose) in both urine and feces combined were ≤ 1% of the administered dose. In the event that total radioactivity in feces and/or urine was >1% of the administered dose at 336 hours, subjects were to remain in the research unit and continue to collect 24-hour urine and feces until the amount of radioactivity had dropped below 1% of the administered dose in 2 consecutive 24-hour collections. Subjects could have remained in the unit for up 21 days. Additionally, a sampling of bile was collected utilizing the Entero-Test to qualitatively assess metabolites of GSK1265744. Safety was assessed by vital signs (heart rate and blood pressure), 12-lead ECG, clinical laboratory tests, AE monitoring, and physical examinations.

Study Design: Part B

Part	Sample Size N	Day 1
B	8	Treatment B:150 mg
	2	Treatment P: Placebo

In Part B, 10 subjects were enrolled to evaluate the single-dose safety, tolerability and PK of supratherapeutic dose of GSK1265744 150 mg compared with placebo. Subjects had a screening period, a treatment phase, and follow-up evaluations. The pre-study screening visit occured within 30 days of the first dose and those who successfully passed pre-study assessments and met eligibility criteria were enrolled into the study. Subjects enrolled in Part B were not the same subjects enrolled in Part A of this study.

After an overnight fast of at least 8 hours, each subject received a single dose of GSK1265744 150 mg or placebo on Day 1. Each dose was administered under fasting conditions in the morning. Serial PK samples were collected for 336 hours 14 days following dosing. Subjects were housed in the unit until completion of 72 hour assessments and returned for PK collection and safety assessments on Days 6, 8, 11 and on Day 14 for follow-up evaluation.

Parts A and B were independent of each other in terms of timing. Part B was dosed prior to or at the same time as Part A.

Number of subjects:

Part A: In Part A, 6 subjects were enrolled such that approximately 4 subjects complete dosing and critical assessments.

Part B: In Part B, 10 subjects were enrolled for dosing and critical assessments.

Diagnosis and main criteria for inclusion:

For Part A, male subjects between 30 and 55 years of age and for part B, male or female between 18 and 60 years of age inclusive, at the time of signing the informed consent with BMI within the range 18.5-31.0 kg/m^2 (inclusive).

Treatment administration:

Part A

Treatment A= GSK1265744 30 mg single dose as solution (containing 70 μCi 14C-GSK1265744). The actual administered mean dose was 26.7 mg (70.2 μCi).

Part B

Treatment B = GSK1265744 150 mg single dose as 5 x 30 mg tablets.

Treatment P = Placebo tablets to match GSK1265744.

Criteria for evaluation:

Part A

Primary

- Percent recovery of total radioactivity in urine and feces.
- Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a profile [AUC (0-t)], Area under the concentration-

time curve from time zero (pre-dose) extrapolated to infinite time [AUC (0-∞)], Maximum observed concentration (Cmax), Time of occurrence of Cmax (tmax), Terminal phase elimination rate constant (λz), apparent terminal phase half-life (t1/2), and oral clearance (CL/F) of plasma GSK1265744 and total radioactivity in plasma and blood following oral solution [14C]-GSK1265744 dosing.

Secondary

- Safety and tolerability parameters, including adverse events (AEs), vital signs, ECGs, and clinical laboratory assessments.
- Blood:Plasma ratio of total drug-related material (radioactivity), Percent of total radioactivity associated with red blood cells.
- Collection of samples for use in a separate study for characterization and quantification of GSK1265744-related metabolites in plasma, bile, urine and fecal homogenates.

Part B

Primary

- Safety and tolerability parameters, including adverse event, concurrent medication, clinical laboratory, ECG, and vital signs assessments.
- Plasma GSK1265744 PK parameters following a single-dose administration of 150 mg under fasted conditions: Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration within a profile [AUC (0-t)], Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time [AUC (0-∞)], Maximum observed concentration (Cmax), Time of occurrence of Cmax (tmax), Terminal phase elimination rate constant (λz), apparent terminal phase half-life (t1/2), and oral clearance (CL/F).

Statistical methods:

This was an investigative study and no hypotheses or treatment comparison was tested, and descriptive summary was provided.

PK analysis of the plasma GSK1265744, plasma radioactivity, and whole blood radioactivity concentration-time data was conducted using non-compartmental methods with WinNonlin (Version 5.2 or higher). Actual elapsed times from dosing were used in the PK analysis and the AUC was determined using the linear up-log down trapezoidal rule. The following PK parameters were calculated for total radioactivity in whole blood and plasma and GSK1265744 in plasma: AUC (0-t), AUC (0-∞), Cmax, tmax, λz, t1/2 and CL/F were calculated for plasma GSK1265744.

Plasma concentration-time profiles for GSK1265744 were compared with those for total radioactivity to estimate how much of the total measured radioactivity was due to metabolites. For plasma containing sufficient radioactivity, profiling and identification of these metabolites were considered in a separate study.

Summary:

A total of 16 subjects (6 in Part A and 10 in Part B) were recruited and 15 subjects completed the trial as planned. Demographic characteristics were mostly similar across treatment groups. Of note, the placebo arm was entirely female White Caucasian in Part B of the study whereas the GSK1265744 arm was more demographically diverse.

Subject Disposition and Demographic Characteristics				
Number of Subjects	Part A	Part B		
	[14C]-GSK1265744	Placebo	GSK1265744 150 mg	Total
Number of subjects planned, N:	6	2	8	10
Number of subjects entered , N:	6	2	8	10
Number of subjects included in All subjects (safety) population, n (%):	6 (100)	2 (100)	8 (100)	10 (100)
Number of subjects included in PK population, n (%):	6 (100)	0	8 (100)	8 (80)
Number of subjects completed as planned, n (%):	6 (100)	2 (100)	7 (87.5)	9
Number of subjects withdrawn (any reason), n (%):	0	0	1 (12.5)	1
Number of subjects withdrawn for SAE, n (%):	0	0	0	0
Number of subjects withdrawn for AE, n (%):	0	0	0	0
Reasons for subject withdrawal, n (%)				
Lost to follow-up	0	0	0	0
Adverse events	0	0	0	0
Protocol violation	0	0	0	0
Other (subject withdrew self)	0	0	1(12.5)	1
Demographics				
Age in Years, Mean (SD)	41.2 (7.22)	41.0 (11.31)	29.4 (9.43)	31.7 (10.36)
Sex, n (%)				
Female:	0	2 (100)	5 (63)	7 (70)
Male:	6 (100)	0	3 (38)	3 (30)
Height (cm), Mean (SD)	176.7 (5.37)	164.3 (3.18)	172.2 (13.00)	170.6 (11.99)
Weight (kg), Mean (SD)	88.8 (9.99)	70.1 (14.78)	81.4 (14.85)	79.1 (14.79)
Ethnicity, n (%)				
Hispanic or Latino:	1 (17)	0	0	0
Not Hispanic or Latino:	5 (83)	2 (100)	8 (100)	10 (100)
Race, n (%)				
African American/African Heritage	4 (67)	0	4 (50)	4 (40)
White – White/Caucasian/European Heritage	2 (33)	2 (100)	4 (50)	6 (60)

The overall mean recovery of radioactivity in urine and feces samples was 85.3% over the 384-hour study, with recovery in individual subjects ranging from 74.5 to 92.2%.

Selected PK parameters summarized by treatment are also presented in (GSK744) and 2 (radioactivity), below. Individual GSK1265744 CL/F and Vz/F were adjusted to reflect an actual dose of 28.0 to 28.4 mg of 14C-GSK1265744 sodium salt prior to summarization.

Summary of Plasma GSK1265744 Pharmacokinetic Parameters Following [14C]-GSK1265744 Single Dose Administration [1]

Treatment	n	Cmax (μg/mL)	AUC(0-∞) (μg.h/mL)	CL/F (L/hr)	Vz/F (L)	t1/2 (hr)	tmax[2] (hr)
[14C]-GSK1265744	6	2.48 (21)	96.5 (25)	0.29 (25)	16.4 (22)	38.8 (10)	2.00 (0.98-3.00)

[1] geometric mean (CV%) with GSK744 Dose: 28.0-28.4 mg
[2] median (range)

Summary of Radioactivity Pharmacokinetic Parameters in Blood and Plasma Following [14C]-GSK1265744 Single Dose Administration [1]

Treatment	n	Cmax (μg/g)	AUC(0-∞) (μg.h/g)	t1/2 (hr)	tmax[2] (hr)
[14C]-GSK1265744	Blood				
	6	1.43 (21)	56.1 (26)	39.4 (14)	1.52 (0.98-4.00)
	Plasma				
	6	2.65 (21)	107 (24)	41.2 (16)	1.52 (0.98-2.00)

[1] geometric mean (CV%) with GSK744 Dose: 28.1-28.4 mg
[2] median (range)

Selected individual pharmacokinetic parameters of plasma GSK1265744 following 150 mg single dose by treatment are also presented in below.

Summary of Plasma GSK1265744 Pharmacokinetic Parameters Following GSK1265744 150 mg Single Dose Administration [1]

Treatment	n	Cmax (μg/mL)	AUC(0-∞) (μg.h/mL)	CL/F (L/hr)	Vz/F (L)	t1/2 (hr)	tmax[2] (hr)
GSK1265744 150 mg	8	10.4 (26)	418 (32)	0.36 (32)	19.7 (29)	38.1 (16)	2.50 (1.00-4.03)

[1] geometric mean (CV%)
[2] median (range)

All events except a Grade 2 AE of abdominal cramping were rated as mild in severity, and there was no event in either part of study which led to withdrawal from study treatment.

Summary of All Adverse Events			
Number of Subjects with Adverse Event n(%)	Part A	Part B	
	GSK1265744 30 mg (n=6)	Placebo (n=2)	GSK1265744 150 mg (n=8)
Any AE, n (%)	2 (33)	1(50)	4(50)
Somnolence	1 (17)	0	0
Nasal congestion	1 (17)	0	0
Haemoglobin decreased	0	0	2 (25)
Blood creatinine increased	0	0	1 (13)
Ecchymosis	0	1 (50)	1 (13)
Leukopenia	0	0	1 (13)
Abdominal pain	0	0	1 (13)
Constipation	0	0	1 (13)
Nausea	0	0	1 (13)
Proteinuria	0	1 (50)	0

Conclusions:

Part A

- A single oral dose of [14C]-GSK1265744 (mean 26.7 mg as the free acid (70.2μCi)) was well tolerated during this study in healthy adult males. No deaths, non-fatal SAEs, or withdrawals due to AEs were reported. AEs were reported with a low incidence, all of which were considered mild in intensity.
- The total mean recovery was 85.3% of the administered dose with a mean recovery of 58.5% in feces and 26.8% in urine.
- GSK1265744 was the predominant circulating compound in plasma.
- GSK1265744 and radioactivity tmax and t1/2 were similar, and exposures to radioactivity were approximately two-fold higher in plasma than in blood.
- GSK1265744 was observed to be present in all duodenal bile samples. The M1 glucuronic acid metabolite was also present in some but not all of the duodenal bile samples.

Part B

- A single 150 mg oral dose of GSK1265744 was generally well tolerated. No deaths, non-fatal SAEs, or withdrawals due to AEs were reported. Few AEs were reported, of which only 1 (cramping) was considered moderate in intensity.
- GSK1265744 150 mg did not achieve exposures significantly higher than steady state exposures observed following the likely clinical dose of 30 mg once daily, suggesting that a repeat dose strategy would be required to achieve supratherapeutic for evaluation of effect of GS1265744 on QTc.

Effective Date: [redacted]-20[redacted]

Synopsis for Study LAI115428

Title: A Randomized, Open Label Study to Investigate the Safety, Tolerability and Pharmacokinetics of Repeat Dose Administration of Long Acting GSK1265744 and Long-Acting TMC278 Intramuscular and Subcantenous Injections in Healthy Adult Subjects

Investigators: [redacted] and [redacted]

Study centers: [redacted] United States [redacted] and [redacted] United States [redacted]

Publications: None at the time of this report.

Study period: 10May2012 - 27Nov2013

Phase of development: I

Objectives:

Primary:

- To investigate the safety, tolerability, and pharmacokinetics (PK) of GSK1265744 LA (744 LA) following each intramuscular or subcutaneous dose in healthy subjects.
- To investigate the safety, tolerability, and PKs of TMC278 LA intramuscular doses when given in combination with 744 LA intramuscular doses in healthy subjects.

Secondary:

- To investigate the safety, tolerability, and PKs of oral GSK1265744 (744) in healthy subjects.
- To examine dose proportionality of 744 LA PK parameters following each intramuscular dose administration.
- To examine relative exposure of 744 LA PK parameters following intramuscular dose administration vs subcutaneous at 200mg 744 LA alone
- To explore concentration-effect relationships for various safety parameters, if appropriate.
- Comparison of TMC278 LA PK parameters across 744 LA Cohorts.

Methodology:

This was a Phase I, randomized, open-label study to investigate the safety, tolerability and PKs of repeat dose administration of long-acting 744 LA intramuscular (IM) and subcutaneous (SC) injections in healthy adult subjects. Subjects were randomized to three once-monthly IM or SC dosing cohorts or to a single once-quarterly IM dosing cohort. Subjects in the once-monthly dosing cohorts received either 744 LA alone for 3 months (cohort 1) or 744 LA alone for 2 months and then in combination with TMC278

LA for an additional 2 months (cohort 2 and 3). Subjects in the once-quarterly dosing cohort received 2 doses of 744 LA alone (cohort 4). This study consisted of a screening visit, an oral 744 run-in period, a treatment period and follow-up evaluations for 52 weeks following the final injection.

Number of subjects:

Approximately 40 subjects were to be enrolled such that approximately 32 subjects completed dosing and critical assessments.

Diagnosis and main criteria for inclusion:

Male or female between 18 and 64 years of age inclusive, at the time of signing the informed consent and with a body weight ≥50 kg for men and ≥45 kg for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive) were included in the study.

Treatment administration:

Subjects were assigned to treatment sequences in accordance with the randomization schedule generated by Discovery Biometrics, prior to the start of the study, using validated internal software.

A description of each regimen was provided in the table below:

Monthly Dosing:

Cohort	Lead-in Day-21 to -8	Month 1	Month 2	Month 3	Month 4
1	Oral 744 30mg q24h X 14 days	744 LA 800mg IM (2X400mg split LD)	744 LA 200mg SC	744 LA 200mg SC	744 LA 200mg SC
2			744 LA 200mg IM	744 LA 200mg IM + TMC278 LA 1200mg IM split LD[1]	744 LA 200mg IM + TMC278 LA 900mg IM
3			744 LA 400mg IM	744 LA 400mg IM + TMC278 LA 1200mg IM split LD[1]	744 LA 400mg IM + TMC278 LA 600mg IM

1. TMC278 LA 1200mg loading dose was split into 2 X 600mg doses. One 600mg dose given with the 744 LA dose and the second one hour after the first dose.

Quarterly Dosing:

Cohort	Lead-in Period Day -21 to -8	Quarter 1 and 2
4	Oral 744 30mg q24h X 14 days	744 LA 800mg IM (2X400mg split)

Criteria for evaluation:

Primary:

- 744 LA safety and tolerability parameters including adverse events (AEs), clinical laboratory, ECGs, and vital sign assessments.

- TMC278 LA safety and tolerability parameters including AEs, clinical laboratory, ECGs, and vital sign assessments.
- 744 LA PK parameters following single and repeat dose intramuscular or subcutaneous administration: area under the plasma concentration time curve over the dosing interval ($AUC_{(0-\tau)}$), maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), concentration at the end of the dosing interval (C_τ).
- 744 PK parameters following repeat dose oral administration: area under the plasma concentration time curve over the dosing interval ($AUC_{(0-\tau)}$), maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), concentration at the end of the dosing interval (C_τ).
- TMC278 LA PK parameters following single and repeat dose intramuscular administration: area under the plasma concentration time curve over the dosing interval ($AUC_{(0-\tau)}$), maximum observed concentration (C_{max}), time to maximum observed concentration (t_{max}), concentration at the end of the dosing interval (C_τ).

Secondary:

- 744 oral safety and tolerability parameters including AEs, clinical laboratory, ECGs, and vital sign assessments.
- 744 LA and TMC278 LA PK parameters: apparent clearance (CL/F_{LA}) following single and repeat dose administration.
- 744 LA $AUC_{(0-\tau)}$, C_{max}, and C_τ following each dose administration at different doses for the assessment of dose proportionality and relative exposure
- Apparent terminal phase half-life for LA administration ($t_{½}$), lambda z as a measure of absorption rate constant (λz) if data allow.
- TMC278 LA $AUC_{(0-\tau)}$, C_{max}, and C_τ in cohort 2 and 3.

Statistical methods:

The primary objectives of this study were to investigate the safety, tolerability, and PKs of repeat doses of 744 LA or in combination for TMC278 LA. No formal statistical hypotheses was to be tested. Where appropriate, an estimation approach was taken, and point estimates and confidence intervals (CI) were constructed.

Plasma GSK1265744 and TMC278 concentration-time data were analyzed by non-compartmental methods with WinNonlin 5.2 or higher. From the plasma concentration-time data, the following PK parameters following repeat dose intramuscular or subcutaneous administration were estimated for each dose in the monthly or quarterly regimen: area under the plasma concentration time curve from time zero to the end of the dosing interval ($AUC(0-\tau)$), maximum observed concentration (Cmax), time to maximum observed concentration (tmax), concentration at the end of the dosing interval ($C\tau$), and apparent clearance after extravascular administration (CL/F). Other parameters including the apparent terminal phase elimination rate constant (λz) and

apparent terminal phase half-life (t1/2) were determined. PK data were presented in graphical and/or tabular form and summarized descriptively.

Summary:

A total of 47 subjects were enrolled and dosed with at least one dose of oral 744 in the oral dosing period of the study. Seven subjects discontinued during the oral dosing period. Three of these were due to AEs (non-drug related n=2, drug-related dizziness n=1). Four subjects withdrew due to non drug related reasons including conflicting work schedules or personal issues.

Forty subjects received at least one 744 LA injection, 37 subjects completed all planned injections. One subject withdrew due to a Grade 1 rash which occurred one week after receiving his first injection and resolved within 5 days. Two others withdrew consent for non-drug related reasons; one received 2 of the 4 planned injections and one received all 4 injections.

Thirty one subjects entered into the long term follow-up phase of the study and 30 completed all safety assessments out to 52 weeks post the last injection. As this long term safety follow-up was added to the study as an amendment after study initiation, subjects were encouraged to enter this phase but could refuse participation.

2.7.6 Synopses of Individual Studies

Number of Subjects	Oral Lead-in period (N=47)	Cohort 1 (n=10)	Cohort 2 (n=10)	Cohort 3 (n=10)	Cohort 4 (n=10)	Total (N=47)
Number of subjects enrolled in oral dosing:	47					
Number of subjects completed in oral dosing:	40					
Number of subjects enrolled in injection dosing:		10	10	10	10	40
Number of subjects completed injection dosing phase:		9	9	10	9	37
Number of subjects enrolled in long term safety phase:		7	7	10	7	31
Number of subjects completed long term safety phase		7	6	10	7	30
Number of subjects included in All subjects (safety) population, n :	47	10	10	10	10	
Number of subjects included in PK population, n :	43	10	10	10	10	
Number of subjects withdrawn from oral dosing (any reason), n :	7	NA	NA	NA	NA	
Number of subjects withdrawn from injection dosing (any reason), n :		1	1	0	1	3
Number of subjects withdrawn from long term follow up (any reason), n :		0	1	0	0	1
Number of subjects withdrawn for SAE, n (%):	0	0	0	0	0	0
Number of subjects withdrawn for AE, n :	3	0	0	0	1	4
Reasons for subject withdrawal, n						
Adverse events	3	0	0	0	1	4
Withdrew consent	4	1	2	0	0	7
Not participating in long term follow up		2	2	0	2	6

Demographics	Oral lead-in period (N=47)	Cohort 1 (n=10)	Cohort2 (n=10)	Cohort3 (n=10)	Cohort4 (n=10)
Age in Years, Mean (SD)	39.5 (13.85)	39.6 (12.96)	36.5 (13.74)	43.0 (14.02)	42.4 (15.79)
Sex, n (%)					
Female:	17 (36)	4 (40)	4 (40)	4 (40)	4 (40)
Male:	30 (64)	6 (60)	6 (60)	6 (60)	6 (60)
BMI (kg/m2), Mean (SD)	26.13 (2.86)	28.11 (2.96)	24.41 (3.03)	26.84 (2.47)	25.26 (2.23)
Height (cm), Mean (SD)	173.8 (8.58)	175.8 (6.41)	174.3 (9.74)	171.6 (9.26)	172.3 (9.44)
Weight (kg), Mean (SD)	79.18 (11.94)	87.19 (11.89)	74.49 (13.66)	79.02 (9.46)	75.07 (9.74)
Ethnicity, n (%)					

Demographics	Oral lead-in period (N=47)	Cohort 1 (n=10)	Cohort2 (n=10)	Cohort3 (n=10)	Cohort4 (n=10)
Hispanic or Latino:	4 (9)	0	1 (10)	2 (20)	0
Not Hispanic or Latino:	43 (91)	10 (100)	9 (90)	8 (80)	10 (100)
Race, n (%)					
African American/African Heritage	10 (21)	3 (30)	1 (10)	1 (10)	3 (30)
Asian – East Asian Heritage	1 (2)	0	0	0	1 (10)
White – White/Caucasian/European Heritage	35 (74)	7 (70)	9 (90)	9 (90)	5 (50)
Mixed Race	1 (2)	0	0	0	1 (10)

Safety

All subjects in the 4 cohorts (Cohort 1, 2, 3 and 4) with LA injections had at least one AE and the most frequent AEs were injection site reactions (ISR) in all cohorts. All AEs by treatment with 744 alone and all AEs by treatment with 744 LA and with TMC278 LA were summarised.

Summary of All AEs by Cohort (SOC Class)				
Number of Subjects with AE n(%) (SOC Class)	**Cohort 1 (n=10)**	**Cohort 2 (n=10)**	**Cohort 3 (n=10)**	**Cohort 4 (n=10)**
Number of Subjects with any AE (SOC Class)	**10 (100)**	**10 (100)**	**10 (100)**	**10 (100)**
General disorders and administration site conditions	10 (100)	10 (100)	10 (100)	8 (80)
Infections and infestations	4 (40)	5 (50)	6 (60)	4 (40)
Nervous system disorders	4 (40)	5 (50)	5 (50)	2 (20)
Musculoskeletal and connective tissue disorders	2 (20)	5 (50)	2 (20)	6 (60)
Injury, poisoning and procedural complications	4 (40)	1 (10)	3 (30)	3 (30)
Gastrointestinal disorders	1 (10)	2 (20)	3 (30)	5 (50)
Respiratory, thoracic and mediastinal disorders	2 (20)	1 (10)	2 (20)	4 (40)
Skin and subcutaneous tissue disorders	1 (10)	0	5 (50)	2 (20)
Reproductive system and breast disorders	0	2 (20)	0	2 (20)
Investigations	0	0	3 (30)	0
Renal and urinary disorders	0	0	2 (20)	0
Metabolism and nutrition disorders	0	0	2 (20)	0
Psychiatric disorders	2 (20)	0	0	0
Ear and labyrinth disorders	1 (10)	0	0	0
Vascular disorders	0	1 (10)	0	0

Cohort 1= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Month 1), 744LA 200mg SC (one dose each month 2, 3 and 4).

Cohort 2= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Month 1), 744 LA 200mg IM (Month 2) 744 LA 200mg IM + TMC278 LA 1200mg IM split LD (Month 3), 744 LA 200mg IM + TMC278 LA 900mg IM (Month 3).

Cohort 3= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Month 1), 744 LA 400mg IM (Month 2), 744 LA 4 400mg IM + TMC278 LA 1200mg IM split LD (Month 3), 744 LA 400mg IM + TMC278 LA 600mg IM (Month 3).

Cohort 4= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Quarter 1 and 2).

Injection Site Reactions: The most commonly reported injection site reaction after receipt of 744 LA and IM TMC278 LA was pain, at 71% and 82% incidence, followed by less frequently observed erythema, warmth and nodules. The top 3 injection site

reactions for SC 744 LA were injection site erythema, pain, and nodule, which occurred at similar rates.

The duration of the top 3 ISR events for 744 IM, 744 SC and TMC278 IM are presented in the below table. The median duration values for pain and erythema were generally of shorter duration lasting ≤8 days while nodules had longer durations and were present for multiple months in subjects.

Summary of Duration (Days) for the Top 3 744 LA and TMC278 LA ISR Events by Treatment and Injection Location

ISR Event	744 LA IM (n=122)	744 LA SC (n=76)	TMC278 IM (n=42)
Injection site pain	5 (1-32)	6.5 (3-14)	4 (1-10)
Injection site erythema	4 (1-31)	8 (1-33)	5 (5-5)
Injection site nodule	23 (5-71)	64.5 (5-198)	56 (24-65)

Data reported in days as median (range)

When described by cohort, ISRs were the most commonly observed AEs. The most frequently described ISR related AE was injection site pain followed by erythema, warmth, nodule, induration, pruritus, swelling and discoloration. Cohort 1, where a single 744 LA IM 800mg injection was followed by three monthly SC injections of 744 LA, had a higher rate of erythema, warmth, nodule, induration, and pruritis, relative to Cohort 2, 3, and 4, where only IM doses were administered. The relative rates of ISR did not differ significantly between Cohorts receiving IM injections throughout the study (Cohorts 2, 3, and 4).

Most common injection site reactions (≥ 3 subjects) by cohort				
Injection Site Reaction	**Cohort 1 (n=10)**	**Cohort 2 (n=10)**	**Cohort 3 (n=10)**	**Cohort 4 (n=10)**
Any Subject with injection site event n(%)	**10 (100)**	**10 (100)**	**10 (100)**	**8 (80)**
Pain	10 (100)	9 (90)	9 (90)	6 (60)
Erythema	10 (100)	2 (20)	3 (30)	2 (20)
Warmth	8 (80)	1 (10)	3 (30)	1 (10)
Nodule	7 (70)	2 (20)	2 (20)	1 (10)
Induration	7 (70)	2 (20)	1 (10)	1 (10)
Pruritis	4 (40)	0	0	0
Swelling	3 (30)	0	1 (10)	0
Discoloration	3 (30)	0	0	0

Cohort 1= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Month 1), 744 LA 200mg SC (one dose each month 2, 3 and 4).
Cohort 2= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Month 1), 744 LA 200mg IM (Month 2) 744 LA 200mg IM + TMC278 LA 1200mg IM split LD (Month 3), 744 LA 200mg IM + TMC278 LA 900mg IM (Month 3).
Cohort 3= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Month 1), 744 LA 400mg IM (Month 2), 744 LA 400mg IM + TMC278 LA 1200mg IM split LD (Month 3), 744 LA 400mg IM + TMC278 LA 600mg IM (Month 3).
Cohort 4= Oral 744 30mg q24h X 14 days, 744 LA 800mg IM (2X400mg split LD) (Quarter 1 and 2).

The summary of ISR AE maximum intensity/grade for 744 LA IM, 744 SC and TMC278 IM at individual subject level are presented in the table below and all ISR events were of Grade 1 or Grade 2.

The overall ISR profile did not appear to change or worsen following repeated injections based on the incidence of ISRs over time.

Summary of incidence, severity of injection site reactions across treatments by event			
Overall Injections	**744 LA IM**	**744 LA SC**	**TMC278 IM**
Subjects with injections (n)	**40**	**10**	**19**
Total injections (n)	156	30	57
Total ISR events n(%)	146 (100)	130(100)	45(100)
Any grade 1 n (%)	118 (81)	128 (98)	39 (87)
Any grade 2 n (%)	28 (19)	2 (2)	6 (13)
Pain	104 (71)	26 (20)	37 (82)
Grade 1	76 (52)	25 (19)	31 (69)
Grade 2	28 (19)	1 (<1)	6 (13)
Erythema	11 (8)	28 (22)	2 (4)
Grade 1	11 (8)	28 (22)	2 (4)
Grade 2	0	0	0
Nodule	7 (5)	22 (17)	3 (7)
Grade 1	7 (5)	22 (17)	3 (7)

Summary of incidence, severity of injection site reactions across treatments by event			
Overall Injections	**744 LA IM**	**744 LA SC**	**TMC278 IM**
Subjects with injections (n)	**40**	**10**	**19**
Grade 2	0	0	0
Warmth at site	9 (6)	15 (12)	1 (2)
Grade 1	9 (6)	15 (12)	1 (2)
Grade 2	0	0	0
Induration	5 (3)	17 (13)	1 (2)
Grade 1	5 (3)	17 (13)	1 (2)
Grade 2	0	0	0

Data reported in days as median (range)

Non-ISR AEs

The summary of drug related non-ISR AEs by maximum intensity/grade are presented in the table below. Headache (9%) was the non-ISR reaction AE recorded most commonly in the oral 30mg 744 treatment group which was of mild in intensity. Headache was seen uncommonly during the injectable phase of the trial. Other non-ISR AEs are reported infrequently, without a clear trend relative to IM or SC dosing.

Summary of Drug Related non-ISR AE by Maximum Intensity/Grade						
	Oral (n=47)		**IM (n=40)**		**SC (n=10)**	
Number of Subjects with AE n (%) Preferred Term	**Mild**	**Moderate**	**Mild**	**Moderate**	**Mild**	**Moderate**
Number of Subjects with any AE	7 (15)	1 (2)	6 (15)	3 (8)	1 (10)	0
Headache	4 (9)	1 (2)	1 (3)	1 (3)	1 (10)	0
Abdominal pain	1(2)	0	1 (3)	0	1 (10)	0
Alanine aminotransferase increased	0	0	1 (3)	0	0	0
Arthralgia	0	0	1 (3)	0	0	0
Dizziness	1(2)	0	0	0	0	0
Erectile dysfunction	0	0	0	1 (3)	0	0
Flatulence	1(2)	0	0	0	0	0
Increased appetite	1(2)	0	0	0	0	0
Micturition urgency	0	0	1 (3)	0	0	0
Oedema peripheral	0	0	1 (3)	0	0	0
Pain	0	0	1 (3)	0	0	0
Pain in extremity	0	0	1 (3)	0	0	0
Pharyngitis	0	0	0	1 (3)	0	0
Pruritus	0	0	1 (3)	0	0	0
Rash	0	0	1 (3)	0	0	0
Rhinorrhoea	0	0	1 (3)	0	0	0

Individual plasma 744 PK parameters following oral, IM, and SC dose administration are listed and are summarized by treatment. Selected PK parameters summarized by treatment are also presented in the table below. Given the relatively short 28-day dosing

interval for monthly dosing cohorts (Cohorts 1 to 3) relative to apparent half-life estimates, data were insufficient to report 744 LA λz and apparent t1/2 for any subjects following the 800mg IM loading dose and all but one subject following Dose 2 or 3. These parameters were reportable more frequently following Dose 4 of the monthly regimens, where PK sampling was continued beyond the 28-day dosing interval, and following both doses of the 800mg IM quarterly regimen (Cohort 4).

Summary of Plasma 744 LA PK Parameters Following Repeat Oral, IM and SC Dose Administration[1]

Treatment	n	AUC(0-τ) (μg.h/mL)	CL/F (L/hr)	Cmax (μg/mL)	Cτ μg/mL)	λ-z (1/day)	t1/2 (day)	tmax[2] (day)
744 30mg oral QD Lead-in	43	147 (27)	0.20 (27)	8.30 (26)	4.87 (30)	ND	ND	2.00 (1.0-8.0)
744 LA 800mg IM LD Overall Cohorts 1-3	30	1178 (63)	0.42[3] (46)	2.50 (80)	1.76 (47)	ND	ND	13.00 (6.0-28.0)
Cohort 1								
800mg IM LD	10	1051 (57)	0.35[4] (63)	2.11 (76)	1.72 (51)	ND	ND	20.00 (6.0-28.0)
200mg SC D2	10	1304 (27)	0.13[5] (16)	2.22 (30)	1.90 (25)	ND	ND	16.50 (6.0-28.0)
200mg SC D3	10	1315 (19)	0.15[6] (16)	2.21 (20)	1.77 (16)	ND	ND	6.00 (0.0-20.0)
200mg SC D4	10	1244 (23)	0.16 (24)	2.11 (21)	1.66 (31)	0.01[7] (42)	46.6[7] (11)	6.00 (2.0-13.0)
200mgSC Overall	30	1287 (23)	0.15[8] (21)	2.18 (23)	1.77 (24)	0.01[7] (42)	46.6[7] (11)	6.00 (0.0-28.0)
Cohort 2								
800mg IM LD	10	1244 (77)	0.38[7] (25)	2.70 (99)	1.78 (54)	ND	ND	13.00 (6.0-28.0)
200mg IM D2	9	1348 (39)	0.13[9] (29)	2.68 (45)	1.71 (25)	0.03[11]	21.8[11]	6.00 (2.0-28.0)
200mg IM + TMC1200mg IM LD	9	1365 (17)	0.15[12] (16)	2.53 (20)	1.64 (36)	ND	ND	6.00 (2.0-28.0)
200mg IM + TMC900mg IM	9	1242 (39)	0.16 (39)	2.15 (31)	1.61 (64)	0.02[12] (30)	46.6[12] (26)	6.00 (2.0-27.0)
Cohort 3								
800mg IM LD	10	1252 (61)	0.48[9] (57)	2.74 (72)	1.78 (41)	ND	ND	6.00 (6.0-28.0)
400mg IM D2	10	2010 (31)	0.16[9] (12)	3.79 (40)	2.60 (24)	ND	ND	6.01 (2.0-28.0)
400mg IM + TMC1200mg IM LD	10	2182 (28)	0.19[6] (32)	4.03 (40)	2.69 (28)	ND	ND	6.00 (2.0-28.0)
400mg IM + TMC600mg IM	10	2473 (26)	0.16 (26)	4.41 (31)	3.27 (27)	0.02[9] (30)	30.5[9] (37)	6.00 (2.0-13.1)

Cohort 4								
800mg IM Q1	10	2917 (53)	0.27[6] (61)	2.70 (99)	0.74 (97)	0.03[12] (39)	23.9[12] (40)	16.50 (2.0-83.0)
800mg IM Q2	9	4468 (52)	0.18 (53)	3.31 (59)	1.10 (140)	0.02[7] (77)	26.8[7] (62)	15.00 (6.0-42.0)
800mg IM Q1, Q2 Overall	19	3570 (57)	0.21[13] (59)	2.97 (79)	0.89 (116)	0.03[14] (55)	24.9[14] (47)	15.00 (2.0-83.0)

ND = none determined
1 geometric mean (CV%)
2 median (range)
[3]n=12; [4]n=2; [5]n=3; [6]n=7; [7]n=4; [8]n=20; [9]n=6; [10]n=10; [11]n=1; [12]n=5; [13]n=16; [14]n=9

Individual plasma TMC278 PK parameters following IM administration are listed and are summarized by treatment. Selected PK parameters summarized by treatment are also presented in the table below. Similar to 744, data were insufficient to report TMC278 λz and t1/2 for most subjects following the 1200mg IM loading dose (TMC278 Dose 1). These parameters were reportable more frequently following TMC278 Dose 2 of the monthly regimens where PK sampling continued beyond the 28-day dosing interval.

Summary of Plasma TMC278 PK Parameters Following Repeat IM Dose Administration [1]								
Treatment	**n**	**AUC(0-τ) (ng.h/mL)**	**CL/F (L/hr)**	**Cmax (ng/mL)**	**Cτ (ng/mL)**	**λ-z (1/day)**	**t1/2 (day)**	**tmax[2] (day)**
Cohort 2								
GSK744 LA 200mg IM + TMC1200mg IM LD	9	52762 (51)	25.9[3] (50)	109 (53)	61.6 (64)	0.05[4]	13.9[4] (11)	6.00 (1.8-20.0)
GSK744 LA 200mg IM + TMC900mg IM	9	74420 (35)	12.1 (35)	168 (37)	79.1 (44)	0.02[5]	36.0[5] (21)	6.00 (2.0-13.0)
Cohort 3								
GSK744 LA 400mg IM + TMC1200mg IM LD	10	52703 (29)	22.3[6] (31)	108 (30)	64.0 (34)	ND	ND	6.00 (2.0-28.0)
GSK744 LA 400mg IM + TMC600mg IM	10	63656 (34)	9.43 (34)	126 (32)	78.9 (39)	0.02[6] (29)	41.9[6] (20)	9.50 (2.0-27.0)

ND = none determined
[1] geometric mean (CV%)
[2] median (range)
[3]n=7; [4]n=2; [5]n=5; [6]n=6

Conclusions:

- 744 LA was generally well tolerated when administered alone or with TMC278 LA. ISRs were common but generally mild in severity with no Grade 3 or 4 ISRs and no subject withdrew from the study due to an ISR. Pain at the injection site

was most commonly reported along with erythema but both were of short duration (median ≤8 days). The incidence of nodules was higher in those receiving subcutaneous 744 LA than in subjects with intramuscular injections.

- There were few drug-related AEs that were not associated with ISRs.
- A 744 LA loading dose of 800 mg IM followed by monthly injections of 200 mg IM or 400 mg IM provided plasma 744 concentrations at the end of the dosing interval that exceed the protein binding-adjusted IC90 by at least 4-fold.
- The concentrations at the end of the dosing interval for the 744 LA 400 mg dose were approximately 1.5 times higher than the 744 LA 200 mg IM dose.
- The PKs of 744 LA were similar between subcutaneous and intramuscular doses of 200 mg.
- Variability in this study was low to moderate with the LA form of 744 and similar to that with the oral dose.
- Both doses of TMC278 LA provided similar mean plasma concentrations at the end of the second dosing interval and comparable exposures to those achieved with 25 mg qd oral dosing of TMC278 (Phase III).

Effective Date: [redacted]

Synopsis for Study 205696

Name of company: ViiV Healthcare

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744 (Cabotegravir)

Study Number: 205696

Title: A Phase I study evaluating the effect of a high fat meal on the pharmacokinetics of cabotegravir in healthy adult volunteers

Investigator: [redacted]

Study Center: [redacted], United States

Publications: None at the time of this report

Study Period: 28-Jun-2016 to 25-Aug-2016

Phase of Development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
To evaluate the effect of a high fat meal on the pharmacokinetics of cabotegravir (CAB) following a single 30 mg dose using the Phase 3 formulation	• Cabotegravir (CAB) area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time (AUC[0-∞]), Area under the concentration time curve from time zero (pre-dose) to last time of quantifiable concentration within a subject across all treatments (AUC [0-t]), maximum observed concentration (Cmax) and concentration at 24 hours post-dose (C24).
Secondary	
To evaluate the effect of a high fat meal on the pharmacokinetics of CAB following a single 30 mg dose using the Phase 3 formulation	• Plasma CAB terminal phase half-life (t½), lag time before observation of drug concentrations in sampled matrix (tlag), time of occurrence of Cmax (tmax), percentage of AUC(0-∞) obtained by extrapolation (%AUCex), time of last measurable concentration (tlast) apparent clearance following oral dosing (CL/F), and apparent volume of distribution (Vz/F)
To assess the safety and tolerability of CAB administered as a single 30 mg dose with and without a high fat meal	• Safety and tolerability parameters, including adverse events, concurrent medication, clinical laboratory screens, electrocardiogram (ECG) and vital signs assessments.

Methodology:

This study was a single-center, randomized, open-label, two-way crossover study in healthy adult subjects. Subjects were randomized to one of the two treatment sequences (AB, BA). There was a 14-day washout between doses. Treatment A comprised of single dose of cabotegravir (CAB) 30 mg, [redacted] mg [redacted] oral tablet administered in fasted state, with at least 10 hours of fast. Treatment B comprised of single CAB 30 mg, [redacted] mg [redacted] oral tablet administered following a high fat meal, consisting of 53% fat and 870 calories.

Number of Subjects:
Twenty-four healthy subjects were planned to be enrolled and randomized to one of the two treatment sequences (AB, BA).

Diagnosis and Main Criteria for Inclusion:

Healthy male or female subjects between 18 and 65 years of age (inclusive) at the time of signing the informed consent having a body weight ≥50 kg and body mass index (BMI) within the range 18.5 – 31 kg/m^2 (inclusive) were included in the study.

Treatment Administration:

	Study Treatment
Product name:	**Cabotegravir Tablet, 30 mg**
Formulation description:	GSK1265744 ([redacted]) [redacted]
Dosage form:	White to almost white, oval-shaped, film coated Tablet, [redacted] mg
Unit dose strength(s)/Dosage level(s):	Tablet strength: 30 mg Dose level: 1 tablet
Route of Administration	Administered orally
Dosing instructions:	With 240 mL of water either fasted state, with at least 10 hours of fast (Treatment A) or following a high fat meal (Treatment B)
Manufacturer/Source of procurement	GlaxoSmithKline
Batch Number:	[redacted]

Statistical Methods:

No formal hypothesis was tested and an estimation approach was used to evaluate the food effect.

Sample size justification:

Based on the CAB formulation comparisons in LAI116585, the within subject coefficients of variation (CV_w%) were 21.6%, 21.4%, 20.7% and 21.0% for area under the concentration-time curve from time 0 extrapolated to infinity [AUC(0-∞)], Area under the concentration-time curve from time 0 to the last measurable timepoint [AUC(0-t)], maximal drug concentration (Cmax) and C24, respectively. The

CV_w% from the pharmacokinetic (PK) parameters AUC(0-∞), AUC(0-t), Cmax and C24 in study LAI117020 and in study 201741 for the 500mg core tablet weight formulation were under 20%. Based on these, a CV_w% of 22% was assumed in sample size calculations.

With a sample size of 24 subjects to have 20 evaluable subjects, it was estimated that the half width of the 90% confidence interval for the treatment difference on log-scale would be within 12% of the point estimate for AUC(0-∞), AUC(0-t), Cmax and C24. If the point estimate of the ratio of geometric means is 1, then the 90% confidence interval would be approximately (0.89, 1.13).

Analysis Populations:

- **Screening Population**

All subjects who had signed the consent form were included in this population. This population was used to present the date of first subject first screen, and numbers of subjects screened and enrolled.

- **Safety Population**

All subjects who were enrolled in the study and received at least one dose of study drug were included in the Safety Population.

This population was used for the safety analyses, as well as for presentation and summarization of baseline/demographic characteristics.

- **Pharmacokinetic Concentration Population**

The PK Concentration Population included all subjects in the study who underwent plasma PK sampling and have had evaluable CAB assays. PK assay results from samples collected from a subject with emesis occurring within 4 hours of the dose were not considered as evaluable.

This population was used for listing, and plotting of concentration-time data and PK parameter listing.

- **Pharmacokinetic Summary Population:**

The PK Summary Population included subjects who had valid CAB PK parameter estimates from both periods.

This population was used for summary and plotting of PK concentrations and parameters and statistical comparisons.

Pharmacokinetic Analyses:

Following $\log_e$-transformation, AUC(0-∞), AUC(0-t), Cmax, and C24 were separately analyzed using a mixed effects model with fixed effect terms for treatment, and period.

Subjects were treated as a random effect in the model. Point estimates and their associated 90% confidence intervals were constructed for the differences in PK parameter values for the following comparisons: Treatment B(test)-A(reference). The point estimates and their associated 90% confidence intervals were then back-transformed to provide point estimates and 90% confidence intervals for the ratios, Treatment B/A on the original scale.

For t1/2, Vz/F, and apparent oral clearance (CL/F), similar treatment comparison were carried out as secondary analyses.

Safety Analyses:

Safety data were presented in tabular and/or graphical format and summarized descriptively according to GSK's Integrated Data Standards Library (IDSL) standards.

2.7.6 Synopses of Individual Studies

Summary

Disposition			
Number of Subjects	**CAB 30 mg Fasted**	**CAB 30 mg + High fat meal**	**Overall**
Number of subjects planned [N]	24	24	24
Number of subjects randomized [N]	24	22	24
Number of subjects included in All subjects (safety) population [n (%)]	24 (100)	22 (100)	24 (100)
Number of subjects included in PK concentration population [n (%)]	24 (100)	22 (100)	24 (100)
Number of subjects included in PK summary population [n (%)]	21 (88)	21 (95)	21 (88)
Number of subjects completed as planned [n (%)]	22 (92)	22 (100)	22 (92)
Number of subjects withdrawn (any reason) [n (%)]	2 (8)	0	2 (8)
Reasons for subject withdrawal [n (%)]			
Withdrew consent	2 (8)	0	2 (8)
Demographics			
Demographic parameters	**CAB 30 mg Fasted (N=24)**	**CAB 30 mg + High fat meal (N=22)**	**Overall N=24**
Age in Years [Mean (SD)]	39.7 (14.69)	39.7 (14.51)	39.7 (14.69)
Sex [n (%)]			
Female:	8 (33)	8 (36)	8 (33)
Male:	16 (67)	14 (64)	16 (67)
BMI (kg/m^2) [Mean (SD)]	25.60 (2.629)	25.71 (2.722)	25.60 (2.629)
Height (cm) [Mean (SD)]	173.02 (8.946)	172.78 (9.262)	173.02 (8.946)
Weight (kg) [Mean (SD)]	77.16 (13.532)	77.34 (14.099)	77.16 (13.532)
Ethnicity [n (%)]			
Not Hispanic or Latino:	24 (100)	22 (100)	24 (100)
Race [n (%)]			
Asian – Central/ South Asian Heritage	1 (4)	1 (5)	1 (4)
Asian – South East Asian Heritage	1 (4)	1 (5)	1 (4)
Black or African American	6 (25)	5 (23)	6 (25)
White – White/Caucasian/European Heritage	16 (67)	15 (68)	16 (67)

Pharmacokinetic Results:

Summary of Selected Plasma CAB PK Parameters Following Single Dose Administration with and without a High Fat Meal

Treatment	AUC(0-∞)[a] (μg.h/mL)	Cmax[a] (μg/mL)	Tmax[b] (h)	C24[a] (μg/mL)	t1/2[a] (h)	CL/F[a] (L/hr)	Vz/F[a] (L)
A: CAB 30 mg Fasted (n=21)	143 [126, 162] (28)	3.33 [2.95, 3.77] (27)	3.0 (1.0-4.0)	1.62 [1.45, 1.81] (25)	40.6 [38.0, 43.5] (15)	0.210 [0.185, 0.239] (28)	12.3 [11.2, 13.6] (22)
B: CAB 30 mg Fed (n=21)	163 [144, 185] (29)	3.85 [3.46, 4.28] (24)	3.0 (1.0-8.0)	1.88 [1.69, 2.10] (24)	40.6 [37.8, 43.7] (16)	0.184 [0.162, 0.209] (29)	10.8 [9.8, 11.9] (21)

Plasma CAB AUC(0-∞), Cmax and C24 were increased 14-17% following single dose administration of 30 mg tablets with a high fat meal as compared to fasted conditions. CAB CL/F and Vz/F were decreased 13% as a result of greater bioavailability when coadministered with food. Apparent terminal phase t1/2 was unaffected by coadministration with a high fat meal.

Safety Results: There were no deaths, serious adverse events (SAEs), and no adverse events (AEs) leading to discontinuation of the study drug or withdrawal of any subject, reported during the study. None of the AEs were considered as related to the study drug. There were 2 treatment emergent grade 2 or 3 laboratory abnormalities reported in 2 subjects, none of which were considered clinically significant. No clinically significant abnormal vital signs or ECG findings were reported during the study. None of the clinical laboratory abnormalities, ECG and vital sign abnormalities were reported as an AE.

Conclusions:

- No new safety signal was detected during the study. There were no SAEs or drug-related AEs reported during the study. None of the laboratory, ECG or vital sign abnormalities were reported as an AE during the study.
- Plasma CAB AUC(0-∞), Cmax and C24 were increased 14-17% following single dose administration of 30 mg tablets with a high fat meal as compared to fasted conditions.

- CAB CL/F and Vz/F were decreased 13% as a result of greater bioavailability when coadministered with high fat meal. Apparent terminal phase t1/2 was unaffected by coadministration with a high fat meal.

- Oral CAB can be administered without regard to fat or caloric content of food.

Effective Date: [redacted]

Synopsis for Study 201120

Synopsis for Study 201120 Week 41

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744

Study Number: 201120

Title: A Phase IIa Study to Evaluate the Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, GSK1265744, in HIV Uninfected Men (ÉCLAIR) – Week 41

Investigators: This was a multicenter study.

Study centers: This study was conducted at 10 study centers in the United States.

Publications: None at the time of this report.

Study Period: 27-Mar-2014 – 15-May-2015 (Week 41)

Phase of Development: IIa

Objectives:

Primary Objective:

To evaluate the safety and tolerability of the injectable agent, GSK1265744 (cabotegravir; CAB), long-acting injectable (800 mg dose administered at 3 time points at 12 week intervals) through Week 41 in HIV-uninfected men.

Secondary Objectives:

Evaluate the pharmacokinetics of CAB following each intramuscular (IM) injection through 41 weeks.

Describe the pharmacokinetics of CAB by age, race, weight, and ethnicity.

Evaluate the safety and tolerability of oral CAB in HIV uninfected men.

Evaluate the acceptability of CAB injections through 41 weeks.

Explore concentration-effect relationships for various safety parameters, if appropriate.

Methodology:

Throughout the remainder of the document, GSK1265744 will be referred to as CAB.

This is a Phase IIa, randomized, multi-site, 2-arm, double-blinded study to evaluate the safety, tolerability, and acceptability of CAB in adult male subjects. After a screening

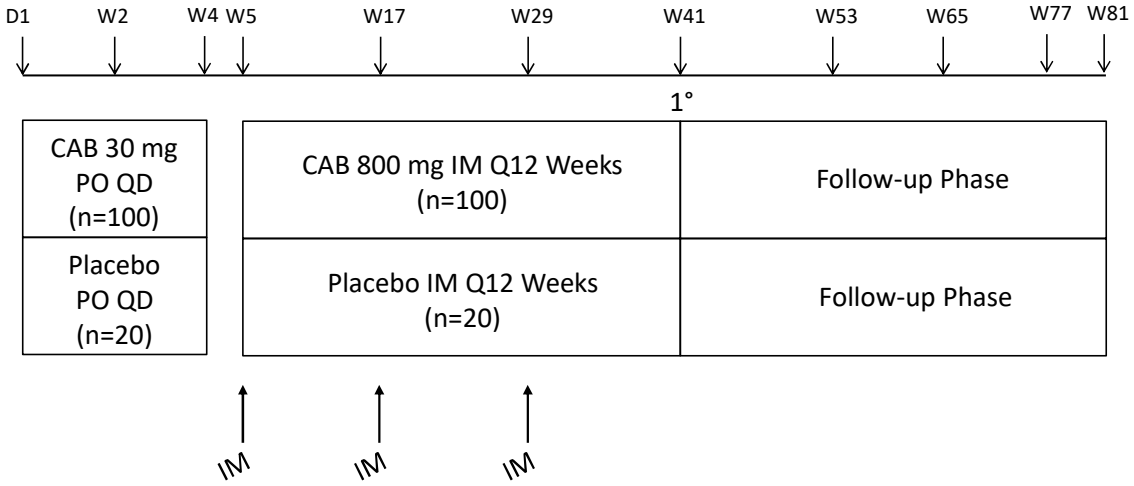
period of up to 30 days, eligible subjects were randomized in a 5:1 ratio to receive CAB or placebo.

Arm 1: Daily oral CAB (30 mg tablets) for 4 weeks during the Oral Phase of the study, followed by a 1-week washout period, to assess for safety and tolerability prior to receiving CAB injections. Following safety laboratory assessments from the Oral Phase, subjects entered the Injection Phase and received IM injections of CAB or placebo at 3 time points at 12-week intervals (Week 5, Week 17, and Week 29). The IM injections consisted of 800 mg of CAB or placebo.

Arm 2: Daily oral matching placebo and IM injections of placebo (0.9% saline) on the same schedule as Arm 1.

Participants in Arm 1 are being followed for 52 weeks following their last injection. Subjects in Arm 2 were followed until all subjects completed Week 41 and the database was cleaned, at which time the study was unblinded and placebo subjects were discontinued.

Study Schematic



CAB = cabotegravir; D = Day ; IM = intramuscular; PO = orally; QD= once a day; Q12 = once every 12; W = Week.

Number of subjects:

It was planned that a sufficient number of subjects would be screened (approximately 200 subjects) in order to ensure that approximately 120 subjects would be randomized into the Injection Phase of the study. Subjects were enrolled from multiple sites in the United States.

A total of 205 subjects were screened. Of the 127 subjects randomized, 126 subjects were treated (105 subjects in the CAB treatment group and 21 in the placebo treatment group); 100 (94%) CAB and 21 (100%) placebo subjects completed oral dosing. Six CAB subjects withdrew after oral dosing but prior to receiving injections. Of the 115 subjects who received injections, 87/94 (93%) CAB subjects, and 20/21 (95%) placebo subjects

completed the Injection Phase. Subjects who were withdrawn from the study were not replaced.

Diagnosis and main criteria for inclusion:

Healthy male subjects between 18 and 65 years of age, excluding subjects at high risk of acquiring HIV-1 at screening; subjects must have had a nonreactive HIV test at Screening or Enrollment.

Treatment administration:

Study Treatments				
Product name:	Oral CAB	Placebo to Match Oral CAB	CAB Injectable Suspension	Placebo CAB Injectable Suspension
Batch No.	[redacted]	[redacted]	[redacted]	Not applicable
Formulation description:	CABB, [redacted]	[redacted]	Sterile Suspension for Injection	Sterile saline 0.9% Sodium Chloride Injection, USP
Dosage form:	Tablet		Vial	
Unit dose strength(s)/Dosage level(s):	Dose level: 1 tablet Tablet strength: 30 mg	Placebo	Each vial contains 2 mL suspension of 200 mg/ml CAB	Injection to match CAB
Route/ Administration/ Duration:	Administer orally, once daily		Intramuscular Injection	
Method for individualizing dosage:	One 30mg tablet taken once a day for 4 weeks.	One tablet taken once a day for 4 weeks.	2 × 2 mL Injections (4 mL [800 mg] total) IM given every 12 weeks. Week 5, 17, and 29.	2 × 2 mL Injections IM given every 12 weeks. Week 5, 17, and 29.

Study Treatments			
Dosing instructions:	Dose in the morning with water.	Gently invert suspension vial for 20 seconds to resuspend sediment. Allow bubbles to subside, then use a syringe to withdraw the required volume of suspension for IM injection. Detailed instructions are provided in the SRM.	Use a syringe to withdraw the required volume of suspension for IM injection.
Manufacturer/ source of procurement:	GlaxoSmithKline		Site to purchase

CAB = cabotegravir, IM = Intramuscular; USP = U.S. Pharmacopeia; SRM = Study Reference Manual.

Criteria for evaluation:

The primary endpoints included safety and tolerability parameters, including adverse events (AEs), concurrent medication, required clinical laboratory tests, electrocardiogram (ECG), vital sign assessments, and injection site reactions (ISRs) for the Injection Phase (Week 5 through Week 41).

The secondary endpoints included the following: plasma CAB area under the concentration-time curve over the dosing interval (AUC[0-τ]), predose (trough) concentration at the end of the dosing interval (Cτ), maximum observed concentration (Cmax), half-life (t½), and lambda z; plasma CAB AUC(0-τ), Cτ, Cmax, t½, and lambda z by demographic factors (age, race, weight, and ethnicity); safety and tolerability parameters, including adverse events, concurrent medication required clinical laboratory assessments (Week 1 through Week 5 and Week 1 through Week 81, for oral CAB and overall); and incidence and severity of ISRs and ISR symptom score for Injection Phase (Week 5 through Week 41). Statistical evaluation of significant concentration-effect relationships could also have been explored.

Statistical methods:

Sample Size and Safety Population: The sample size of approximately 100 subjects in the CAB treatment arm and 20 subjects in the placebo arm were chosen to ensure an adequate evaluation of safety, tolerability and pharmacokinetics data in the CAB treatment arm prior to moving into a large Phase III study. The 20 placebo subjects served as a control to allow for clear interpretation of any safety findings. The Safety Population consists of all subjects enrolled in the study who received at least 1 dose of study drug. The Safety Injection Population consists of all subjects enrolled in the study who received at least 1 injection of study drug. In the analyses, subjects were grouped based on the treatment they received regardless of how they were randomized.

The Safety Population was the primary population for safety analyses. All safety analyses were produced using the Safety Population; some of the safety analyses were also produced using the Safety Injection Population.

Safety Analyses: Extent of exposure, Grade 2 or higher clinical and laboratory events, ISRs, AEs, serious AEs (SAEs), AEs leading to discontinuation of investigational product (IP) and/or withdrawal from the study, other significant AEs, clinical laboratory evaluations, vital signs, 12-lead ECGs, liver events, Bayesian analysis, and substance use were analyzed.

Pharmacokinetic Analyses: Individual plasma concentration-time profiles and median/mean profiles were plotted for Pharmacokinetic (PK) Parameter Population. Individual plasma CAB parameters were generated for each of the 3 quarterly 800 mg IM injections.

Health Outcomes Analyses: To assess tolerability of CAB, the proportion (with 95% confidence interval [CI] for the CAB arm) of subjects who terminated from receiving injections prior to the full course due to AE, intolerability of injection, frequency of injections, or burden of procedures related to injections, out of those subjects who received at least 1 injection, by treatment arm, was provided. The Study Medication Satisfaction Questionnaire (SMSQ) was also used to assess subject tolerability and satisfaction with the study medication.

Changes in the Planned Analyses: There was a typo in Section 8.4.1.1 of the protocol for the definition of primary endpoint. The protocol stated that “The primary safety analysis will include Grade 2 or higher clinical and laboratory events that occur from the initial injection to 24 weeks after the last injection among subjects who receive at least 1 injection.” It should have been 12 weeks after the last injection instead of 24 weeks. This typo was not fixed in Protocol Amendment 1.

As part of a secondary analysis regarding subject acceptability of CAB injections, Section 8.4.1.2 of the protocol, and Section 13.1 of the Reporting and Analysis Plan (RAP), state that to assess acceptability of CAB, the proportion of subjects who would consider using CAB for HIV prevention in the future will be calculated among all enrolled subjects (including those who terminated product use during the trial) and summarized by treatment arm. Subjects were to be asked if they would consider using CAB for HIV prevention in the future at their Week 41 visit or at their withdrawal visit, whichever occurred first. Neither health outcomes assessments nor the electronic case report form/study database included a specific question regarding consideration of future use of CAB at Week 41 or withdrawal visit. GSK/ViiV Healthcare made a decision during the study start-up period that the nature of the above stated secondary analysis could be similarly and effectively captured and analyzed based on health outcome questions. These questions are part of the Study Medication Satisfaction Questionnaires, including the SMSQ (status version; SMSQs), Study Medication Questionnaire (Injection) administered following injections on Weeks 6, 18, and 30, and the SMSQ (current version; SMSQc) administered at Week 18. Data collected from the Study Medication Satisfaction Questionnaires was summarized, and reported as detailed within the RAP.

To further explore ISR AEs, needle length (1.5 inch vs 2.0 inch) was incorporated into summaries of ISR events. No formal statistical comparisons for injection needle lengths were performed.

The Medical Dictionary for Regulatory Activities (MedDRA) v18.0 groups AEs of injection site swelling and injection site bumps into a single category. Since both of these events are of interest to the clinical study team, individual summaries of these distinct reaction types were created by utilizing the reported (uncoded) AE terms.

The SMSQc and SMSQs scores were calculated and summarized. When the RAP was finalized, the psychometric properties of the questionnaires had not been assessed.

Summary:

Summary of Demographic Characteristics (Randomized Population):

Demographic Characteristics	Placebo (N=21)	CAB (N=106)	Total (N=127)
Age (years)[a]			
Mean	33.7	35.1	34.9
Standard deviation (SD)	11.56	11.75	11.68
Median	30	31	31
Minimum, maximum	21, 57	20, 61	20, 61
Sex, n (%)			
Male	21 (100)	106 (100)	127 (100)
Race, n (%)			
African American/African Heritage	7 (33)	33 (31)	40 (31)
American Indian or Alaska Native	0	3 (3)	3 (2)
Asian - Central/South Asian Heritage	1 (5)	2 (2)	3 (2)
Asian - East Asian Heritage	1 (5)	2 (2)	3 (2)
Asian - Japanese Heritage	0	0	0
Asian - South East Asian Heritage	0	1 (<1)	1 (<1)
Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)
White - Arabic/North African Heritage	0	3 (3)	3 (2)
White - White/Caucasian/European Heritage	12 (57)	59 (56)	71 (56)
Missing	0	2 (2)	2 (2)
Ethnicity, n (%)			
Hispanic/Latino	3 (14)	16 (15)	19 (15)
Not Hispanic/Latino	18 (86)	90 (85)	108 (85)
Height (cm)			
Mean	175.5	176.5	176.3
Standard deviation	8.82	6.84	7.17
Median	175	176	176
Minimum, maximum	158, 193	160, 198	158, 198
Weight (kg)			
Mean	83.4	86.0	85.5
Standard deviation	22.56	20.10	20.45
Median	79	81	80
Minimum, maximum	48, 132	52, 167	48, 167
Body mass index (kg/m^2)			
Mean	26.8	27.5	27.4
Standard deviation	6.00	5.52	5.58
Median	25	26	26
Minimum, maximum	18, 40	18, 48	18, 48
HIV Risk Factors, n (%)			
Homosexual contact	16 (76)	90 (85)	106 (83)
Heterosexual contact	6 (29)	22 (21)	28 (22)
Occupational exposure	1 (5)	2 (2)	3 (2)

CAB = cabotegravir

a. For age, the number of subjects were as follows: placebo: n = 21, CAB: n = 105, and total: n = 126.

Safety Results:

During the Injection Phase, 75/94 (80%) subjects in the CAB treatment group reported a Grade 2 or higher AE compared with 10/21 (48%) subjects in the placebo treatment group. The statistically significant difference between treatment groups ($p<0.01$) was largely driven by events in the general disorders and administration site conditions system organ class (SOC), in which 56/94 (60%) subjects in the CAB treatment group and 1/21 (5%) subjects in the placebo treatment group reported an event. The most frequently reported event was injection site pain, which was reported by 55/94 (59%) subjects in the CAB treatment group and 1/21 (5%) subjects in the placebo treatment group ($p<0.01$). Of note, Subject [redacted], was randomly assigned to receive placebo, but was inadvertently dosed with CAB for the third injection on 09-FEB-2015 and reported a Grade 2 AE of injection site pain on that same day; this subject was included in the placebo treatment group for the Safety Population. No other preferred terms were statistically different in Grade 2 or higher AEs between treatment groups.

Primary Analysis of Grade 2 or Higher Adverse Events that Occurred in At Least 2 Subjects in Either Group During the Injection Phase (Safety Injection Population)

System Organ Class Preferred Term	Placebo (N=21) n (%, 95% CI)	CAB (N=94) n (%, 95% CI)	P-value
Any Grade 2 or higher event	10 (48, 26-70)	75 (80, 70-87)	<0.01
General disorders and administration site conditions			
Any event	1 (5, 0-24)	56 (60, 49-70)	<0.01
Injection site pain	1 (5, 0-24)	55 (59, 48-69)	<0.01
Pyrexia	0 (0, 0-16)	7 (7, 3-15)	0.35
Injection site pruritus	0 (0, 0-16)	6 (6, 2-13)	0.59
Injection site swelling	0 (0, 0-16)	6 (6, 2-13)	0.59
Chills	0 (0, 0-16)	3 (3, 1-9)	>0.99
Injection site induration	0 (0, 0-16)	3 (3, 1-9)	>0.99
Fatigue	0 (0, 0-16)	2 (2, 0-7)	>0.99
Injection site warmth	0 (0, 0-16)	2 (2, 0-7)	>0.99
Malaise	0 (0, 0-16)	2 (2, 0-7)	>0.99
Infections and infestations			
Any event	3 (14, 3-36)	19 (20, 13-30)	0.76
Gastroenteritis	0 (0, 0-16)	4 (4, 1-11)	>0.99
Upper respiratory tract infection	2 (10, 1-30)	4 (4, 1-11)	0.30
Nasopharyngitis	0 (0, 0-16)	3 (3, 1-9)	>0.99
Pharyngitis streptococcal	0 (0, 0-16)	3 (3, 1-9)	>0.99
Influenza	0 (0, 0-16)	2 (2, 0-7)	>0.99
Viral infection	0 (0, 0-16)	2 (2, 0-7)	>0.99
Musculoskeletal and connective tissue disorders			
Any event	0 (0, 0-16)	14 (15, 8-24)	0.07
Back pain	0 (0, 0-16)	4 (4, 1-11)	>0.99
Myalgia	0 (0, 0-16)	3 (3, 1-9)	>0.99
Arthralgia	0 (0, 0-16)	2 (2, 0-7)	>0.99

System Organ Class Preferred Term	Placebo (N=21) n (%, 95% CI)	CAB (N=94) n (%, 95% CI)	P-value
Bursitis	0 (0, 0-16)	2 (2, 0-7)	>0.99
Musculoskeletal chest pain	0 (0, 0-16)	2 (2, 0-7)	>0.99
Investigations			
Any event	2 (10, 1-30)	8 (9, 4-16)	>0.99
Blood CPK increased	1 (5, 0-24)	3 (3, 1-9)	0.56
Lipase increased	1 (5, 0-24)	2 (2, 0-7)	0.46
Nervous system disorders			
Any event	1 (5, 0-24)	6 (6, 2-13)	>0.99
Headache	1 (5, 0-24)	3 (3, 1-9)	0.56
Blood and lymphatic system disorders			
Any event	0 (0, 0-16)	4 (4, 1-11)	>0.99
Neutropenia	0 (0, 0-16)	2 (2, 0-7)	>0.99
Gastrointestinal disorders			
Any event	0 (0, 0-16)	4 (4, 1-11)	>0.99
Diarrhoea	0 (0, 0-16)	2 (2, 0-7)	>0.99
Vomiting	0 (0, 0-16)	2 (2, 0-7)	>0.99

CAB = cabotegravir; CI = confidence interval; CPK = creatine phosphokinase.
Note: Only events that were initiated before or on the subject's Week 41 visit or before the data cut-off date of [redacted]-20[redacted] for subjects who terminated study drug early were included. Injection Phase was defined as the period from the initial injection to 12 weeks after the last injection among subjects who received at least 1 injection. Exact binomial 95% CI were calculated for both arms for each System Organ Class and each AE term. Fisher's exact test was used to assess the differences in event rates between the 2 arms and no formal multiple comparison adjustments were employed.

Few subjects developed Grade 2 or higher laboratory abnormalities, and there were no statistically significant differences between the treatment groups for these events. Of note, a larger percentage of subjects in the CAB group than in the placebo treatment group developed Grade 2 or higher lipase events (11% versus 5%, respectively), while a smaller percentage of CAB subjects developed Grade 2 or higher creatine kinase events than in the placebo treatment group (6% versus 14%, respectively).

Primary Analysis of Grade 2 or Higher Laboratory Results for the Injection Phase (Safety Injection Population)

Laboratory Test	Placebo (N=21) n (%, 95% CI)	CAB (N=94) n (%, 95% CI)	P-value
Activated prothrombin time/standard	1 (5, 0-24)	0 (0, 0-4)	0.18
Activated partial thromboplastin time	1 (5, 0-24)	0 (0, 0-4)	0.18
Alanine aminotransferase	0 (0, 0-16)	2 (2, 0-7)	>0.99
Aspartate aminotransferase	0 (0, 0-16)	2 (2, 0-7)	>0.99
Bilirubin	0 (0, 0-16)	4 (4, 1-11)	>0.99
Carbon dioxide	0 (0, 0-16)	1 (1, 0-6)	>0.99
Cholesterol	1 (5, 0-24)	4 (4, 1-11)	>0.99

Laboratory Test	Placebo (N=21) n (%, 95% CI)	CAB (N=94) n (%, 95% CI)	P-value
Creatine kinase	3 (14, 3-36)	6 (6, 2-13)	0.36
Glucose	2 (10, 1-30)	7 (7, 3-15)	0.97
Leukocytes	0 (0, 0-16)	2 (2, 0-7)	>0.99
Lipase	1 (5, 0-24)	10 (11, 5-19)	0.69
Neutrophils	0 (0, 0-16)	3 (3, 1-9)	>0.99
Prothrombin time	1 (5, 0-24)	0 (0, 0-4)	0.18
Urate	1 (5, 0-24)	0 (0, 0-4)	0.18

CAB = cabotegravir; CI = confidence interval.
Note: Only events that were initiated before or on the subject's Week 41 visit or before the data cut-off date of [redacted]-20[redacted] for subjects who terminated study drug early were included. Injection Phase was defined as the period from the initial injection to 12 weeks after the last injection among subjects who received at least 1 injection. Exact binomial 95% CI were calculated for both arms for each System Organ Class and each AE term. Fisher's exact test was used to assess the differences in event rates between the 2 arms and no formal multiple comparison adjustments were employed.

On-Treatment Overall AEs and Grade 2 through Grade 4 AEs

The majority of subjects in both treatment groups reported at least 1 on-treatment AE. Overall, the most commonly reported on-treatment AEs for both groups included injection site pain (86/105 CAB subjects and 12/21 placebo subjects), headache (24/105 CAB subjects and 4/21 placebo subjects), and upper respiratory tract infection (18/105 CAB subjects and 5/21 placebo subjects).

Overall, the majority of subjects in both treatment groups reported a Grade 2 through Grade 4 AE on-treatment (84/105 CAB subjects and 13/21 placebo subjects). In the CAB treatment group, the most frequently reported Grade 2 through Grade 4 AEs included injection site pain (55/105 CAB subjects), blood creatine phosphokinase (CPK) increased (7/105 CAB subjects), and pyrexia (7/105 CAB subjects).

Injection Phase Overall AEs and Grade 2 through Grade 4 AEs

During the Injection Phase, AEs occurred at a similar frequency for both treatment groups (98% and 90% for the CAB and placebo treatment groups, respectively). The most frequently reported AEs overall included injection site pain, which occurred in 86/94 CAB subjects and 12/21 placebo subjects, and injection site pruritus (18/94 subjects vs 3/21 subjects, respectively).

During the Injection Phase, Grade 2 through Grade 4 AEs occurred more frequently in the CAB treatment group (75/94 subjects) than in the placebo treatment group (10/21 subjects); in the CAB treatment group this was driven primarily by ISRs including injection site pain (55/94 subjects) and injection site swelling and pruritus, (6/94 subjects each). No discernable patterns or trends were observed among subjects in the placebo treatment group.

Oral Phase Overall AEs and Grade 2 through Grade 4 AEs

During the Oral Phase, there was a higher incidence of AEs in the CAB treatment group (56/105 subjects) than in the placebo treatment group (8/21 subjects). The most frequently reported events were diarrhea (8/105 subjects in the CAB treatment group and 2/21 subjects in the placebo treatment group) and headache (9/105 subjects in the CAB treatment group and 1/21 subjects in the placebo treatment group). No discernable patterns or trends for differences between individual AEs between treatment groups were observed during the Oral Phase.

During the Oral Phase, the overall frequency of Grade 2 through Grade 4 AEs reported was similar for both treatment groups (23% of CAB subjects and 19% of placebo subjects). In the CAB treatment group, blood CPK increased, neutropenia, dizziness, and lipase increase was reported by 2 or more subjects each. All other Grade 2 through Grade 4 AEs during the Oral Phase were reported by 1 subject each.

Drug-Related AEs On-treatment, During the Injection Phase, and During the Oral Phase

Overall, 101/105 (96%) subjects in the CAB treatment group and 15/21 (71%) subjects in the placebo treatment group experienced drug-related AEs on-treatment. The majority of the drug-related events were Grade 1 or Grade 2 in severity. There were few Grade 3 or Grade 4 drug-related events in the CAB treatment group (20/105 [19%] subjects and 2/105 [2%] subjects, respectively) and none in the placebo treatment group. Injection site pain was the most frequently reported event in both treatment groups (86/105 [82%] subjects in the CAB treatment group and 12/21 [57%] subjects in the placebo treatment group), as well as the most commonly reported Grade 3 drug-related event among subjects in the CAB treatment group (18 of 105 subjects). All other Grade 3 drug-related AEs were reported for single subjects in the CAB treatment group and included neutropenia, myalgia, and chills. Two subjects (Subject [redacted] and Subject [redacted]) in the CAB treatment group developed Grade 4 drug-related events of blood CPK increased. Both events of blood CPK increased were nonserious and resolved without intervention. There was no clinical suspicion in either subject of rhabdomyolysis or renal failure accounting for the observed transient Grade 4 CPK elevations. Both subjects discontinued treatment and were withdrawn from the study. No other drug-related Grade 4 events were reported.

During the Injection Phase, 92/94 (98%) subjects in the CAB treatment group and 15/21 (71%) subjects in the placebo treatment group reported drug-related AEs. Most subjects with drug-related events reported at least 1 AE in the general disorders and administration site conditions SOC related to ISRs. The majority of events were Grade 1 or Grade 2 in severity, with injection site pain representing the most common event in both treatment groups. A total of 18/94 (19%) subjects with Grade 3 drug-related events reported drug-related injection site pain in the CAB treatment group. There were few other Grade 3 drug-related events and no Grade 4 drug-related events reported during the Injection Phase.

During the Oral Phase, 38/105 (36%) subjects in the CAB treatment group and 3/21 (14%) subjects in the placebo treatment group reported drug-related AEs. In the

CAB treatment group, the most commonly reported events were in the gastrointestinal disorders, nervous system disorders, general disorders and administrative site conditions SOCs, with headache, fatigue, and diarrhea, as the most common individual AEs. The majority of events were Grade 1 or Grade 2 in severity. Two Grade 4 drug-related AEs of increased blood CPK and 1 Grade 3 drug-related AE of neutropenia occurred during the Oral Phase in the CAB treatment group. In the placebo treatment group, there were 3 Grade 2 drug-related AEs (reported by 1 subject each); these were constipation, hyperglycemia, and insomnia. No other Grade 1, Grade 2, or Grade 3 drug-related AEs occurred among subjects in the placebo treatment group.

No deaths were reported during this study at the time of this Week 41 analysis.

Other Serious Adverse Events On-treatment, During the Injection Phase, and During the Oral Phase

Overall, 2 SAEs were reported on-treatment, one of which occurred in a subject on placebo and was considered drug-related. Both events occurred during the Injection Phase.

An SAE of appendicitis was reported in the CAB treatment group, and an SAE of deep vein thrombosis (DVT) was reported in the placebo treatment group; both events resolved. The SAE of DVT was considered related to study drug while the SAE of appendicitis was considered not related to study drug.

No SAEs were reported during the Oral Phase.

Other Significant Adverse Events On-treatment

Characteristics of Adverse Events of Headache

Overall, 26/105 (25%) subjects in the CAB treatment group and 4/21 (19%) subjects in the placebo treatment group reported AEs of headache while on-treatment. All AEs of headache were nonserious, none was Grade 3 or 4 in severity, and none led to study withdrawal. Adverse events of headache were considered drug-related in 12/105 (11%) subjects in the CAB group and none was considered drug-related in the placebo treatment group. The majority of the AEs of headache were reported once per subject, and those single occurrences were reported for 19/105 (18%) subjects in the CAB group, and 2/21 (10%) subjects in the placebo treatment group. The median duration of headaches was 3.0 hours for the CAB group and 2.0 hours for the placebo treatment group. The majority of subjects recovered from AEs of headache at a similar rate in both treatment groups. The majority of subjects in both treatment groups reported mild AEs of headache (21/105 [20%] subjects in the CAB treatment group and 3/21 [14%] subjects in the placebo treatment group) and continued study medication.

Abdominal Pain Adverse Events

Twelve of 105 (11%) subjects in the CAB treatment group and no subjects in the placebo treatment group reported abdominal pain AEs while on-treatment.

Hypersensitivity Reactions/Skin Rash Adverse Events

There were no AEs of hypersensitivity reactions or skin rashes reported for subjects on-treatment.

Injection Site Reaction Adverse Events

Each injection consisted of 2 x 2 mL injections totaling 800 mg of study drug.

During the Injection Phase, in the CAB treatment group, 94 subjects had a total of 272 injections with needles of either length; 197 injections were with a 1.5 inch needle, and 75 injections were with a 2.0 inch needle. In the placebo treatment group, 21 subjects had a total of 62 injections with needles of either length; 53 injections with a 1.5 inch needle, and 9 injections with a 2.0 inch needle. Both treatment groups had a similar proportion of subjects reporting ISR events with the 1.5 inch needle length and with the 2.0 inch needle length (56% and 67%; respectively for placebo and 94% and 88%, respectively for CAB).

Also during the Injection Phase, 87/94 (93%) subjects in the CAB treatment group experienced a total of 382 ISR events and 12/21 (57%) subjects in the placebo treatment group experienced 23 ISR events, regardless of needle length. In the CAB treatment group, most ISR AEs were Grade 1 (75/94 [80%] subjects) or Grade 2 (53/94 [56%] subjects) in severity. A total of 27 ISR events in 18/94 (19%) subjects were reported as a Grade 3 ISR AE (16/69 [23%] subjects with a 1.5 inch needle, and 2/25 [8%] subjects with a 2.0 inch needle), and no events were reported as a Grade 4 ISR AE in the CAB treatment group. In the placebo treatment group, most ISR AEs were Grade 1 in severity (11/21 [52%] subjects); there was 1 Grade 2, and no Grade 3 or Grade 4 ISR AEs. Overall, the severities of ISR AEs were similar regardless of needle length in both treatment groups.

The majority of the ISR AEs were attributed to injection site pain in both treatment groups. In the placebo treatment group, ISR AEs of pain were reported primarily as Grade 1 in severity.

In both treatment groups injection site pruritus AEs were primarily Grade 1 in severity regardless of needle length. Fewer Grade 2 injection site pruritus AEs occurred among subjects in the CAB treatment group compared to other ISR AEs and no Grade 2 injection site pruritus occurred among subjects in the placebo treatment group.

Injection site bruising, bumps, discoloration, erythema, induration, swelling, and warm touch were other symptoms commonly reported by subjects in the CAB treatment group and lasted between 2.5 and 9.7 days regardless of needle length.

Common ISR events are defined as all ISR events that occurred in at least 5 or more subjects. In both treatment groups, none of the common ISR events was considered serious or led to withdrawal, and the majority was considered drug-related. The majority of subjects in the CAB treatment group experienced 3 or more common ISR events, while the majority of subjects in the placebo treatment group experienced 1 ISR event,

regardless of needle length. In both treatment groups, all common ISR AEs resolved and study medication was continued.

Injection Site Reaction Events of Pain

Twelve subjects reported a total 17 ISR events of pain on placebo (15 with a 1.5 inch needle and 2 with a 2.0 inch needle), while 86 subjects reported a total of 250 ISR events of pain in the CAB treatment group (194 with a 1.5 inch needle and 56 with a 2.0 inch needle). Seventy-nine of the 86 subjects reported more than 1 ISR event of pain on CAB, while only 3 of the 12 subjects reported more than 1 ISR event of pain on placebo. All ISR events of pain were considered drug related, resolved, and study medication was continued. Most events in subjects on CAB were considered mild or moderate (Grade 1 or Grade 2). However, 18 subjects on CAB did report a Grade 3 ISR of pain (16 subjects with a 1.5 inch needle, and 2 subjects with a 2.0 inch needle). All ISR events of pain on the placebo treatment group were mild in severity. Of note, there was one Grade 2 ISR of pain reported for the placebo group; Subject [redacted], who was randomly assigned to receive placebo, but was inadvertently dosed with CAB for the third injection on 09-FEB-2015 and reported a Grade 2 AE of injection site pain on that same day; this subject was included in the placebo treatment group for the Safety Population.

Injection Site Reaction Events of Swelling and Bumps

Only subjects in the CAB treatment group reported ISR events of swelling. Fifteen subjects reported a total of 22 ISR events of swelling (18 subjects with a 1.5 inch needle and 4 subjects with a 2.0 inch needle). Five of the 15 subjects reported more than 1 ISR event of swelling. All ISR events of swelling were considered drug related, resolved, and study medication was continued. Most subject events were considered mild (Grade 1) (8 subjects with a 1.5 inch needle, and 3 subjects with a 2.0 inch needle), only 4 subjects reported a Grade 2 ISR of swelling (all with a 1.5 inch needle).

Only subjects in the CAB treatment group experienced ISR events of bumps. Twelve subjects reported a total of 21 ISR events of bumps (13 subjects with a 1.5 inch needle, and 8 subjects with a 2.0 inch needle). Eight of the 12 subjects reported more than 1 ISR event of bumps. All were considered drug related, recovered, and study medication was continued. Most subject events were considered mild (Grade 1) (4 subjects with a 1.5 inch needle, and 5 subjects with a 2 inch needle), and 3 subjects reported a Grade 2 ISR of bumps (all with a 1.5 inch needle).

Adverse Events Leading to Withdrawal From the Study

Overall, 7 subjects in the CAB treatment group and 1 subject in the placebo treatment group experienced an event that led to withdrawal or permanent discontinuation of study drug. All of the events leading to withdrawal in the CAB treatment group occurred during the Oral Phase; the event leading to withdrawal in the placebo treatment group occurred during the Injection Phase.

Clinical Laboratory Results

Mean changes from Baseline in chemistry, hematology, and urinalysis laboratory parameters were similar over the course of the study for the placebo and CAB treatment groups. Increases in lipid concentrations were not significant.

While On-treatment, the overall incidence of clinical chemistry laboratory abnormalities was similar between the CAB and placebo treatment groups, and most out of-range values were Grade 1 abnormalities. These results were representative of those obtained during the Injection Phase.

During the Oral Phase, clinical chemistry laboratory abnormalities were reported by a higher proportion of subjects in the CAB treatment group compared with the placebo treatment group, and most out-of-range values were Grade 1 abnormalities.

Clinical laboratory parameters of special interest included alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), bilirubin, leukocytes, neutrophils, creatine kinase, creatinine, hemoglobin, and platelets. The majority of subjects had Baseline laboratory values of special interest that were <Grade 1 and did not shift to a higher grade at any point on-treatment. Shifts from <Grade 1 at Baseline to a maximum toxicity ≥Grade 1 postbaseline were rare in the placebo treatment group. Postbaseline shifts to Grade 1 were observed with AST, leukocytes, and neutrophils in 5% to 10% of placebo subjects. None of the placebo subjects had a postbaseline shift to a Grade 2, 3, or 4 toxicity. The most common shift in the CAB group was from <Grade 1 at baseline to Grade 1 postbaseline. This on-treatment shift was observed for ALT (9% of subjects), AST (9% of subjects), bilirubin (5% of subjects), leukocytes (2% of subjects), and neutrophils (6% of subjects) for all on-study values. Shifts from <Grade 1 to higher toxicity grades were rare but occurred for ALT (shift to Grade 2 in 2% of subjects), AST (shift to Grade 2 in 3% of subjects, and shift to Grade 4 in 1% of subjects), and bilirubin (shift to Grade 2 in 3% of subjects).

Electrocardiogram Results

The majority of subjects had normal ECG findings over the course of the study. Of the abnormal ECG findings reported, all were considered not clinically significant, occurred with similar incidence across the treatment groups, and did not increase in incidence post baseline. There were no clinically significant abnormal ECG findings during the study and no ECG-related AEs. None of the subjects met protocol-specified withdrawal criteria of QTc using the Bazett formula (QTcB) >500 msec.

Most subjects in both treatment groups had a maximum change from Baseline in QTcB of <30 msec and the majority of subjects in both treatment groups had a change from Baseline in QTc using the Fridericia formula (QTcF) <30 msec. In the CAB treatment group, 2 subjects (2%) had a maximum change from Baseline in QTcB of ≥60 msec; 1 of these 2 subjects had a concurrent maximum change from Baseline in QTcF of ≥60 msec. For both subjects QTc values decreased at subsequent visits.

Vital Sign Measurement Results

Systolic and diastolic blood pressure findings were graded per the Division of Acquired Immunodeficiency Syndrome (DAIDS) toxicity scale. Mean vital signs were within normal limits throughout the study and were similar across the placebo and CAB groups.

During the Injection Phase of the study, 4 of 105 subjects in the CAB group developed Grade 1, blood pressure-related AEs, (hypertension [n=2], blood pressure increased [n=1]), and diastolic blood pressure increased [n=1]). None of the events was considered treatment-related by the investigator.

Mean changes from Baseline in vital signs across treatment groups did not show clinically relevant changes. Similar mean changes were observed between the placebo and CAB groups.

Health Outcomes Results

The majority of subjects in both treatment groups found it neither inconvenient nor difficult (score of 0) to receive the study medication as recommended, and most subjects in both treatment groups experienced little to no pain or discomfort (scores of 0 to 2) when receiving the study medication during the Injection Phase.

In general, the overall SMSQs and SMSQc mean scores were higher in the placebo treatment group than in the CAB treatment group at each time point; however, given the overlapping CIs, no clear separation between treatment groups can be concluded. In the CAB treatment group, satisfaction with study medication was consistent for the duration of the Injection Phase with similar overall scores at Weeks 6, 18, and 30.

Conclusions:

Safety

- Oral CAB 30 mg once daily and IM CAB 800 mg Q12 weekly were well tolerated in the Oral and Injection Phases, respectively, with few AEs leading to withdrawal.

- Few subjects developed Grade 2 or higher laboratory abnormalities. Elevations in laboratory parameters of special interest, including ALT, AST, bilirubin, creatine kinase, neutrophils, and lipase, were primarily Grade 1, with few subjects in either group developing Grade 3 or Grade 4 elevations.

- During the Injection Phase, Grade 2 through Grade 4 AEs occurred more frequently in the CAB treatment group compared to saline placebo, driven by ISRs including a statistically significant difference in injection site pain ($p<0.01$).

- Overall, 2 SAEs (appendicitis and DVT) were reported on-treatment, one of which was considered drug-related (DVT, in a subject on placebo). Both events occurred during the Injection Phase.

Pharmacokinetics

- Pharmacokinetic parameters following CAB treatment were not as predicted, driven by a faster absorption rate from the depot injection site.

- Mean Cτ concentrations are roughly one-third of expected; therefore, approximately two-thirds of subjects had Week 12 concentrations below the target value of 4 times PA-IC90.

- Based on PK results, there is a need to investigate alternative dosing strategy of 600 mg every 8 weeks in subsequent clinical trials.

Health Outcomes

- SMSQc results demonstrated that following repeat injections, Week 18 a majority of subjects receiving CAB favored IM CAB injections when compared with oral daily tablets.

- SMSQs results indicated that satisfaction with IM CAB injections was consistent for the duration of the Injection Phase with a majority of subjects both satisfied with, and willing to continue with CAB treatment.

- One week following second injection, subjects were universally more satisfied with IM CAB compared with once-daily oral CAB, on all 11 items included in the SMSQ.

Effective Date: [redacted]

Synopsis for Study 201120 Week 81

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744

Study Number: 201120

Title: A Phase IIa Study to Evaluate the Safety, Tolerability and Acceptability of Long Acting Injections of the HIV Integrase Inhibitor, GSK1265744, in HIV Uninfected Men (ÉCLAIR) – Week 81 Results

Investigators: This was a multicenter study.

Study centers: This study was conducted at 10 study centers in the United States.

Publications: None at the time of this report.

Study Period: 27-Mar-2014 – 23-Feb-2016 (Week 81)

Phase of Development: IIa

Objectives:

Primary Objective:

- To evaluate the safety and tolerability of the injectable agent, GSK1265744 (cabotegravir; CAB), long-acting injectable (800-mg dose administered at 3 time points at 12-week intervals) through Week 41 in human immunodeficiency virus (HIV)-uninfected men.

Secondary Objectives:

- Evaluate the pharmacokinetics of CAB following each intramuscular (IM) injection through 41 weeks.
- Describe the pharmacokinetics of CAB by age, race, weight, and ethnicity.
- Evaluate the safety and tolerability of oral CAB in HIV-uninfected men.
- Evaluate the acceptability of CAB injections from Week 5 to Week 41.
- Explore concentration-effect relationships for various safety parameters, if appropriate.

Methodology:

Throughout the remainder of the document, GSK1265744 will be referred to as CAB.

This was a Phase IIa, randomized, multi-site, 2-arm, double-blinded study to evaluate the safety, tolerability, and acceptability of CAB in adult male subjects. After a screening

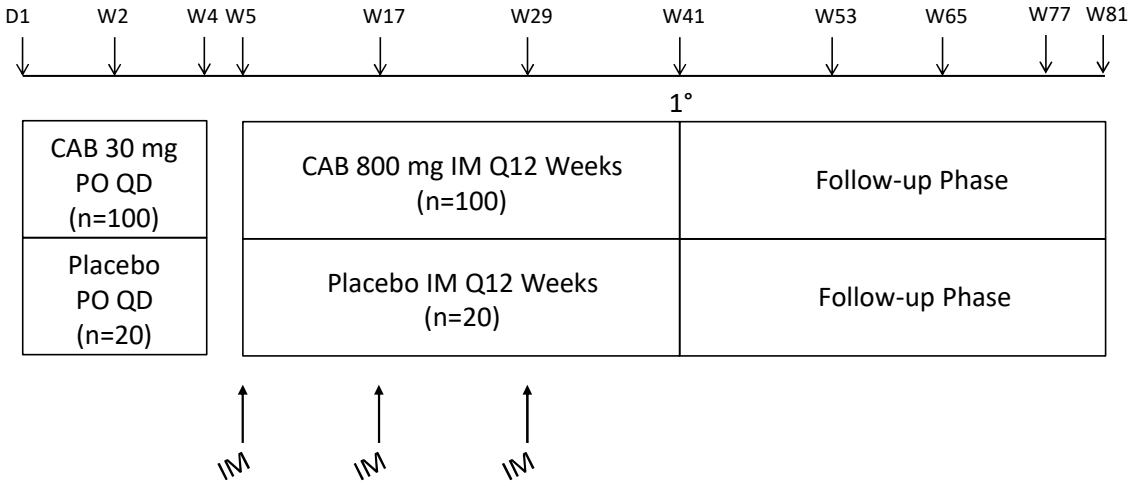
period of up to 30 days, eligible subjects were randomized in a 5:1 ratio to receive CAB or placebo.

Arm 1 (CAB treatment arm): Daily oral CAB (30 mg tablets) for 4 weeks during the Oral Phase of the study, followed by a 1-week washout period to assess for safety and tolerability prior to receiving CAB injections. Following safety laboratory assessments from the Oral Phase, subjects entered the Injection Phase and received IM injections of CAB at 3 time points at 12-week intervals (Week 5, Week 17, and Week 29). The IM injections consisted of 800 mg of CAB.

Arm 2 (placebo treatment arm): Daily oral matching placebo tablets during the Oral Phase, followed by a 1-week washout period, and IM injections of placebo (0.9% saline) during the Injection Phase, on the same schedule as Arm 1.

Participants in Arm 1 were followed for 52 weeks following their last injection at Week 29. Subjects in Arm 2 were followed until all subjects completed Week 41 and the database was cleaned, at which time the study was unblinded and placebo subjects were discontinued.

Study Design



CAB = cabotegravir; D = Day; IM = intramuscular; PO = orally; QD = once a day; Q12 = once every 12; W = Week.

Note: Subjects in Arm 2 were followed until all subjects completed Week 41, at which time the study was unblinded and placebo subjects were discontinued.

Number of subjects:

It was planned that a sufficient number of subjects would be screened (approximately 200 subjects) in order to ensure that approximately 120 subjects would be randomized into the Injection Phase of the study. Subjects were enrolled from multiple sites in the United States.

A total of 205 subjects were screened. Of the 127 subjects randomized, 126 subjects were treated (105 subjects in the CAB treatment arm and 21 subjects in the placebo arm); 100 (94%) CAB and 21 (100%) placebo subjects completed oral dosing. Six CAB subjects withdrew after oral dosing but prior to receiving injections. Of the 115 subjects who entered the Injection Phase, 87/106 (82%) CAB subjects, and 20/21 (95%) placebo subjects completed the Injection Phase. Subjects who were withdrawn from the study were not replaced.

Diagnosis and main criteria for inclusion:

Healthy male subjects between 18 and 65 years of age, excluding subjects at high risk of acquiring HIV type 1 (HIV-1) at Screening, with a nonreactive HIV test at Screening or Enrollment.

Treatment administration:

Study Treatments				
Product name:	Oral CAB	Placebo to Match Oral CAB	CAB Injectable Suspension	Placebo to Match CAB Injectable Suspension
Batch No.	[redacted]	[redacted]	[redacted]	Not applicable
Formulation description:	CAB, [redacted]	[redacted]	Sterile Suspension for Injection	Sterile saline 0.9% Sodium Chloride Injection, USP
Dosage form:	Tablet		Vial	
Unit dose strength(s)/Dosage level(s):	Dose level: 1 tablet Tablet strength: 30 mg	Placebo	Each vial contains 2 mL suspension of 200 mg/ml CAB	Injection to match CAB
Route/ Administration/ Duration:	Administer orally, once daily		Intramuscular Injection	
Method for individualizing dosage:	One 30mg tablet taken once a day for 4 weeks.	One tablet taken once a day for 4 weeks.	2 × 2 mL IM Injections (4 mL [800 mg] total) given every 12 weeks. (Weeks 5, 17, and 29).	2 × 2 mL IM Injections given every 12 weeks. (Weeks 5, 17, and 29).
Dosing instructions:	Dose in the morning with water.		Gently invert suspension vial for 20 seconds to resuspend sediment. Allow bubbles to subside, then use a syringe to withdraw the required volume of suspension for IM injection. Detailed instructions are provided in the SRM.	Use a syringe to withdraw the required volume of suspension for IM injection.
Manufacturer/ source of procurement:	GlaxoSmithKline			Site was to purchase

1. CAB = cabotegravir, IM = Intramuscular; USP = U.S. Pharmacopeia; SRM = Study Reference Manual.

Criteria for evaluation:

The primary endpoints included safety and tolerability parameters, including adverse events (AEs), concurrent medications, required clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs assessments, and injection site reactions (ISRs) for the Injection Phase (Week 5 through Week 41).

The secondary endpoints included the following: plasma CAB area under the concentration-time curve over the dosing interval (AUC[0-τ]), predose (trough) concentration at the end of the dosing interval (Cτ), maximum observed concentration (Cmax), terminal plasma half-life (t½), and lambda z; plasma CAB AUC(0-τ), Cτ, Cmax, t½, and lambda z by demographic factors; safety and tolerability parameters, including AEs, concurrent medications, and required clinical laboratory assessments; and incidence and severity of ISRs and ISR symptom score.

Statistical methods:

Sample Size and Safety Population: The sample size of approximately 100 subjects in the CAB treatment arm and 20 subjects in the placebo treatment arm were chosen to ensure an adequate evaluation of safety, tolerability and pharmacokinetics data in the CAB treatment arm prior to moving into a large Phase III study. The 20 placebo subjects served as a control to allow for clear interpretation of any safety findings. The Safety Population consisted of all subjects enrolled in the study who received at least 1 dose of study drug. The Safety Injection Population consisted of all subjects enrolled in the study who received at least 1 injection of study drug. In the analyses, subjects were grouped based on the treatment they received regardless of how they were randomized.

The Safety Population was the primary population for safety analyses. All safety analyses were produced using the Safety Population; some of the safety analyses were also produced using the Safety Injection Population.

Safety Analyses: Extent of exposure, Grade 2 or higher clinical and laboratory events, ISRs, AEs, serious AEs (SAEs), AEs leading to discontinuation of study drug and/or withdrawal from the study, other significant AEs, clinical laboratory evaluations, vital signs, 12-lead ECGs, liver events, and substance use were analyzed.

Pharmacokinetic Analyses: Individual plasma concentration-time profiles and median/mean profiles were plotted for Pharmacokinetic (PK) Parameter Population. Individual plasma CAB parameters were generated for each of the 3 quarterly 800 mg IM injections.

Health Outcomes Analyses: To assess acceptability of injections, the rate of unacceptability was calculated and summarized, by treatment arm, as the proportion (with 95% confidence interval [CI]) of subjects who withdrew from the Injection Phase due to injection intolerability among all subjects who received at least 1 injection. The following withdrawal reasons were attributed to injection intolerability: ISR AE leading to withdrawal, intolerability to injections, frequency of visits, or burden of procedures. The Study Medication Satisfaction Questionnaire (SMSQ) was also used to assess subject tolerability and satisfaction with the study medication.

Changes in the Planned Analyses: As part of a secondary analysis regarding subject acceptability of CAB injections, Section 8.4.1.2 of the protocol, and Section 13.1 of the Reporting and Analysis Plan (RAP), state that to assess acceptability of the CAB, the proportion of subjects who would consider using CAB for HIV prevention in the future will be calculated among all enrolled subjects (including those who terminated product use during the study) and summarized by treatment arm. Subjects were to be asked if they would consider using CAB for HIV prevention in the future at their Week 41 visit or at their withdrawal visit, whichever occurred first. Neither health outcomes assessments nor the electronic case report form/study database included a specific question regarding consideration of future use of CAB at Week 41 or withdrawal visit. GSK/ViiV Healthcare made a decision during the study start-up period that the nature of the above stated secondary analysis could be similarly and effectively captured and analyzed based on health outcome questions. These questions are part of the Study Medication Satisfaction Questionnaires, including the SMSQ (status version; SMSQs), Study Medication Questionnaire (SMQ) (Injection) administered following injections on Week 6, Week 18, and Week 30, and the SMSQ (change version; SMSQc) administered at Week 18. Data collected from the Study Medication Satisfaction Questionnaires were summarized and reported as detailed within the RAP. The RAP was amended to incorporate this analysis.

To further explore ISR AEs, needle length (1.5-inch versus 2-inch) was incorporated into summaries of ISR events. No formal statistical comparisons for injection needle lengths were performed.

The Medical Dictionary for Regulatory Activities (MedDRA) v18.0 groups AEs of injection site swelling and injection site bumps into a single category. Since both of these events are of interest to the clinical study team, individual summaries of these distinct reaction types were created by utilizing the reported (uncoded) AE terms.

Summary:

Summary of Demographic Characteristics (Randomized Population):

Demographic Characteristics	CAB (N=106)	Placebo (N=21)
Age (years)[a]		
Mean	35.1	33.7
SD	11.75	11.56
Median	31	30
Minimum, maximum	20, 61	21, 57
Sex, n (%)		
Male	106 (100)	21 (100)
Race, n (%)		
African American/African Heritage	33 (31)	7 (33)
American Indian or Alaska Native	3 (3)	0
Asian - Central/South Asian Heritage	2 (2)	1 (5)
Asian - East Asian Heritage	2 (2)	1 (5)

Demographic Characteristics	CAB (N=106)	Placebo (N=21)
Asian - Japanese Heritage	0	0
Asian - South East Asian Heritage	1 (<1)	0
Native Hawaiian or other Pacific Islander	1 (<1)	0
White - Arabic/North African Heritage	3 (3)	0
White - White/Caucasian/European Heritage	59 (56)	12 (57)
Missing	2 (2)	0
Ethnicity, n (%)		
Hispanic/Latino	16 (15)	3 (14)
Not Hispanic/Latino	90 (85)	18 (86)
Height (cm)		
Mean	176.5	175.5
SD	6.84	8.82
Median	176	175
Minimum, maximum	160, 198	158, 193
Weight (kg)		
Mean	86.0	83.4
SD	20.10	22.56
Median	81	79
Minimum, maximum	52, 167	48, 132
Body mass index (kg/m^2)		
Mean	27.5	26.8
SD	5.52	6.00
Median	26	25
Minimum, maximum	18, 48	18, 40
HIV risk factors, n (%)		
Homosexual contact	90 (85)	16 (76)
Heterosexual contact	22 (21)	6 (29)
Occupational exposure	2 (2)	1 (5)

1. CAB = cabotegravir.
2. a. For age, the number of subjects was: n = 105 in the CAB treatment arm.

Safety Results

The last dose of study drug was administered at Week 29; no additional study drug was administered from the time of the Week 41 analysis to the time of the Week 81 analysis. Through Week 81, the majority of subjects (101/105 [96%]) who received CAB experienced at least 1 on-treatment AE, with the most frequently reported on-treatment AE being injection site pain (86/105 [82%] subjects), which is consistent with the Week 41 analysis. Since the Week 41 analysis, additional on-treatment AEs reported during the Follow-up Phase through Week 81 that occurred in ≥ 2 CAB subjects and in ≥ 5% of CAB subjects included: diarrhea (n=3); as well as headache, upper respiratory tract infection, nasopharyngitis, nausea, and seasonal allergy (n=2 subjects each). At Week 81, no new types of AEs (i.e., preferred terms not previously reported) occurring in > 1 subject were reported since the Week 41 analysis. The reported number of CAB subjects who experienced the AE of injection site swelling decreased by 1 subject at Week 81 (20 [19%] subjects) since the Week 41 analysis (21 [20%] subjects): Subject [redacted] experienced on-treatment symptoms of "[redacted]"

that were coded to the preferred term of injection site swelling at the time of the Week 41 analysis; however, the symptoms were coded to the preferred term of injection site reaction at Week 81. One subject ([redacted]) had a reported AE of food poisoning at the time of the Week 41 analysis that was re-classified as Grade 1 diarrhea for the Week 81 analysis. One subject ([redacted]) had reported AEs of Grade 2 increased blood cholesterol and Grade 3 increased low density lipoprotein cholesterol at the time of the Week 41 analysis but were not recorded as AEs in the Week 81 analysis.

Summary of All On-Treatment Adverse Events in Greater Than or Equal to 5% Subjects in the CAB Treatment Arm by Overall Frequency at the Week 41 and Week 81 Analyses (Safety Population)

	Week 41 Analysis	Week 81 Analysis
Preferred Term	CAB (N=105) n (%)	CAB (N=105) n (%)
Any adverse event	101 (96)	101 (96)
Injection site pain	86 (82)	86 (82)
Headache[a]	24 (23)	26 (25)
Upper respiratory tract infection[a]	18 (17)	20 (19)
Injection site pruritus	18 (17)	18 (17)
Injection site swelling[a, b]	21 (20)	20 (19)
Pyrexia	17 (16)	17 (16)
Diarrhoea[a]	13 (12)	16 (15)
Fatigue[a]	15 (14)	16 (15)
Injection site bruising	11 (10)	11 (10)
Injection site warmth	12 (11)	12 (11)
Nasopharyngitis[a]	11 (10)	13 (12)
Myalgia	10 (10)	10 (10)
Viral upper respiratory tract infection[a]	10 (10)	11 (10)
Blood CPK increased	8 (8)	8 (8)
Injection site induration	10 (10)	10 (10)
Neutropenia	8 (8)	8 (8)
Dizziness	6 (6)	6 (6)
Gastroenteritis	6 (6)	6 (6)
Injection site erythema	6 (6)	6 (6)
Nausea[a]	5 (5)	7 (7)
Rhinitis allergic[a]	5 (5)	6 (6)
Seasonal allergy[a]	5 (5)	7 (7)
Chills[a]	5 (5)	6 (6)
Pharyngitis streptococcal	5 (5)	5 (5)
Influenza[a]	4 (4)	5 (5)
Back pain[a]	4 (4)	5 (5)
Vomiting[a]	4 (4)	5 (5)

1. CAB = cabotegravir; CPK = creatine phosphokinase.
a. Indicates a change from Week 41 to Week 81.
b. Subject [redacted] experienced on-treatment symptoms of "[redacted]" that was coded to the preferred term of injection site swelling at the time of the Week 41 analysis; however, the symptoms were coded to the preferred term of injection site reaction at the time of the Week 81 analysis.
1. Note: On-treatment was defined as the period from Day 1 to subjects' last day on study for subjects who received at least 1 dose of study drug.

On-Treatment Grade 2 through Grade 4 AEs

At Week 81, 87/105 (83%) subjects in the CAB treatment arm reported a Grade 2 or higher AE, compared with 84/105 (80%) subjects at Week 41. Through Week 81, the most frequently reported on-treatment Grade 2 through Grade 4 AEs in the CAB treatment arm included injection site pain (55/105 [52%]), increased blood CPK (7/105 [7%]), and pyrexia (7/105 [7%]), with no additional reports of these individual events since the Week 41 analysis. At Week 81, for AEs occurring in 2 or more subjects overall, additional Grade 2 AEs of procedural pain, back pain, chills, diarrhea, bursitis, influenza, aspartate aminotransferase (AST) increased, decreased appetite, weight decreased, and pruritus were reported since the Week 41 analysis. Procedural pain, which was reported by 2 subjects, was the only event reported by more than 1 subject since the time of the Week 41 analysis. There were 3 Grade 3 AEs reported since the time of the Week 41 analysis: hernia, affect lability, and erectile dysfunction (occurring in 1 subject each); there were no Grade 4 AEs reported since the time of the Week 41 analysis. One subject reported Grade 3 AEs of abdominal pain and appendicitis that occurred during the Follow-up Phase; however, these events had previously been reported in the Week 41 analysis as occurring during the Injection Phase. At the time of the Week 41 analysis, 1 subject experienced a nonserious Grade 2 AE of procedural pain considered not related to study drug; Subject [redacted] experienced postoperative pain following an osteotomy of the proximal right tibia. At Week 81, 2 additional subjects experienced nonserious Grade 2 AEs of procedural pain, both considered not related to study drug: Subject [redacted] experienced postoperative pain following a breast augmentation 233 days after the last dose of study drug, and Subject [redacted] experienced postoperative pain following a left groin hernia repair 343 days after the last dose of study drug. No additional Grade 2 through Grade 4 ISR AEs occurred from the Week 41 analysis through Week 81.

Drug-Related AEs On-treatment

Through Week 81, 101/105 (96%) subjects in the CAB treatment arm experienced on-treatment drug-related AEs, with no additional subjects who experienced on-treatment drug-related AEs since the Week 41 analysis. The reported number of CAB subjects who experienced the on-treatment drug-related AE of injection site swelling decreased by 1 subject at Week 81 (14 [13%] subjects) since the Week 41 analysis (15 [14%] subjects), due to recoding of the preferred term for 1 subject. Through Week 81, the majority of the drug-related AEs reported for the CAB treatment arm were Grade 1 or Grade 2 in severity. Through Week 81, there were few Grade 3 or Grade 4 drug-related AEs in the CAB treatment arm (20 [19%] and 2 [2%] subjects, respectively). Through Week 81, injection site pain was the most frequently reported Grade 1 or Grade 2 drug-related AE, and was the only Grade 3 drug-related AE experienced by ≥ 2 subjects in the CAB treatment arm. Through Week 81, all other on-treatment Grade 3 drug-related AEs (chills, neutropenia, anemia, myalgia, and night sweats) were reported for 1 subject each in the CAB treatment arm.

No deaths were reported during this study.

Other Serious Adverse Events On-treatment

At Week 81, no additional SAEs were reported since the Week 41 analysis. At the time of the Week 41 analysis, 2 on-treatment SAEs were reported: 1 SAE in the CAB treatment arm (appendicitis) and 1 SAE in the placebo treatment arm (deep vein thrombosis; DVT). Both SAEs were reported as having occurred during the Injection Phase in the Week 41 analysis; however, the SAE of appendicitis actually occurred during the Follow-up Phase and was reported as such for the Week 81 analysis. As reported in the Week 41 clinical study report, the event of DVT was the only SAE considered to be related to study drug. Both SAEs were resolved at the time of the Week 41 analysis.

Characteristics of Adverse Events of Headache

At Week 81, 2 additional subjects in the CAB treatment arm (28/105 [27%]) reported AEs of headache compared with 26/105 (25%) CAB subjects in the Week 41 analysis; neither of these additional AEs were considered to be related to study drug. All on-treatment AEs of headache were nonserious; none were Grade 3 or Grade 4 in severity, and none led to study withdrawal for any subjects in the CAB treatment arm.

Abdominal Pain Adverse Events

At Week 81, 13/105 (12%) subjects in the CAB treatment arm reported on-treatment abdominal pain AEs, compared with 12/105 (11%) subjects in the CAB treatment arm at the time of the Week 41 analysis.

Hypersensitivity Reactions/Skin Rash Adverse Events

Through Week 81, there were no reported on-treatment AEs of hypersensitivity reactions or skin rashes.

Injection Site Reaction Adverse Events

The last dose of study drug was administered at Week 29; therefore, ISR AEs reported at Week 81 are data carried forward from the Week 41 analysis. At Week 81, no additional ISR events were reported since the Week 41 analysis. At the time of the Week 41 analysis, all ISR events reported in the CAB treatment arm were considered recovered/resolved. During the study, 67/94 (71%) of the subjects in the CAB treatment arm who received injections experienced 3 or more occurrences of an ISR; none of these ISR events were considered serious. The majority (>99%) of the ISR events were considered to be related to study drug, and 27/377 (7%) were considered to be severe or Grade 3/4.

Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal From the Study

Through Week 81, 7 subjects in the CAB treatment arm, and 1 subject in the placebo treatment arm experienced AEs that led to withdrawal from the study; no additional

subjects experienced an AE that led to permanent discontinuation of study drug or withdrawal from the study since the Week 41 analysis.

Clinical Laboratory Results

Over the course of the study, mean changes from Baseline in chemistry, hematology, and urinalysis laboratory parameters were similar for the placebo and CAB treatment arms. At Week 81, no additional trends or increases of clinical concern in mean changes from Baseline in chemistry, hematology, or urinalysis laboratory parameters for the CAB treatment arm were observed since the Week 41 analysis.

At Week 81, increases in Grade 1 abnormalities since the Week 41 analysis were reported in the CAB treatment arm for alanine aminotransferase (ALT), 18 (17%) subjects, compared with 12 (11%) subjects; AST, 11 (10%) subjects, compared with 9 (9%) subjects; and glucose, 61 (58%) subjects, compared with 60 (57%) subjects. Increases in Grade 2 abnormalities since the Week 41 analysis were reported in the CAB treatment arm for AST, 5 (5%) subjects, compared with 4 (4%) subjects, and for cholesterol 4 (4%) subjects, compared with 3 (3%) subjects. Two Grade 3 abnormalities since the Week 41 analysis were reported in 1 subject each (<1%) in the CAB treatment arm for ALT (Subject [redacted], who contracted HIV-1 during the Follow-up Phase, developed a Grade 2 ALT abnormality during an unscheduled laboratory analysis on 11-Jun-2015 that increased to Grade 3 on 17-Jun-2015 at the 24-week follow-up visit) and AST (Subject [redacted] developed a new abnormality, onset: 48-week follow-up visit that returned to within the normal range at the 52-week follow-up visit). No new Grade 4 laboratory abnormalities were reported in the CAB treatment arm since the Week 41 analysis.

Similar to the results at the time of the Week 41 analysis, at Week 81, the most common shift in the CAB treatment arm was from <Grade 1 at baseline to Grade 1 postbaseline. This on-treatment shift was observed for ALT (13% of subjects), AST (10% of subjects), leukocytes (2% of subjects), and neutrophils (6% of subjects) for all on-study values. At Week 81, shifts from <Grade 1 to higher toxicity grades were rare but occurred for ALT (shift to Grade 2 in 1% of subjects, and shift to Grade 3 in 1% of subjects), AST (shift to Grade 2 in 4% of subjects, shift to Grade 3 in 1% of subjects, and shift to Grade 4 in 1% of subjects), and bilirubin (shift to Grade 2 in 3% of subjects).

Clinical laboratory-related AEs were reported during the study. At Week 81, 1 additional subject (22 [21%]) in the CAB treatment arm developed a laboratory AE since the time of the Week 41 analysis (21 [20%]). The most commonly reported clinical laboratory-related AEs (occurring in ≥5% of subjects in the CAB treatment arm) were neutropenia (8 [8%] subjects) and increased blood CPK (8 [8%] subjects). At Week 81, increased ALT and increased AST were reported for 1 additional subject each in the CAB treatment arm since the Week 41 analysis; no additional subjects developed neutropenia, increased CPK, or increased lipase since the Week 41 analysis.

Vital Sign Measurement Results

Systolic and diastolic blood pressure findings were graded per the Division of Acquired Immunodeficiency Syndrome (DAIDS) toxicity scale. Mean vital signs were within

normal limits throughout the study and were similar across the placebo and CAB treatment arms. Changes in vital sign parameters from Baseline to Week 41 were reported in a separate report. No differences were observed in changes in vital sign parameters from Baseline to Week 81 compared with changes from Baseline to Week 41.

Health Outcome Results

Health outcomes assessments were conducted in the study. Assessments were administered at the study visit, 1 week after the injections. The results of the health outcome assessments were reported in the Week 41 clinical study report and are not repeated in this report. No additional health outcome assessments were conducted after Week 41.

Pharmacokinetic Results

Geometric mean peak exposures (Cmax) ranged from 4.26 μg/mL to 5.22 μg/mL across the 3 injections. Geometric mean total exposure AUC(0-τ) increased by 19% for Injection 3 compared with Injection 1. Trough concentrations (Cτ) following each injection had geometric mean values of 0.302 μg/mL, 0.331 μg/mL, and 0.387 μg/mL for Injections 1, 2, and 3, respectively. The geometric mean t½ estimated for Injection 1 was 18.4 days, suggesting that the dosing interval of 84 days was approximately 4.6 half-lives in duration. Estimation of t½ following Injection 1 was limited by the short sampling period of 12 weeks prior to administration of Injection 2, likely biasing reportable t½ values to those of shorter duration. There were not sufficient data to estimate t½ for Injection 2. The geometric mean t½ estimated following Injection 3 was 40 days, and included individual PK data obtained during the Follow-up Phase. A majority of subjects (~60) had no or 1 measurable PK concentration in the Follow-up Phase. For these subjects, estimation of t½ was limited by the sparse sampling collection during the Follow-up Phase. Fourteen subjects, however, still had measurable concentrations at Week 81, 52-weeks after the final injection at Week 29. The prolonged t½ estimated based on terminal slopes in the Follow-up Phase could reflect ongoing slow absorption of drug into the plasma, rather than reflecting only the elimination process.

Virology Genotyping/Phenotyping

One subject in the CAB treatment arm had a confirmed positive HIV (wildtype infected) test result during the Follow-up Phase (Week 53), 172 days after the last dose of study drug. This subject completed the Follow-up Phase of the study, but started on a highly active antiretroviral therapy (HAART) regimen (darunavir, emtricitabine/tenofovir disoproxil fumarate, and ritonavir) on Study Day 470. The subject had on-treatment genotypic and phenotypic data collected at the Week 53 and Week 65 visits. This subject had no protease, reverse transcriptase, integrase, or genotypic resistance mutations at either the Week 53 or Week 65 visits. No notable on-treatment changes in phenotype relative to wildtype were identified at either visit. On-treatment genotypic substitutions reported at the Week 65 visit but not present at the Week 53 visit were G273G/R and V276V/I (reverse transcriptase) and S255S/G (integrase), none of which are associated with resistance to any ART drug class.

Conclusions:

Safety

- Overall, oral CAB 30 mg once daily and IM CAB 800 mg once every 12 weeks were well-tolerated in the Oral and Injection Phases, respectively, with few AEs leading to withdrawal. Treatment with CAB continued to be well tolerated during the Follow-up Phase with decreasing and residual exposures to CAB.

- Over the course of the study, Grade 2 or higher clinical chemistry laboratory abnormalities were observed in 33% of subjects in the CAB treatment arm. Elevations in laboratory parameters of special interest, including ALT, AST, bilirubin, creatine kinase, neutrophils, and lipase, were primarily Grade 1, with few subjects in either treatment arm who experienced Grade 3 or Grade 4 elevations.

- At the time of the Week 81 analysis, no additional ISR events were reported since the Week 41 analysis. All ISR events reported in the CAB treatment arm were considered recovered/resolved at the time of the Week 41 analysis.

- Overall, 2 SAEs were reported on-treatment: 1 SAE of DVT during the Injection Phase, considered to be drug-related, in a subject who received placebo, and 1 SAE of appendicitis during the Follow-up Phase, in a subject who received CAB. No new SAEs were reported since the Week 41 analysis.

Pharmacokinetics

- CAB PK parameters were not as predicted, driven by a faster absorption rate from the injection site.
- Mean Cτ values were approximately one-third of expected values; therefore, approximately two-thirds of participants had Week 12 concentrations below the target value of 4 times PA IC90.
- Based on PK results, there is a need to investigate the alternative dosing strategy of 600 mg every 8 weeks with the aim of achieving targeted exposure prior to conduct of Phase 3 efficacy trials.
- Approximately one-sixth of the PK subjects still had measurable concentrations at 52 weeks after the third injection; these subjects generally had BMI values above the median, suggesting an inverse relationship between BMI and the rate of drug absorption.

Virology Genotyping/Phenotyping

- One subject in the CAB treatment arm was withdrawn from the study during the Follow-up Phase due to confirmed positive HIV (wildtype infected) results.

Effective Date: [redacted]

Synopsis for Study ITZ112929

Identifier: RM2009/00485/00 **Study Number:** ITZ112929

Title: A Phase 2a Study to Compare Antiviral Effect, Safety, Tolerability and Pharmacokinetics of GSK1265744 Monotherapy Versus Placebo in HIV-1 Infected Adults (ITZ112929)

Investigator(s): This was a multicenter study.

Study center(s): This study was conducted at 4 centers in the United States.

Publication(s): None at the time of this report.

Study period:

Initiation Date: 09 JUN 2009

Completion Date: 13 AUG 2009

Phase of development: IIa

Objectives:

Primary

To evaluate antiviral activity of GSK1265744 vs. placebo in HIV-1 infected patients during 10 days of monotherapy.

To characterize pharmacokinetics of GSK1265744 in HIV-1 infected patients.

To assess safety and tolerability of GSK1265744 vs. placebo when administered as monotherapy over 10 days.

To explore the relationship between GSK1265744 exposure and change in plasma HIV-1 RNA.

Secondary

To assess the immunologic effect of GSK1265744 vs. placebo when administered over 10 days in HIV-1 infected subjects.

To explore the relationship between GSK1265744 exposure and safety or immunologic parameters, if appropriate.

To assess the development of viral resistance (genotypic and phenotypic) over 10 days and correlate with viral response, if appropriate.

To estimate GSK1265744 accumulation and time invariance and assess attainment of steady state following repeat dose administration in HIV-infected subjects.

To examine dose proportionality of GSK1265744 pharmacokinetic parameters following repeat dose administration in HIV-infected subjects.

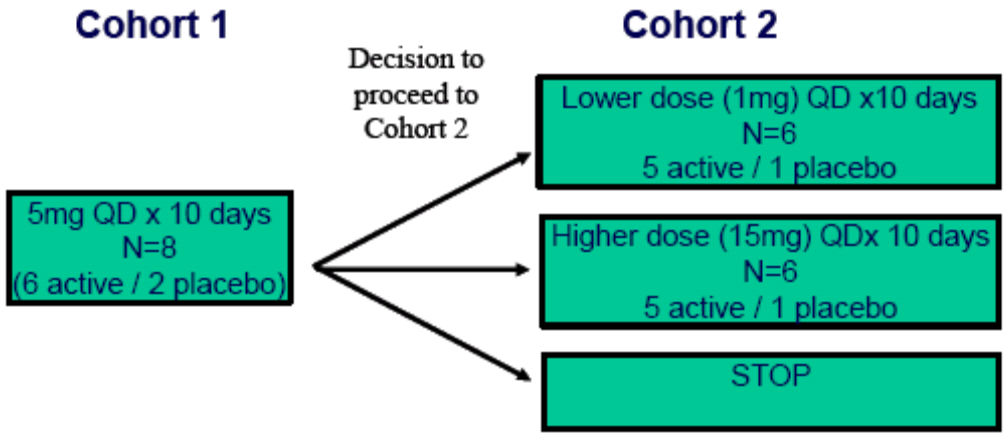
Exploratory

To evaluate the antiviral effect of GSK1265744 in HIV-1 infected subjects in subjects with <50copies/mL with a more sensitive viral load assay

Methodology:

Utlizing a blinded adaptive design, antiretroviral (ART)-naïve and experienced (integrase inhibitor naïve) HIV-1 infected subjects were randomized to receive 10 days of GSK1265744 monotherapy or placebo at the planned doses of either 1mg, 5mg and/or 15mg. This was followed by at least 14 days of investigator chosen optimized therapy. Treatment was unblinded on Day 11 so that subjects receiving placebo had the option to decline optimized therapy(OT).

Below is a graphic of the study design:



The dose of GSK1265744 to be chosen for Cohort 2, if any, was contingent on the safety, tolerability and antiviral activity of the preceding Cohort. The criteria for deciding to proceed to Cohort 2 are outlined in Section 1.2 of study protocol ITZ112929, Dose Rationale.

The Day 11 mean change from baseline of plasma HIV-1 RNA was predicted to be -2.2 log10 copies/mL for the GSK1265744 5mg QD dose studied in Cohort 1 of ITZ112929. This prediction was based on data from study ITZ111451 Cohort C where GSK1265744 30mg QD monotherapy was administered to HIV infected subjects as well as data following administration of the integrase inhibitor GSK1349572 in ING111521. Assuming dose proportionality with GSK1265744 30mg QD, the IQ following GSK1265744 5mg QD was predicted to be 3.3 (range 1.7- to 4.8-fold) above the PA-IC_{90}. This is consistent with the results, where the mean IQ achieved following 5mg QD in this study was 3.4 (range 2.3-fold to 5.5-fold). In addition, actual Day 11 mean change

from baseline of plasma HIV-1 RNA was -2.2 log10. Given the results observed with Cohort 1, both pharmacokinetic and pharmacodynamic predictions were met.

The dose-ranging studies completed with GSK1265744 5mg and 30mg doses provided sufficient data to progress into longer-term clinical studies. Therefore, no additional doses need be studied and the study was stopped after Cohort 1.

This report represents data from Cohort 1 only.

Number of subjects:

Approximately 8 subjects (6 active/ 2 placebo) were planned to be enrolled in the first Cohort and approximately 6 subjects (5 active/ 1 placebo) were planned to be enrolled in the second Cohort.

Subject Disposition and Demographics:

Number of Subjects	**GSK1265744 5mg**	**Placebo**	**Total**
Number of subjects planned, N:	6	2	8
Number of subjects randomized, N:	7	2	9
Number of subjects included in All subjects (safety) population, n (%):	7 (100%)	2 (100%)	9 (100%)
Number of subjects included in PK population, n (%):	7 (78%)	0	7 (78%)
Number of subjects completed as planned, n (%):	7 (78%)	2 (22%)	9 (100%)
Number of subjects withdrawn (any reason), n (%):	0	0	0
Number of subjects withdrawn for SAE, n (%):	0	0	0
Number of subjects withdrawn for AE, n (%):	0	0	0
Demographics	**GSK1265744 5mg**	**Placebo**	**Total**
Age in Years, Mean (SD)	39.7 (5.82)	37.5 (9.19)	39.2 (6.08)
Sex, n (%)			
Female:	2 (29%)	0	2 (22%)
Male:	5 (71%)	2 (100%)	7 (78%)
BMI, (kg/m2), Mean (SD)	27.38 (6.00)	29.82 (1.26)	27.92 (5.32)
Height, (cm), Mean (SD)	175.3 (11.59)	173.5 (4.95	174.9 (10.22)
Weight, (kg), Mean (SD)	83.16 (14.31)	89.90 (8.91)	84.66 (13.13)
Ethnicity, n (%)			
Hispanic or Latino:	1 (14%)	0	1 (11%)

Continued

Number of Subjects	GSK1265744 5mg	Placebo	Total
Not Hispanic or Latino:	6 (86%)	2 (100%)	8 (89%)
Race, n (%)			
African American/African Heritage	2 (29%)	0	2 (22%)
White – White/Caucasian/European Heritage	5 (71%)	2 (100%)	7 (78%)

Diagnosis and main criteria for inclusion:

HIV-1 infected male and female subjects between 18 and 55 years of age with CD4+ cell count ≥ 200 cells/mm^3 and plasma HIV-1 RNA ≥ 5,000 copies/mL at screening. Subjects were not on antiretroviral therapy and had not received any antiretroviral therapy in the 12 weeks prior to first dose. Subjects had adequate treatment options to construct highly active antiretroviral therapy (HAART) with at least 3 active antiretrovirals (selected by the Investigator).

Treatment administration: The following treatments were administered during the 10 days of dosing:

Drug	Dose/Form/Route	Frequency/Duration	Batch Number
GSK1265744	1 x 5mg / tablet / oral	Repeat Doses, QD, for 10 days	[redacted]
Placebo	1 / tablet / oral	Repeat Doses, QD, for 10 days	[redacted]

Study treatment was followed by at least 14 days of investigator chosen optimized therapy (OT). Treatment was unblinded on Day 11 so that subjects receiving placebo had the option to decline OT.

Criteria for evaluation:

Primary

Change from baseline in plasma HIV-1 ribonucleic acid (RNA) to Day 11.

GSK1265744 PK parameters following dose administration on Day 1 and 10:

area under the plasma concentration time curve (AUC(0-24))

maximum observed concentration (Cmax)

time to maximum observed concentration (tmax)

concentration at 24 hours post dose (C24)

terminal half-life (t1/2)

absorption lag time (tlag), and apparent clearance (CL/F)

GSK1265744 PK parameters following last repeat administration on Day 10:

AUC(0-τ)

predose concentration (C0)

concentration at end of dosing interval (Cτ)

minimum observed concentration during one dosing interval (Cmin)

Cmax, tmax, t1/2, and CL/F, if data permit.

Safety and tolerability parameters, including adverse events (AEs), clinical laboratory results, vital signs, and electrocardiogram (ECG) assessments.

Secondary

Change from baseline in plasma HIV-1 RNA

Change from baseline in plasma HIV-1 RNA to nadir (maximum change) over 11 days.

Plasma HIV-1 RNA rate of decline (slope) over 11 days.

Proportion of subjects with HIV-1 RNA<400 copies/mL

Proportion of subject with HIV-1 RNA<50 copies/mL

Change from baseline in CD4+ cell count to Day 11

Emergence of drug resistance mutations, if appropriate

GSK1265744 Day 10 AUC(0-τ), Cmax, and Cτ compared to Day 1 AUC(0-24), Cmax, and C24, respectively, to estimate accumulation ratios (R) for AUC, Cmax, and Cτ; pre-morning dose concentrations (C0) from Day 7 through Day 10 (actual measurements collected on Days 2 through 4 and Days 7 through 10) to assess the achievement of steady state of GSK1265744 following repeat administration.

Day 1 AUC(0-24), Cmax, and C24, and Day 10 AUC(0-τ), Cmax, C0, Cτ, and Cmin at different doses for the assessment of dose proportionality.

Exploratory

Quantify plasma HIV-1 RNA concentration in those subjects receiving GSK1265744 with HIV-1 RNA <50 copies/mL, if warranted.

Statistical methods:

Sample Size Assumptions

The sample size for this study was based primarily on feasibility to provide adequate precision for the estimations.

Interim Analyses

An informal analysis of preliminary safety, tolerability and antiviral activity was completed after all subjects of Cohort 1 had completed their Day 11 visit. The study team was unblinded in order to provide OT for subjects on active drug and to determine whether there is a need to conduct Cohort 2.

Efficacy Analyses

The ITT Population was used for all efficacy analyses.

Change from baseline of plasma HIV-1 RNA to Day 11 was statistically compared between each active treatment and placebo, using the t-test based on analysis of covariance (ANCOVA). No adjustment for multiple comparisons was made.

Plasma HIV-1 RNA change from baseline and from baseline to the on-treatment nadir (maximum change) was calculated for each subject on each assessment day. Plasma HIV-1 RNA was listed by treatment, subject, and assessment day and summarized by treatment and assessment day along with change from baseline. Plots of mean and median plasma HIV-1 RNA actual and change from baseline data was generated by treatment and assessment day.

Statistical Analyses of PK Data

Data from GSK1265744 30mg in HIV patients (Study ITZ111451 part C HIV cohort) was combined with data from this study for dose proportionality assessment and PK/PD relationships.

The power model was fitted by restricted maximum likelihood (REML) using SAS Proc Mixed. A fixed effects power model was used. The mean slope was estimated from the power model with the corresponding 90% confidence interval.

The accumulation ratio (R), time invariance, and steady-state assessments at 5mg dose were performed. Comparisons of Day 10 with Day 1 PK for each dose was used for the accumulation ratio (R) evaluation. Pre-dose concentration between Days 7-10 was used for steady-state assessment. Plasma GSK1265744 PK parameters was log-transformed.

Pharmacokinetic/Pharmacodynamic Analyses

The accumulation ratio (R) and steady-state assessments following GSK1265744 5mg were performed. Time invariance was not determined since Day 1 AUC(0-∞) could not be estimated with the data collected. Comparisons of Day 10 with Day 1 PK for each dose was used for the accumulation ratio (R) evaluation. Pre-dose concentration between Days 7-10 was used for steady-state assessment. Plasma GSK1265744 PK parameters were log-transformed.

Pharmacokinetic/Pharmacodynamic Analyses

Relationships between various PK parameters (AUC, Cmax, Cmin, Cτ, etc.) and PD measures (e.g., Log10 reduction in plasma HIV-1 RNA on Day 11 from baseline or safety parameters) was explored using various models including Emax model on combined data from this study and Part C of the ITZ111451 study. Details of the PK/PD exploratory analyses are provided in the RAP.

Viral Genotyping and Phenotyping Analyses

The viral genotypic/phenotypic data were listed and descriptive summaries provided.

Summary:

Safety:

GSK1265744 5 mg QD x 10 days was generally well-tolerated. There were no serious adverse events (SAEs) reported and only mild to moderate AEs were reported. No subject withdrew from the study due to an AE. No AEs were reported on the GSK1265744 5mg arm.

In general, there were few clinical laboratory abnormalities reported during the study and period. Intrasubject vital signs measurements varied modestly during the study period; there were no consistent intra-or inter-subject trends in vital signs changes noted in Cohort 1. No clinically significant vital signs were noted during GSK1265744 dosing. No consistent trends or clinically significant changes were noted on ECG.

Summary of All Adverse Events

Adverse Event	GSK126574 4 5mg (N=7)	Placebo (N=2)	OT (N=8)	Overall (N=9)
Any AE, n (%)	0 (0%)	2 (100%)	3 (38%)	5 (56%)
Nausea	0 (0%)	1 (50%)	1 (13%)	2 (22%)
Abdominal Pain	0 (0%)	0 (0%)	1 (13%)	1 (11%)
Constipation	0 (0%)	0 (0%)	1 (13%)	1 (11%)
Blood Bilirubin Increase	0 (0%)	1 (50%)	1 (13%)	2 (22%)
Ocular Icterus	0 (0%)	0 (0%)	1 (13%)	1 (11%)
Pain in Extremity	0 (0%)	1 (50%)	0 (0%)	1 (11%)
Headache	0 (0%)	0 (0%)	1 (13%)	1 (11%)

Summary of Grade 2 or Higher Laboratory Evaluations

Laboratory Analyte	Treatment	Time point	Grade		
			2	3	4
Increased Total Bilirubin	GSK1265744 5 mg	Follow Up	2 (29%)	0 (0%)	0 (0%)
Hyperglycemia	GSK1265744 5 mg	Day 1, Day 3, Day 10	1 (14%)	0 (0%)	0 (0%)
		Follow Up	0 (0%)	1 (14%)	0 (0%)
Decreased Neutrophils	GSK1265744 5 mg	Screening, Day 3	1 (14%)	0 (0%)	0 (0%)
		Day 10	0 (0%)	1 (14%)	0 (0%)
Elevated Triglycerides	GSK1265744 5 mg	Day 7	0 (0%)	0 (0%)	1 (17%)

Pharmacokinetics:

The results of the statistical comparison of GSK1265744 plasma PK parameters are presented in the tables below.

Summary of Dose Proportionality of Single Dose GSK1265744 PK Parameters Using Power Model

Plasma GSK1265744 PK Parameter	Slope [90% CI]	
	Day 1	Day 10
AUC(0-24) or AUC(0-τ)[1]	0.952 [0.802, 1.10]	0.988 [0.841, 1.14]
Cmax	0.950 [0.812, 1.09]	1.03 [0.903, 1.15]
C24 or Cτ[2]	0.949 [0.777, 1.12]	0.980 [0.808, 1.15]
C0	NA	0.936 [0.761, 1.11]

GSK1265744 exposure (AUC and Cmax) showed dose proportional increase following both Days 1 and 10 dose administration.

Summary of GSK1265744 Accumulation Assessment

Plasma GSK1265744 PK Parameter	GLS Mean Ratio [90% CI]
AUC	2.36 [2.09, 2.66]
Cmax	1.96 [1.68, 2.28]
Cτ	2.48 [2.14, 2.88]

Following 10-day repeat dose administration of GSK1265744, the steady state plasma concentration of GSK1265744 was reached by 7 days of dosing; the accumulation ratio for AUC(0-τ), Cmax, and Cτ were estimated to be 2.36, 1.96, and 2.48, respectively.

Viral Genotyping and Phenotyping:

Seven of the nine subjects had genotype and phenotype available for both Day 1 and Day 11. An eighth subject, receiving placebo, had genotype and phenotype available for the Screen sample, taken 26 days prior to Day 1. These data were substituted for the unavailable data at Day 1. While differences were observed between Day 1 and Day 11 genotypes in seven of the eight subjects, the variation in phenotype was remarkably small. The lack of a substantial increase in GSK1265744 or raltegravir IC50 between Day 1 and Day 11 is reflective of the mutations observed. In no case was a mutation associated with clinical resistance to Raltegravir or Elvitegravir selected in subjects receiving GSK1265744. In addition, none of the treatment emergent mutations were associated with *in vitro* resistance to GSK1265744. Raltegravir IC50s were approximately 7-fold higher than GSK1265744 IC50s.

Efficacy: Virology and Immunology:

There was a statistically significant change ($p<0.001$) from baseline plasma HIV-1 RNA of GSK1265744 subjects compared to Placebo subjects.

Summary of HIV-1 RNA Change from Baseline to Day 11

	GSK1265744 5 mg (n=7)	**Placebo (n=2)**
Mean change from Baseline (SD) (Log10 copies/mL)	-2.169 (0.2405)	-0.092 (0.1499)
Adjusted mean difference: active vs. placebo	-2.090	Not applicable
95% CI for adjusted mean difference	-2.547, -1.632	Not applicable
p-value for adjusted mean difference	<0.001	Not applicable

Subjects receiving GSK1265744 generally reached plasma HIV-1 RNA <400 c/mL copies by Day 11 (5/7, 71%).

Two subjects receiving GSK1265744 5 mg were able to reach plasma HIV-1 RNA <50 c/mL by Day 11 (2/7, 29%).

All GSK1265744 subjects (7/7, 100%) reached a >1.7 log drop by Day 11.

Increases in CD4+ cell counts were observed for subjects receiving GSK1265744 from Baseline to Day 11 (Table 13.7). In contrast CD4+ cell counts decreased from Baseline to Day 11 for subjects receiving placebo.

Conclusions:

GSK1265744 5mg was well tolerated in HIV-1 infected adults.

Following 5 mg QD GSK1265744 administration for 10 days, there was a statistically significant decrease (mean change -2.169 for GSK1265744 5mg vs. -0.092 for placebo) in plasma HIV-1 RNA from baseline to Day 11.

Following 5 mg QD GSK1265744 administration for 10 days, 2 of 7 subjects were able to reach a plasma HIV-1 RNA < 50 c/mL after 10 days of monotherapy.

Following 5 mg QD GSK1265744 administration for 10 days, 5 of 7 subjects were able to reach HIV-1 RNA < 400 c/mL after 10 days of monotherapy.

GSK1265744 exhibited proportionality in plasma exposures following both single and repeat dose administration in HIV infected patients when comparing GSK1265744 5mg QD to GSK1265744 30mg QD (ITZ111451).

GSK1265744 5mg steady state was reached by Day 7 following repeat dose administration in HIV infected patients.

The accumulation ratios for AUC, Cmax and $C\tau$ following repeat dose administration of GSK1265744 at 5mg were estimated to be 2.36, 1.96, and 2.48, respectively.

No mutations associated with in vitro resistance to GSK1265744 were selected in this 10-day monotherapy trial.

No phenotypic resistance to GSK1265744 5mg occurred at Day 1 or at Day 11 in any of the subjects.

There was no association between genotypic changes in integrase and changes in GSK1265744 IC50.

Date of Report: [redacted] 20[redacted]

Synopsis for Study 2015N258625_00

Sponsor: GlaxoSmithKline, Park Road, Ware, Hertfordshire, SG12 0DP, UK

Study Site: Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Park Road, Ware, Hertfordshire, SG12 0DP, UK

Study Director: [redacted]

Personnel Involved: [redacted]

Primary Applications Used to Acquire Data: Microsoft Excel

Summary: A mechanistic static mathematical model was used to predict the effect of cabotegravir on exposure of substrates of UGT1A3, UGT1A9, OAT1, OAT3, MATE1 or MATE2-K. The results of the model showed cabotegravir has a low risk of being a perpetrator of DDIs with substrates of UGT1A3, UGT1A9, OAT1, OAT3, MATE1 or MATE2-K (predicted AUC change < 2-fold).

Date of Report: [redacted] 20[redacted]

Synopsis for Study 2018N389974_01

Sponsor: GlaxoSmithKline, David Jack Centre, R&D, Park Road, Ware, Hertfordshire, SG12 0DP, UK

Test Facility: [redacted], UK

Test Site: [redacted], UK

Author: [redacted], [redacted]

Personnel Involved: [redacted], [redacted], [redacted], [redacted], [redacted]

Primary Applications Used to Acquire Data: Simcyp® Version 17 release 1

Executive Summary: In vitro studies indicated that Cabotegravir inhibits renal transporters organic anion transporter (OAT)1 and OAT3 with IC50 values of 0.81 μM and 0.41 μM, respectively. PBPK model-based analysis to further assess the clinical risk of OAT1 and/or OAT3 inhibition-mediated drug-drug interactions (DDI) by Cabotegravir was conducted using Simcyp® v17.1 software. CAB is primarily metabolized by UGT1A1 and to a lesser extent by UGT1A9. Hence the PBPK model was also used to further assess the DDIs with relevant clinical UGT1A1 and UGT1A9 inhibitors. A Cabotegravir PBPK model was developed based on its physicochemical properties, in vitro measurements of enzyme clearance (UGT1A1 and UGT1A9) and in vitro measured values of OAT1/OAT3 inhibition, and clinical PK observations.

The PBPK model was verified through comparison with available clinical studies following single and multiple administration of 30 mg PO Cabotegravir to healthy volunteers. CAB PBPK model accurately described Cabotegravir PK parameters (within acceptable bioequivalence criteria (0.80-1.25) for single as well as multiple dose studies). The PBPK model was further verified by simulating CAB PK parameters in severe renally impaired patents. The CAB PBPK model was also verified for predicting UGTmediated DDIs. Clinical DDI with UGT1A1 inducer Rifampin was simulated and was within the 80-125% limits of acceptance when compared with the actual clinical data. Simulations of CAB AUC/Cmax ratios in Simcyp® in-built UGT1A1 poor metabolizers was also comparable to that observed in clinic in the UGT1A1 polymorphic population in the clinic.

PBPK models of several OAT1/OAT3 substrates and inhibitors were verified in the Simcyp® simulator by comparing the predicted clinical DDI with observed clinical DDI in published reports. Simulated DDIs of OAT1/OAT3 substrates (methotrexate, tenofovir, ciprofloxacin, cidofovir, cefuroxime, oseltamivir carboxylate, baricitinib, and S44121) and inhibitors (probenecid, diclofenac) predicted the AUC ratios accurately within 5-30% of observed values. On this basis, the Simcyp® simulator and related files were verified as accurate and appropriately sensitive for predicting OAT1/OAT3 inhibition-mediated clinical DDIs.

OAT1/OAT3 inhibition-mediated effects on exposure of co-dosed substrates (methotrexate, tenofovir, ciprofloxacin, cidofovir, cefuroxime, oseltamivir carboxylate, baricitinib, and S44121) were simulated at the maximal concentrations of Cabotegravir after multiple oral doses of 30 mg QD. This enabled assessment of the OAT1/OAT3 inhibition potential by Cabotegravir at a simulated maximal clinical exposure. PBPK DDI simulations predicted a mean increase of less than 25% in systemic exposure for tested OAT1/OAT3 substrates after co-administration with oral Cabotegravir. Similar Cabotegravir concentrations following oral and Long-acting (LA) administration suggest that these predictions would also apply to Cabotegravir LA. The repeat dose Cabotegravir maximal concentrations were considered clinically relevant to assess DDIs at expected Cabotegravir systemic concentrations during LA dosing as well as during the PK tail following LA discontinuation. Further sensitivity analysis for orally administered CAB renal OAT inhibition, dose or fraction unbound in plasma to cause clinically relevant DDIs with methotrexate, a narrow therapeutic index OAT3 substrate, provides further confidence in the predicted no risk of DDIs when administered with Cabotegravir.

Simulated AUC and Cmax ratio in DDI studies between UGT1A1 substrate Raltegravir and UGT1A1 inhibitor Atazanavir; UGT1A1 substrate Raltegravir and UGT1A1 inducer Rifampin; and UGT1A9 substrate Dapagliflozin and UGT1A9 inhibitor Mefenamic acid were within 30% of the observed clinical data. The verified CAB PBPK model was applied to predict the extent of DDI with UGT1A1 or UGT1A9 inhibitors. The predicted mean systemic increase in CAB exposure was less than 11% when co-administered with UGT1A1 or UGT1A9 inhibitors such as Atazanavir or Mefenamic acid respectively.

A CAB PBPK model for predicting the clinical exposure as well as either victim or perpetrator DDIs for CAB was successfully developed using the Simcyp® platform. The predicted lack of interactions by verified CAB PBPK model simulations supports coadministration with OAT1/OAT3 substrates without dose adjustments. Similarly, predicted lack of interactions between CAB and UGT1A1 or UGT1A9 inhibitors supports co-administration with UGT1A1 or UGT1A9 inhibitors such as Atazanavir or Mefenamic acid without any dose adjustments. Clinical DDI data (rifampin, rifabutin) and PBPK simulations (phenobarbital) indicated that the impact of UGT inducers on CAB exposure was proportional to their in vitro induction potency. These data suggested that co-medication exclusions may not be required for weak and moderate inducers.

Date of Report: [redacted] 20[redacted]

Synopsis for CAB PK Population Analysis (2018N384611_01)

Study Numbers: LAI116585, LAI117010, LAI117011, LAI117020, 201741, 201479, 201480, 205696, LAI116482 (LATTE), LAI115428, LAI116815, 200056 (LATTE-2), 201120 (ECLAIR), 201103 (HPTN077), 201584 (FLAIR), and 201585 (ATLAS)

Title: Population Pharmacokinetic Analysis of Cabotegravir

Phases of Development: 1, 2, and 3

Objectives:

- To further characterize cabotegravir (CAB) pharmacokinetics (PK) based on data from healthy subjects and Human Immunodeficiency Virus Type-1 (HIV-1)-infected subjects following administration as oral (PO) tablet and long acting (LA) intramuscular (IM) injection.
- To provide post-hoc PK parameters and exposure metrics for the overall population and subgroups of various subject characteristics.
- To evaluate the association between intrinsic and extrinsic factors and the variability of CAB PK parameters and exposure.
- To perform simulations that guide dosing strategies under various scenarios (e.g., dosing errors, unplanned and planned dosing delays, concomitant medications, and treatment discontinuation).

Methodology:

The population pharmacokinetic (PopPK) analysis was performed in the following sequence of steps: (1) exploratory data analysis, (2) base model development, (3) covariate analysis, (4) model refinement, (5) model evaluation, and (6) evaluation of the impact of covariates on exposure. The final PopPK model was then used in simulations of various dosing scenarios to inform dosing strategy recommendations. The target outcome was that approximately 95% or more of the simulated subjects should have trough concentrations above the Phase 3 benchmark (BMPh3) of 0.65 µg/mL.

The starting point of the PopPK analysis was the base model from the previous analyses including fixed effects, random effects, and residual variability. This starter model was evaluated and refined to build the base structural model. M3 method was used to model concentrations below the quantitation limit. Covariates that showed potential correlation with PK parameters or were considered important based on previous experience were added to the base model (one covariate into one parameter at a time) to identify covariates that improved (reduced) the objective function value (OFV) by ≥6.64 points. This process was iterated until no covariate whose inclusion provided an OFV improvement significant at the $\alpha = 0.01$ level remained. Afterwards, the continued significance of each covariate was then tested by iteratively dropping covariate effects from the model, one at a time. Only effects whose removal resulted in the OFV worsening (increasing) by >10.83 points were retained.

After statistically significant covariates had been included in the model, the model was refined. Covariate effects were removed if the PK parameter estimate of a typical person differed by less than 15% from a person with an extreme covariate value (10th and 90th percentiles for a continuous covariate). Model performance for the final PopPK model was assessed through bootstrap analysis and prediction-corrected visual predictive checks of 500 replications in addition to standard goodness-of-fit plots.

The relative contributions of covariates included in the final model on CAB trough concentration following the first injection (Cmin-LD) and steady-state trough (Cmin-SS) and peak concentration (Cmax-SS) were evaluated through a series of simulations following the standard CAB LA every 4 weeks (Q4W) regimen. Two thousand virtual subjects were resampled from each subgroup in the model-building dataset. The median and 5th and 95th percentiles of Cmin-LD, Cmin-SS, and Cmax-SS were calculated and compared across subgroups.

To inform dosing strategies, the final PopPK model was used to simulate CAB plasma PK profiles in virologically suppressed, HIV-1-infected subjects for a variety of dosing scenarios: dosage errors, unplanned dosing delays of varying durations, oral bridging between injection visits for pre-planned injection delays, concomitant administration of enzyme inducers and inhibitors, and LA treatment discontinuation. To visually and quantitatively assess the impact on CAB PK, median PK profiles with 90% prediction intervals were simulated and the percentage of subjects above BMPh3 of 0.65 μg/mL (%POP>0.65μg/mL) was calculated, where appropriate, for each scenario. In each simulated scenario, 5000 virtual HIV-1-infected subjects were simulated.

Results:

A two-compartment model with first-order PO and IM absorption and first-order elimination adequately described the data from 23,926 concentration records in 1647 subjects. PK parameters included absorption rate constant for PO tablet (KA1), absorption rate constant of the LA IM formulation (KA2), apparent central clearance (CL/F), apparent central volume of distribution (V2/F), apparent inter-compartmental clearance (Q/F), apparent peripheral compartment volume of distribution (V3/F), and oral bioavailability relative to the LA IM formulation (F1). The base PopPK model implemented WT scaling on CL/F, Q/F, V2/F, and V3/F. In the final PopPK model, KA2 was 50.9% lower in females compared to males and 47.8% higher if the injection was split. In addition, KA2 decreased with increasing BMI, and was lower with longer needle length. CL/F was 17.4% higher in current smokers. Bootstrap analysis and prediction-corrected visual predictive checks demonstrated adequate model performance.

Gender and BMI had the largest contribution on Cmin-LD. Median Cmin-LD was 31% lower in females compared to males and 31% lower in subjects with BMI ≥30 kg/m2 than subjects with BMI <30 kg/m2. Smoker status, split injection, body weight and needle length had relatively small contribution of <20% on Cmin-LD. All covariates had relatively small contribution of ≤15% on Cmin-SS and ≤21% on Cmax-SS, indicating no need for dose adjustment based on these covariates.

Results from the simulation of various dosing scenarios support the following for the CAB LA Q4W regimen:

- Higher-than-planned dosing: increased exposure due to higher-than-planned dosing (up to 1200 mg of a single injection) was predicted to be below the Cmax that was observed in previous studies without safety concerns.
- Underdosing: if the first IM injection was given as 200 mg or 400 mg instead of 600 mg, delivering a corrective dose of at least 400 mg as soon as possible was predicted to raise the trough concentration above BMPh3. Underdosing of maintenance doses at any visit was predicted to result in no suboptimal concentrations.
- Unplanned dosing delay: if the second injection was delayed by ≤1 week, or if the third and subsequent injections were delayed by ≤3 weeks, trough concentrations were predicted to remain above BMPh3, supporting the injection window of ±1 week. For any delay of up to 12 weeks, resumption with 400 mg or 600 mg was predicted to sufficiently raise the trough concentration above BMPh3. However, a delay of ≥4 weeks of the second injection was predicted to result in %POP>0.65µg/mL of as low as 10%, and thus reinitiation with 600 mg followed by 400 mg monthly injections is recommended to further reduce the risk of underexposure.
- Planned dosing delay: oral bridging with daily 30 mg CAB (up to 12 weeks) was predicted to maintain CAB concentration above BMPh3 for planned interruption of CAB LA.
- Metabolism induction: co-administration with inducers such as rifampin (RIF) and rifabutin (RBT) starting at the initial IM injection resulted in Cmin-LD below BMPh3. A dose increase by 200 mg during RIF co-administration increased %POP>0.65µg/mL above 80% at Cmin-LD and approximately above 95% for all troughs thereafter. A dose increase by 200 mg during RBT co-administration increased %POP>0.65µg/mL above 95% for all troughs.
- Reduced metabolism: increased CAB exposure due to reduced or inhibited metabolism was predicted to remain below the safety threshold.
- Treatment discontinuation: following discontinuation, sustained measurable CAB concentrations for prolonged periods were predicted: 47% and 17% of subjects had measurable concentrations at 52 and 96 weeks after the last IM injection, respectively, while 17% of female subjects had measurable concentrations at 156 weeks after the last IM injection.

Conclusions:

A robust PopPK model was built based on data from healthy subjects and HIV-1-infected subjects to adequately characterize the PK of CAB following PO and IM administration and evaluate the association between intrinsic and extrinsic factors with the variability of CAB PK parameters and exposure. No dose adjustment based on subject characteristics (e.g. race, age, smoker status, WT, BMI, UGT polymorphism) is recommended. Simulations supported the current CAB Q4W dosing regimen consisting of an oral lead-in of 30 mg CAB PO QD for 4 weeks, followed by 600 mg CAB LA IM (loading dose) within 2 hours after the last PO dose, and 400 mg CAB LA IM (maintenance dose) Q4W thereafter. Furthermore, the simulations supported the injection window of ±1 week for

the Q4W regimen. Simulations informed recommendations on various dosing scenarios for the Q4W regimen as follows:

- Higher-than-planned doses of up to 1200 mg in a single injection: no corrective action necessary.
- Underdosing:
  - Underdosing of the first injection: deliver a corrective dose of 400 mg or 600 mg as soon as possible.
  - Underdosing of maintenance doses (≥200 mg): no corrective action necessary.
- Dosing interruption of CAB LA with or without oral bridging:
  - CAB LA injection is delayed by <1 month (<2 months between injections): resume 400 mg monthly injections.
  - CAB LA injection is delayed by ≥1 month (≥2 months between injections): reinitiate with a 600 mg injection followed by 400 mg monthly injections thereafter.
- Co-administration with RIF or RBT: increase CAB LA dose by 200 mg during co-administration (loading dose of 800 mg followed by 600 mg monthly injections).
- Reduced UGT activity or co-administration with UGT inhibitors: no dose adjustment necessary.

Discontinuation of CAB LA: initiate alternative highly active antiretroviral therapy as soon as possible.

Synopsis for Study LAI117009

Name of company: ViiV Healthcare and the GlaxoSmithKline group of companies.

Name of finished product: Not available/known at the time of this report

Name of active substance: GSK1265744 (cabotegravir)

Study Number: LAI117009

Title: A Study to Evaluate the Effect of GSK1265744 150mg Administered Orally Every 12h x 3 Doses on Cardiac Conduction as Assessed by 12-lead Electrocardiogram Compared to Placebo and a Single Oral Dose of Moxifloxacin.

Investigator: [redacted], MD

Study Center: [redacted], United States

Publication: None at the time of this report

Study Period: 21 JAN 2014 - 10 JUN 2014

Phase of development: I

Objectives and Endpoints (criteria for evaluation):

Objectives	Endpoints
Primary	
• To demonstrate a lack of effect of repeat oral doses of GSK1265744 (150 mg) (supratherapeutic dose) as determined by the baseline-adjusted, maximum time-matched QTcF effect as compared to placebo	• Change from baseline in QTcF for GSK1265744
Secondary	
• To estimate the effect of repeat doses GSK1265744 (150 mg) on QTcB, QTCi, QT interval and heart rate (HR) as compared to placebo.	• Change from baseline in QTcB, QTci, QT, QRS, PR, and HR for GSK1265744.
• To estimate the effect of single dose moxifloxacin (400 mg) on QTcF, QTcB, QTci, QT interval, and heart rate (HR) compared to placebo.	• Change from baseline in QTcF, QTcB, QTci, QT, QRS, PR, and HR for placebo.
• To describe the pharmacokinetics of	• Change from baseline in QTcF, QTcB,

Objectives	Endpoints
GSK1265744. • To describe the single dose pharmacokinetics of moxifloxacin (if needed). • To evaluate the safety and tolerability of GSK1265744 following repeat150 mg doses. • To characterize any PK/PD relationship between exposure of GSK1265744 and changes in QTcF, QTcB and QTci.	QTci, QT, QRS, PR, and HR for moxifloxacin • AUC(0-t), AUC(0-∞), Cmax, tmax, CL/F, Vdz/F, and t1/2 from plasma concentrations of GSK1265744 and moxifloxacin (if needed). • Safety and tolerability of GSK1265744 as assessed by 12-lead ECGs, vital signs, adverse events, and clinical laboratory tests. • Change from baseline in QTcF, QTcB, and QTci for GSK1265744, difference between GSK1265744 and placebo in QTcF, QTcB, and QTci change from baseline. AUC(0-24), AUC(0-t), AUC(0-∞), and Cmax, from plasma concentrations of GSK1265744.

Methodology:

This was a randomized partial-blind, repeat dose, three-period, balanced crossover study to assess the cardiac conduction effect of a supratherapeutic dose of GSK1265744 compared to placebo in eligible healthy male and female subjects. Moxifloxacin served as a positive control.

Screening	N	Periods 1 – 3					Follow-up
At least 30 Days	42	Period 1	Wash-out At least 21days	Period 2	Wash-out At least 21 days	Period 3	10 – 14 days post final dose

Subjects underwent a screening visit within 30 days of the first dose of study drug, three treatment periods, and a follow-up period. Subjects were admitted to the clinical unit on Day -2 of each dosing period and remained in the unit until the completion of the 24 hour assessments on Day 3. On Day -1, subjects underwent continuous holter monitoring for approximately 24 hours. On the morning of Day 1, subjects randomized to either GSK1265744 or GSK1265744 placebo began the first of 3 doses of 150 mg GSK1265744 or placebo every (q) 12 hours. On Day 2, all subjects began continuous holter monitoring approximately 2 hours prior to the 3rd dose of GSK1265744, GSK1265744 placebo or the 400 mg dose of Moxifloxacin. Twelve-lead electrocardiograms (ECGs), continuous Holter monitoring, clinical laboratory safety

tests, vital sign measurements, physical examinations, adverse event reports, and pharmacokinetic samples were collected throughout the study.

Subjects received each of the three treatments in a randomized fashion, with a washout period of at least 21 days between doses. Subjects and the investigator were blinded to the GSK1265744/placebo treatments. Moxifloxacin was administered open label.

Cardiac conduction was measured for all subjects using a 24-hour continuous 12-lead Mortara H12 plus, 1000 Hz Holter monitor on Day -1 and again beginning 2 hours prior to dosing on the morning of Day 2 until 30 minutes after the last collection time point on the morning of Day 3 of each dosing period.

A follow-up visit was conducted 10-14 days after administration of the last dose of study medication in treatment period 3.

Diagnosis and Main Criteria for Inclusion:

Healthy males and females of non-childbearing potential aged between 18 to 55 years with body weight ≥50 kg for men and ≥45 kg for women and body mass index (BMI) within the range 18.5-31.0 kg/m^2 (inclusive) were included.

Number of Subjects:

A total of 42 subjects were enrolled. Thirty-six subjects completed all three treatment periods.

Treatment Administration:

Subjects were assigned to one of the six treatment sequences as shown in table below in accordance with the randomization schedule:

Sequence	Period 1	Period 2	Period 3
1	A	B	C
2	A	C	B
3	B	A	C
4	B	C	A
5	C	A	B
6	C	B	A

Study treatment and their description is provided in table below

Treatment	Description
A	Three doses of GSK1265744 150 mg (5 x 30mg tablets) q 12 hours, Batch no. [redacted]
B	Three doses of GSK1265744 placebo (5 tablets) q 12 hours, Batch no. [redacted]
C	A single dose of moxifloxacin 400mg (one 400mg tablet), Batch no. [redacted]

Statistical Methods:

All the statistical analyses were done as per protocol and reporting and analysis plan.

The primary statistical framework was to demonstrate a lack of effect of GSK1265744 administration on the QTc interval as compared to placebo.

Final analyses performed were as following:

Pharmacokinetic Analyses: Plasma GSK1265744 concentration-time data were analyzed by non-compartmental methods with WinNonlin 5.2 or higher. From the plasma concentration-time data, the following pharmacokinetic parameters were determined, as data permited: Area under the concentration-time curve from time zero (pre-dose) to 24 hours post dose (AUC[0-24]) after Dose 3, AUC(12-36h), maximum observed concentration (Cmax), time of occurrence of Cmax (tmax), apparent clearance following oral dosing (CL/F), and apparent volume of distribution at steady state after oral administration (Vdz/F).

Pharmacodynamic Analyses: The primary endpoint, change from baseline in QTcF was analyzed for the comparisons between placebo and GSK1265744 by a repeated measures analysis of covariance (ANCOVA) model, fitting subject as a random effect, and period, time, treatment, and time-by-treatment interaction as fixed effect terms.

Pharmacokinetic/Pharmacodynamic Analyses: To explore the concentration/QTc relationship, individual QTcF, individual QTcF change from baseline (ΔQTcF), and individual time-matched GSK1265744 treatment groups -placebo QTcF in change from baseline difference (ΔΔQTcF) were plotted against concentration at each time point. Linear correlations of plasma GSK126744 concentration and the QTcF variables were plotted with a fitted regression line superimposed.

The relationship between QTc interval and plasma GSK1265744 concentration were investigated using a linear mixed-effects modeling approach.

Summary

Subject Disposition:

Number of Subjects	GSK1265744[a] 150mg N=40	GSK1265744[b] Placebo N=39	Moxifloxacin[c] 400mg N=36	Overall N=42
Number of subjects planned, [N]	42	42	42	42
Number of subjects randomized, [N]	40	39	36	42
Number of subjects included in All subjects (safety) population, [n (%)]	40 (100)	39 (100)	36 (100)	42 (100)

Number of Subjects	GSK1265744[a] 150mg N=40	GSK1265744[b] Placebo N=39	Moxifloxacin[c] 400mg N=36	Overall N=42
Number of subjects completed as planned, [n (%)]	36 (90)	37 (95)	36 (100)	36 (86)
Number of subjects withdrawn (any reason), [n (%)]	4 (10)	2 (5)	0	6 (14)
Number of subjects withdrawn for SAE, [n (%)]	0	0	0	0
Number of subjects withdrawn for AE, [n (%)]	1 (3)	0	0	1 (2)
Reasons for subject withdrawal, [n (%)]				
Lost to follow-up	1 (3)	1 (3)	0	2 (5)
Adverse events	1 (3)	0	0	1 (2)
Protocol violation: Did not meet continuation criteria	1 (3)	1(3)	0	2(5)
Protocol violation: Did not return for period 2 and 3	1(3)	0	0	1(2)

a. Three doses of GSK1265744 150mg (5X30mg tablets) q 12 hours;
b. Three Doses of GSK1265744 placebo (5 tablets) q 12 hours;
c. A single dose of moxifloxacin 400mg (one 400mg tablet)

Subject Demography:

Demography	GSK1265744[a] 150mg N=40	GSK1265744[b] Placebo N=39	Moxifloxacin[c] 400mg N=36	Overall N=42
Age in Years [Mean (SD)]	34.6 (11.23)	33.6 (11.53)	34.0 (11.37)	33.9 (11.37)
Sex [n (%)]				
Female	9 (23)	8 (21)	8 (22)	9 (21)
Male	31 (78)	31 (79)	28 (78)	33 (79)
BMI (kg/m2) [Mean (SD)]	26.58 (3.237)	26.40 (3.181)	26.50 (3.272)	26.54 (3.177)
Height (cm) [Mean (SD)]	172.51 (7.938)	172.63 (7.839)	172.64 (8.154)	172.49 (7.754)
Weight (kg) [Mean (SD)]	79.10 (11.119)	78.69 (10.909)	79.00 (11.221)	78.96 (10.932)
Ethnicity [n (%)]				
Hispanic or Latino	3 (8)	3 (8)	3 (8)	3 (7)
Not Hispanic or Latino	37 (93)	36 (92)	33 (92)	39 (93)
Race [n (%)]				
Black/African Heritage	16 (40)	16 (41)	15 (42)	17 (40)
American Indian or Alaskan Native	2 (5)	2 (5)	2 (6)	2 (5)

Demography	GSK1265744[a] 150mg N=40	GSK1265744[b] Placebo N=39	Moxifloxacin[c] 400mg N=36	Overall N=42
Native Hawaiian or Other Pacific Islander	0	1 (3)	0	1 (2)
White	22 (55)	20 (51)	19 (53)	22 (52)

a. Three doses of GSK1265744 150mg (5X30mg tablets) q 12 hours;
b. Three Doses of GSK1265744 placebo (5 tablets) q 12 hours;
c. A single dose of moxifloxacin 400mg (one 400mg tablet)

Safety:

Summary of Frequent Adverse Events

Most Frequent Adverse Events	GSK1265744[a] 150mg N=40	GSK1265744[b] Placebo N=39	Moxifloxacin[c] 400mg N=36
	n (%)	n (%)	n (%)
Any AE	13 (33)	16 (41)	12 (33)
Any AE related to investigational product	1 (3)	3 (8)	6 (17)
Most Common AEs: (≥ 5% in any treatment group):			
Dermatitis contact	6 (15)	9 (23)	2 (6)
Headache	1 (3)	2 (5)	2 (6)
Nausea	0	0	2 (6)

a. Three doses of GSK1265744 150mg (5X30mg tablets) q 12 hours;
b. Three Doses of GSK1265744 placebo (5 tablets) q 12 hours;
c. A single dose of moxifloxacin 400mg (one 400mg tablet)

There were no deaths, no serious AEs, and no significant AEs during the study. All adverse events were mild except for two grade 2 events. One subject had a ruptured Achilles tendon and another subject had an elevation of creatine phosphokinase neither of which was considered to be related to study medication. No clinically significant trends in clinical laboratory values, vital signs, or Electrocardiogram (ECG)s were observed.

Pharmacokinetics (PK):

The results of plasma GSK1265744 PK parameters are presented in the table below

Summary of Plasma GSK1265744 Pharmacokinetic Parameters (PK Summary Population)[a]

Treatment	Sex	n	Cmax[a] (μg/mL)	AUC(0-12)[a] (μg.h/mL)	AUC(0-24)[a] (μg.h/mL)	tmax[b] (h)
GSK1265744[c] 150 mg	F	9	25.1 (22) [21.2, 29.6]	234 (22) [198, 277]	409 (22) [345, 484]	2.0 (1.0 – 4.0)

2.7.6 Synopses of Individual Studies

Treatment	Sex	n	Cmax[a] (μg/mL)	AUC(0-12)[a] (μg.h/mL)	AUC(0-24)[a] (μg.h/mL)	tmax[b] (h)
	M	31	21.9 (19) [20.4, 23.4]	213 (15) [202, 225]	380 (15) [359, 402]	2.0 (1.0 – 4.0)
	Overall	40	22.5 (20) [21.1, 24.0]	217 (17) [206, 229]	386 (17) [366, 408]	2.0 (1.0– 4.0)

a. geometric mean (CVb%) [90%CI]
b. median (range)
c. Three doses of GSK1265744 150 mg (5 x 30 mg tablets) q 12 hours

Pharmacodynamic Results:

The primary endpoint for the effect of GSK1265744 and moxifloxacin on cardiac repolarization was evaluated with the time-matched change from Baseline in QTcF compared to placebo (ΔΔQTcF). The change from the ΔΔQTcF by time-point from Mixed Effect model and 90% Confidence Interval (CI)s are summarized in table below

Results of Repeated Measures Statistical Analysis of QTcF (msec)

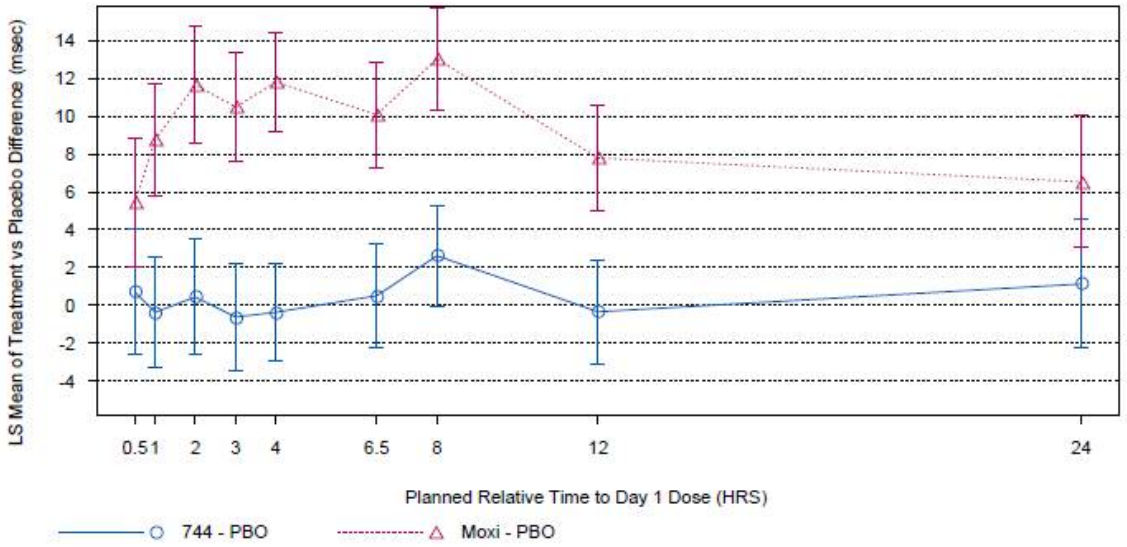
Time Point (hours)	GSK1265744 150 mg q12hr		Moxifloxacin 400 mg	
	Change from Baseline (GSK1265744 – Placebo)[a, c] Mean (SE)	90% CI	Change from Baseline (Moxifloxacin – Placebo)[c, b] Mean (SE)	90% CI
0.5	0.70 (1.999)	-2.62, 4.02	5.40 (2.051)	2.00, 8.81
1	-0.37 (1.742)	-3.26, 2.53	8.75 (1.787)	5.78, 11.71
2	0.44 (1.831)	-2.61, 3.48	11.67 (1.878)	8.55, 14.79
3	-0.62 (1.690)	-3.43, 2.19	10.49 (1.734)	7.60, 13.37
4	-0.37 (1.526)	-2.91, 2.17	11.81 (1.565)	9.20, 14.42
6.5	0.50 (1.633)	-2.21, 3.22	10.08 (1.675)	7.29, 12.86
8	2.62 (1.589)	-0.02, 5.26	13.03 (1.630)	10.32, 15.74
12	-0.34 (1.659)	-3.10, 2.42	7.79 (1.690)	4.98, 10.60
24	1.13 (2.047)	-2.27, 4.53	6.53 (2.100)	3.04, 10.02

Note: Lack of effect is demonstrated if the upper limit of 90% CI (95th percentile) for active (GSK1265744) - placebo at each time point is completely contained within 10 msec.
Note: Subjects [redacted], [redacted] and [redacted] are excluded from analysis due to missing baseline values.
Treatments:

a. 744= Three doses of GSK1265744 150mg (5X30mg tablets) q 12 hours;
b. PBO= Three Doses of GSK1265744 placebo (5 tablets) q 12 hours;
c. Moxi= A single dose of moxifloxacin 400mg (one 400mg tablet)

The treatment difference from placebo for QTcF change from baseline is presented in figure below.

Plot of Least Squares Mean of Treatment Difference from Placebo for QTcF Change from Baseline (90% CIs)



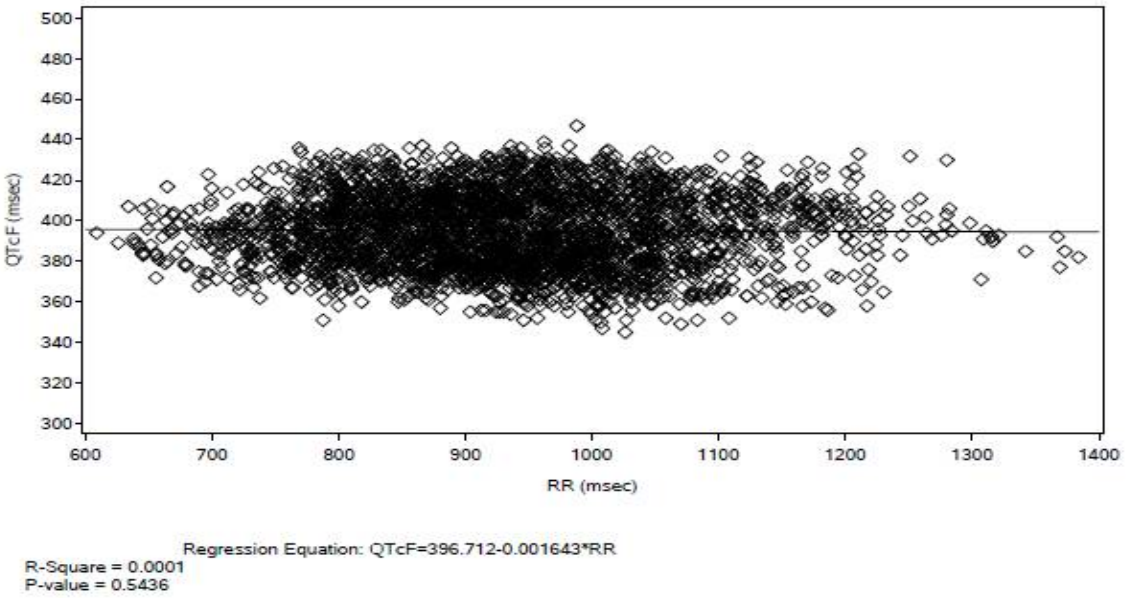
Treatments
a. 744= Three doses of GSK1265744 150mg (5X30mg tablets) q 12 hours;
b. PBO= Three Doses of GSK1265744 placebo (5 tablets) q 12 hours;
c. Moxi= A single dose of moxifloxacin 400mg (one 400mg tablet)

For the primary endpoint, QTcF, all time-matched values, and their corresponding upper bounds of the 90% CI were below 10 msec for GSK1265744. The maximum observed time-matched change from Baseline for GSK1265744 150 mg was at 8h (2.62 msec, 90% CI: -0.02, 5.26 msec). The maximum observed time-matched change from Baseline for moxifloxacin was at 8h (13.03 msec, 90% CI: 10.32, 15.74 msec). Since the study had adequate sensitivity to detect a positive QT effect with moxifloxacin, it is concluded that this study was valid. In contrast, there was no significant effect on cardiac repolarization for GSK1265744.

Mean values for the change from Baseline in QTcF values assessed as secondary endpoints were consistently highest in the moxifloxacin treatment group. Results for the secondary endpoints QTcB and QTc interval based on an individual correction (QTci) were consistent with the primary endpoint results for these secondary endpoints in that all time-matched values and their corresponding upper bounds of the 90% CI were below the upper bound of 10 msec. GSK1265744 and moxifloxacin had no effect on heart rate.

QTcF was considered the valid primary endpoint as Fridericia's correction adequately accounted for the effect of RR.

Plot of Individual Subject Predose QTcF vs. Predose RR



PK/PD

Parameter Estimates of the Relationship between Double-Delta QTcF and time-matched GSK1265744 Concentration Over 24 Hours

Model	Parameter	Estimate (msec)	95% CI (msec)
ddQTcF=INT+Slope*CONC	Mean Intercept	1.3822	-3.328, 6.092
	Mean Slope	-0.00005	0.000, 0.000

As 95% CI of parameter estimates contain zero, it can be concluded from this study that there was no relationship between GSK1265744 plasma concentration and ΔΔQTcF. As GSK1265744 did not have an effect on ΔΔQTcF at exposures ~3 fold above that of the likely clinical dose, study results suggest that GSK1265744 will not have effect on ΔΔQTcF at concentrations of 7.49 ug/mL, the expected Cmax in a clinical setting of GSK1264744 30 mg once daily.

Conclusions:

- GSK1265744 was generally well tolerated. No deaths or SAEs were reported and all AEs were mild or moderate in severity.

- GSK1265744 had no effect on cardiac repolarization at a supratherapeutic dose of 150 mg q 12 hours x 3 doses.

- The maximum concentration of GSK1265744 achieved in this study was approximately 3-fold higher than that of the standard clinical dose of 30 mg once daily at steady-state.

The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QTcF confirming the validity of the results.

Effective Date: [redacted]

Synopsis for Study LAI116482

Synopsis for Study LAI116482 Week 96

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available at the time of this report

Name of active substance: GSK1265744, Cabotegravir

Study Number: LAI116482

Title: A Phase IIb, Dose Ranging Study of Oral GSK1265744 in Combination with Nucleoside Reverse Transcriptase Inhibitors for Induction of HIV-1 Virologic Suppression Followed by an Evaluation of Maintenance of Virologic Suppression when Oral GSK1265744 is combined with Oral Rilpivirine (RPV) in HIV-1 Infected, Antiretroviral Therapy Naive Adult Subjects - Week 96 Results

Investigator(s):

This is a multi-center study; 49 investigators screened subjects, 48 sites randomized subjects.

Study center(s):

This study was conducted at 49 centers in two countries (41 in the US, 8 in Canada).

Publication(s):

Margolis DA, Brinson CC, Smith GH, de Vente J, Hagins DP, Eron JJ, Griffith SK, St. Clair MH, Stevens MC, Williams PE, Ford SL, Stancil BS, Bomar MM, Hudson KJ, Smith KY, Spreen WR. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis*. 2015 Jul 17. pii: S1473-3099(15)00152-8. doi: 10.1016/S1473-3099(15)00152-8. [Epub ahead of print].

Study Period: 06Aug2012 (First subject screened) – 11Sep2014 (Last subject Week 96); this study is ongoing in an open label phase.

Phase of Development: Phase IIb

Objectives:

Primary Objective:

To select a dose of cabotegravir (CAB, GSK1265744) for further evaluation as part of a two drug combination antiretroviral therapy (ART) regimen with RPV for 24 weeks, following a 24 week induction period of CAB with two NRTIs (Nucleoside reverse

transcriptase inhibitor), in HIV-1- (Human Immunodeficiency Virus Type 1) infected, antiretroviral naïve subjects.

Secondary Objectives:

Overall secondary objectives:

- To evaluate the safety, efficacy and tolerability of 10, 30, and 60 mg of CAB once daily both in combination with two NRTIs and as part of a two drug combination maintenance ART regimen with RPV, relative to efavirenz (EFV), through Week 96;
- To evaluate the effect of 10, 30, and 60 mg of CAB on selected virologic and immunologic markers of HIV infection over 96 weeks.

Induction Phase – Specific Secondary Objectives:

- To select and confirm a dose of CAB in combination with two NRTIs through Week 24 for induction of virologic suppression;
- To evaluate the antiviral activity, safety, and tolerability of 10, 30, and 60 mg of CAB once daily relative to EFV, all in combination with two NRTIs, through Week 24;
- To characterize the pharmacokinetic (PK) parameters of CAB and to explore exposure-response relationships (e.g., the relationship between CAB plasma exposure at Weeks 2 and 12 and virologic response or occurrence of adverse events [AEs] through Week 24);
- To assess the development of viral resistance to CAB and other on-study ART in subjects experiencing virologic failure through Week 24;
- To evaluate the effect of various demographic factors and adherence on exposure-response parameters of CAB through Week 24.

Maintenance Phase – Specific Secondary Objectives:

- To evaluate the ability of a two drug ART regimen, consisting of CAB plus RPV, to maintain virologic suppression through Week 96 in subjects who achieved plasma HIV-1 RNA (Ribonucleic acid) <50 c/mL by Week 24 in the Induction Phase with dual nucleoside reverse transcriptase inhibitor (NRTI) background ART;
- To evaluate the effect of 10, 30, and 60 mg of CAB and RPV on selected virologic and immunologic markers of HIV-1 infection from Week 24 through Week 96;
- To evaluate the safety and tolerability of 10, 30, and 60 mg of CAB and RPV from Week 24 through Week 96;
- To characterize the PK parameters of CAB and RPV and to explore exposure-response relationships (e.g., the relationship between CAB and RPV plasma exposure at Weeks 26 and 36 and virologic response or occurrence of adverse events [AEs] from Week 24 through Week 96);

- To assess the development of viral resistance to CAB and RPV in subjects experiencing virologic failure from Week 24 through Week 96;
- To evaluate the effect of various demographic factors and adherence on exposure-response parameters of CAB and RPV from Week 24 through Week 96.

Methodology:

This Phase IIb study in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral therapy (ART)-naive adult subjects consisted of two parts, an Induction Phase and a Maintenance Phase. The Induction Phase consisted of a 24 week dose-ranging evaluation of CAB at blinded doses of 10 mg, 30 mg and 60 mg once daily and a contemporary control arm of open-label EFV 600 mg once daily. The background dual NRTI for all arms was either abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) fixed dose combination (FDC) tablets, as chosen by the Investigator. Randomization was stratified by screening viral load and choice of background NRTIs. CAB once daily blinded doses in combination with background NRTIs were evaluated on the basis of antiviral activity, safety and PK over 24 weeks. Subjects randomized to a CAB containing arm, who successfully completed 24 weeks on study and demonstrated virologic suppression (defined as having a plasma HIV-1 RNA <50 c/mL before Week 24, with no signs of virologic rebound) were eligible for the Maintenance Phase of this study. During the Maintenance Phase, the background NRTIs were discontinued and the subject's ART regimen was simplified to their randomized dose of CAB in combination with RPV 25 mg once daily for an additional 72 weeks. The Maintenance Phase evaluated the ability of this two drug ART regimen to maintain virologic suppression through Week 48, Week 72 and Week 96. Subjects randomized to the EFV arm continued on their randomized regimen through Week 96.

Number of subjects: The study planned to randomize approximately 200 subjects. A total of 244 subjects were randomized and 243 subjects received at least one dose of investigational product (IP).

Diagnosis and main criteria for inclusion and exclusion:

The main <u>Inclusion</u> criteria included:

- HIV-1 infected subjects ≥ 18 years of age;
- HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 c/mL;
- CD4+ cell count ≥200 cells/mm^3 (or higher as local guidelines dictate);
- ART-naive defined as having ≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection (Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor was exclusionary).

The main <u>Exclusion</u> criteria included:

- Women who were pregnant or breastfeeding;

- Any evidence of an active CDC (Centers for disease control and prevention) Category C disease;
- Moderate to severe hepatic impairment;
- Any subject who posed a significant suicide risk;
- History of ongoing or clinically relevant hepatitis within the previous 6 months; anticipated need for HCV (Hepatitis C Virus) therapy;
- History of liver cirrhosis with or without hepatitis viral co-infection;
- Ongoing or clinically relevant pancreatitis;
- History of cardiac diseases: myocardial infarction, congestive heart failure, documented hypertrophic cardiomyopathy, sustained ventricular tachycardia;
- Personal or known family history of prolonged QT syndrome;
- Any evidence of primary resistance or any historical resistance;
- Estimated creatinine clearance <50 mL/min;
- Alanine aminotransferase (ALT) ≥5 times upper limit of normal (ULN);
- Alanine aminotransferase (ALT) ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin).

Treatment administration:

Investigational Product (IP) in this study included CAB, matching placebo, RPV, and EFV. Background antiretrovirals (ABC/3TC, TDF/FTC, protocol-permitted switch agents) were not considered Investigational Product. Subjects and Investigators on the CAB arms were blinded to CAB dose assignment. To blind treatment of CAB doses, subjects on the 10 and 30 mg CAB treatment arms received matching placebo tablets once daily together with the CAB dose.

During the Induction Phase, CAB was taken orally as 10 mg, 30 mg, or 60 mg tablets once daily in combination with ABC/3TC or TDF/FTC, with a meal.

In the Maintenance Phase, subjects randomized to CAB took once daily with a meal, plus RPV 25 mg instead of ABC/3TC or TDF/FTC.

In the Open-Label Phase, all subjects randomized to CAB were switched to the Sponsor selected dose of CAB and will continue to receive RPV 25 mg.

Subjects randomized to EFV taken one 600 mg tablet orally once daily in combination with ABC/3TC or TDF/FTC. ABC/3TC and TDF/FTC could be taken with or without food while EFV was recommended to be taken on an empty stomach at bedtime.

Investigational Product	Strength and Packaging	Batch Numbers
CAB	10 mg tablets; 34 tablets per bottle	[redacted]
	30 mg tablets; 34 tablets per bottle	[redacted]
CAB Placebo to Match (PTM)	PTM CAB; 34 tablets per bottle	[redacted]
EFV	600 mg tablets; 30 tablet per bottle	[redacted]
RPV	25 mg tablets; 30 tablets per bottle	[redacted]

Criteria for evaluation:

Primary Efficacy Endpoint:

The primary endpoint is the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 based on ITT-E (Intent-to-Treat-Exposed) population using the Missing, Switch, or Discontinuation equals Failure (MSDF) algorithm. Dose selection will be based primarily on antiviral activity and tolerability in conjunction with immunologic, safety, virologic resistance and PK measures.

Overall Secondary Endpoints:

- Proportion of subjects with plasma HIV-1 RNA <400 and <50 c/mL over time by visit using the MSDF and Observed algorithm;
- Absolute values and change from baseline in plasma HIV-1 RNA by visit;
- Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome (AIDS) and death);
- Absolute values and changes from baseline in CD4+ cell counts by visit;

- Incidence of treatment-emergent genotypic and phenotypic resistance to CAB, RPV and other on-study ART for protocol-defined virologic failures;
- Medication adherence to IP based on pill counts by visit.

Induction Phase – Specific Secondary Endpoint:

- The proportion of subjects with HIV-1 RNA <50 c/mL at Week 16 and Week 24 based on ITT-E population using the MSDF algorithm. Dose selection for induction will be based primarily on antiviral activity and tolerability in conjunction with immunologic, safety, virologic resistance and PK measures at Week 16 and confirmed at Week 24.

Maintenance Phase – Specific Secondary Endpoints:

- The proportion of subjects with HIV-1 RNA <50 c/mL from Week 24 through Week 96 by visit for the ITT-ME population (MSDF);
- Incidence of AEs and laboratory abnormalities over time from Week 24 through Week 96, maintenance safety population.

Statistical methods:

The sample size of 50 subjects per arm was chosen to ensure a high probability that a dosage arm with truly poor response was not selected for further study, while allowing for the formal consideration of other factors in dose selection should efficacy be similar across dosage arms.

The primary efficacy endpoint is the response rate at Week 48 (proportion of subjects with plasma HIV-1 RNA <50 c/mL). The efficacy decision criteria were based on an observed difference of >8% between the CAB dosage arms (i.e., a difference of more than 4 responders in 50 subjects).

With 50 subjects per arm, and assuming true response rates of 85% and 75%, respectively in 2 dosage arms, there was at least 55% chance that the superior dose would be selected (i.e., the observed difference in the two dosage arms would be greater than 8%), while the chance of incorrectly selecting the inferior dose was <1% (i.e., the observed difference in the two dosage arms is less than -8%). The chance of not being able to make a selection between the 2 doses was 44% (i.e., the observed difference in the two dosage arms would be between -8% and 8%).

The ITT-E population is the primary population used for the efficacy analyses. The ITT-E population consists of all randomized subjects who received at least one dose of IP. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received.

The ITT-Maintenance Exposed (ITT-ME) population consists of all randomized who received at least one dose of IP during the Maintenance Phase of the study. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received. The ITT-ME population is the secondary population for some efficacy analyses.

The Per Protocol (PP) population consists of subjects in the ITT-E population with the exception of major protocol violators. The PP population was a secondary population for efficacy purposes. The PP Population could have been used for a supporting analysis of the primary endpoint comparisons only. Such a supporting analysis would not be performed if the PP Population comprises more than 95% of the ITT-E Population.

The Per Protocol Maintenance (PP-M) population consists of subjects in the ITT-ME population with the exception of major protocol violators. The PP-M population was a secondary population for efficacy purposes.

The Safety population is the primary population used for the safety analyses. The Safety Population consists of all randomized subjects who were exposed to investigational products with the exception of any subjects with documented evidence of not having consumed any amount of investigational product. Subjects were analyzed according to the actual treatments received. Subjects were not excluded from this population as a result of changes to the background regimen.

The Maintenance Safety Population consists of all randomized subjects who were exposed to investigational products during the Maintenance Phase of the study with the exception of any subjects with documented evidence of not having consumed any amount of investigational product during the Maintenance Phase of the study. Subjects were analyzed according to the actual treatments received. Subjects were not excluded from this population as a result of changes to the background regimen. The Maintenance Safety Population is an additional population for safety analyses.

The PK Summary Population includes all subjects who received CAB or RPV, had intensive and/or limited/sparse PK sampling during the study, and provided evaluable CAB or RPV plasma concentration data. Subjects in this population were included in listings.

Efficacy analyses performed included summaries of the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 48 and 96 were summarized using the Snapshot and observed algorithm. Additional summaries by stratification subgroups were also performed.

Other efficacy analyses performed included summaries of the proportion of subjects with plasma HIV-1 RNA <400 c/mL at Week 48 and 96, absolute values and changes from Baseline in CD4+ counts and HIV-1 RNA over time, and the incidence of disease progression (HIV-associated conditions, AIDS and death).

The occurrence of protocol-defined virologic failures was summarized by visit for each treatment group. Viral genotyping and phenotyping analyses were conducted to explore the relationship between treatment with CAB and EFV and the evolution of HIV-1 resistance. The incidence of treatment-emergent genotypic and phenotypic resistance to integrase inhibitors (INIs) at time of protocol defined virologic failure (PDVF) were summarized by treatment group.

The following AEs were summarized overall and by treatment group: all AEs, drug-related AEs, AEs by grade, fatal and non-fatal SAEs (serious adverse events), and AEs leading to withdrawals.

SAEs were summarized on-therapy. Mean values and changes from Baseline for laboratory parameters and vital signs were summarized by treatment group. Treatment-emergent laboratory toxicity grades were also summarized by treatment group.

Pharmacokinetic Analytical Methods:

The following CAB pharmacokinetic parameters were estimated for subjects in the intensive PK sampling group at Week 2: AUC (0-τ) (area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state), Cmax (maximum plasma drug concentration), C0 (pre-dose plasma drug concentration), Cτ (concentration at the end of a dosing interval), tmax (time at which Cmax was observed), and CL/F (Apparent clearance following oral dosing). CAB C0 was estimated from pre-dose concentrations for all subjects in the Sparse PK Concentration Population and also Weeks 12 and 26 and 36 of the PK Summary Population. RPV C0 was estimated from pre-dose concentrations for all subjects in the Sparse PK Concentration Population during the Maintenance Phase of the study. An individual average C0 (which includes Cτ for intensive PK group) was created for each phase of the study.

Pharmacokinetic data were presented in graphical and/or tabular form and summarized descriptively.

Derived PK parameters were listed. For all parameters except tmax, the following summary statistics were calculated for each treatment group: median, maximum, minimum, arithmetic mean, standard deviation, coefficient of variation on arithmetic mean, geometric mean, coefficient of variation on geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. For tmax, median, maximum, minimum, arithmetic mean, and standard deviation were calculated.

PK parameters were summarized by treatment, Baseline plasma HIV-1 RNA (≤100,000, >100,000 c/mL) and background dual NRTI (ABC/3TC, TDF/FTC, or other), and overall.

Dose proportionality of CAB PK parameters (Week 2: AUC (0-τ), Cmax, C0, and Cτ) was assessed using the power model: $y = \alpha \times dose^{\beta}$.

Log-transformed PK parameter individual subject C0 average from the Induction Phase was compared with Maintenance Phase for each treatment with SAS PROC MIXED model.

Pearson's correlations and p-values between dose-normalized CAB PK parameters (AUC (0-τ), Cmax, C0, individual subject average C0) and age, weight, height, body mass index, body surface area, gender, and race (African-American vs. others) were calculated.

PK/PD analyses including exposure-antiviral activity, exposure-immunology, and exposure-toxicity analyses were performed using Pearson's correlations.

Summary:

Summary of Demographic Characteristics:

Demographic Characteristic	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	EFV 600 mg N=62	Total N=243
Age (yrs), n (%)					
Mean	34.0	34.4	36.2	35.6	35.1
SD	9.91	10.24	10.15	12.30	10.68
Median	32.0	32.5	36.0	32.5	33.0
Min.	19	20	19	18	18
Max.	54	57	56	70	70
Sex, n (%)					
Female	3 (5)	2 (3)	4 (7)	1 (2)	10 (4)
Male	57 (95)	58 (97)	57 (93)	61 (98)	233 (96)
Ethnicity, n (%)					
Hispanic/Latino	9 (15)	16 (27)	14 (23)	12 (19)	51 (21)
Not Hispanic/Latino	51 (85)	44 (73)	47 (77)	50 (81)	192 (79)
Race, n (%)					
African American/African Heritage	21 (35)	17 (28)	18 (30)	20 (32)	76 (31)
American Indian or Alaskan Native	0	0	2 (3)	2 (3)	4 (2)
Asian - Central/South Asian Heritage	1 (2)	1 (2)	1 (2)	0	3 (1)
Asian - Japanese/East Asian Heritage/South East Asian Heritage	0	1 (2)	2 (3)	0	3 (1)
White	37 (62)	39 (65)	36 (59)	39 (63)	151 (62)
African American/African Heritage & Asian & White	0	0	1 (2)	0	1 (<1)
African American/African Heritage & Native Hawaiian or Other Pacific Islander	0	0	1 (2)	0	1 (<1)
African American/African Heritage & White	0	2 (3)	0	0	2 (<1)
American Indian or Alaskan Native & White	1 (2)	0	0	0	1 (<1)
Asian & White	0	0	0	1 (2)	1 (<1)

SD = Standard Deviation

Summary of Baseline Characteristics:

	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	EFV 600 mg N=62	Total N=243
HIV-1 RNA (log_{10} c/mL)					
Median HIV-1 RNA (IQR)	4.285 (4.035, 4.745)	4.175 (3.840, 4.645)	4.350 (3.970, 4.790)	4.340 (3.880, 4.760)	4.310 (3.940, 4.730)
HIV-1 RNA c/mL, n (%)					
<1000	0	0	0	1 (2)	1 (<1)
1000 to <10,000	13 (22)	24 (40)	16 (26)	20 (32)	73 (30)
10,000 to <50,000	30 (50)	22 (37)	25 (41)	24 (39)	101 (42)
50,000 to <100,000	9 (15)	7 (12)	8 (13)	9 (15)	33 (14)
≥100,000	8 (13)	7 (12)	12 (20)	8 (13)	35 (14)
CD4+ (cells/mm^3), n (%)					
Median CD4+ (IQR)	415 (342, 541)	404 (319, 551)	420 (343, 548)	417 (304, 651)	416 (323, 552)
CD4+ (cells/mm^3), n (%)					
<200	2 (3)	4 (7)	2 (3)	1 (2)	9 (4)
200 to 350	14 (23)	18 (30)	16 (26)	18 (29)	66 (27)
>350	44 (73)	38 (63)	43 (70)	43 (69)	168 (69)
Hepatitis B, Non-Reactive, n (%)[a]					
Non-Reactive	60 (100)	60 (100)	61 (100)	62 (100)	243 (100)
Hepatitis C, n (%)					
Non-Reactive	60 (100)	55 (92)	58 (95)	61 (98)	234 (96)
Reactive	0	5 (8)	3 (5)	1 (2)	9 (4)
CDC Classification, n (%)					
A: Asymptomatic or lymphadenopathy or acute HIV	57 (95)	53 (88)	60 (98)	59 (95)	229 (94)
B: Symptomatic, not AIDS	2 (3)	6 (10)	1 (2)	2 (3)	11 (5)
C: AIDS	1 (2)	1 (2)	0	1 (2)	3 (1)
HIV risk factor known, n (%)[b]					
Yes	59 (98)	60 (100)	59 (97)	61 (98)	239 (98)
Homosexual contact	52 (88)	50 (83)	51 (86)	55 (90)	208 (87)
Heterosexual contact	10 (17)	8 (13)	9 (15)	9 (15)	36 (15)
Injectable drug use	1 (2)	2 (3)	1 (2)	0	4 (2)
Other	0	2 (3)	1 (2)	1 (2)	4 (2)

b. Subjects infected with Hepatitis B were excluded from the study.
c. Subjects may have more than one HIV risk factor.

Efficacy:

Primary and Secondary Endpoints:

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits- Snapshot (MSDF) Analysis (ITT-E Population)

Visit	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Baseline	0	0	0	0	0
Week 16	54 (90)	50 (83)	53 (87)	157 (87)	46 (74)
Week 24	52 (87)	51 (85)	53 (87)	156 (86)	46 (74)
Week 48	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)
Week 72	43 (72)	44 (73)	52 (85)	139 (77)	42 (68)
Week 96	41 (68)	45 (75)	51 (84)	137 (76)	39 (63)

Proportion of Subjects with Plasma HIV-1 RNA <50c/mL at Key Visits - Snapshot (MSDF) Analysis (Per Protocol Population)

Actual Visit for MSDF	CAB 10 mg N=47 n (%)	CAB 30 mg N=46 n (%)	CAB 60 mg N=49 n (%)	CAB Subtotal N=142 n (%)	EFV 600 mg N=54 n (%)
Week 16	43 (88)	46 (87)	48 (89)	137 (88)	43 (77)
Week 24	42 (86)	47 (89)	49 (91)	138 (88)	43 (77)
Week 48	38 (78)	44 (83)	48 (89)	130 (83)	41 (73)
Week 72	36 (73)	40 (75)	47 (87)	123 (79)	39 (70)
Week 96	36 (73)	41 (77)	47 (87)	124 (79)	36 (64)

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits - Snapshot (MSDF) Analysis (ITT-ME Population)

Visit	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)	EFV 600 mg N=47 n (%)
Baseline	0	0	0	0	0
Week 16	50 (96)	49 (92)	52 (95)	151 (94)	43 (91)
Week 24	50 (96)	50 (94)	53 (96)	153 (96)	45 (96)
Week 48	48 (92)	48 (91)	53 (96)	149 (93)	44 (94)
Week 72	43 (83)	44 (83)	52 (95)	139 (87)	42 (89)
Week 96	41 (79)	45 (85)	51 (93)	137 (86)	39 (83)

Proportion (95% CI) of Subjects with Plasma HIV-1 RNA <50c/mL at Key Visits - Snapshot (MSDF) Analysis (Per Protocol Maintenance Population)

Actual Visit for MSDF	CAB 10 mg N=42 n (%)	CAB 30 mg N=49 n (%)	CAB 60 mg N=50 n (%)	CAB Subtotal N=141 n (%)	EFV 600 mg N=44 n (%)
Week 16	40 (95)	45 (92)	47 (94)	132 (94)	41 (93)
Week 24	40 (95)	46 (94)	49 (98)	135 (96)	42 (95)
	(89, 100)	(87, 100)	(94, 100)	(92, 99)	(89, 100)
Week 48	38 (90)	44 (90)	48 (96)	130 (92)	41 (93)
	(82, 99)	(81, 98)	(91, 100)	(88, 97)	(86, 100)
Week 72	36 (86)	40 (82)	47 (94)	123 (87)	39 (89)
	(75, 96)	(71, 92)	(87, 100)	(82, 93)	(79, 98)
Week 96	36 (86)	41 (84)	47 (94)	124 (88)	36 (82)
	(75, 96)	(73, 94)	(87, 100)	(83, 93)	(70, 93)

Summary of Study Outcomes:

Summary of Study Outcomes (HIV-1 RNA <50 c/mL) at Week 96 - Snapshot (MSDF) Analysis (ITT-E Population)

Outcome	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Virologic Success	**41 (68)**	**45 (75)**	**51 (84)**	**137 (76)**	**39 (63)**
Virologic Failure	**9 (15)**	**6 (10)**	**3 (5)**	**18 (10)**	**10 (16)**
Data in window not below threshold (<50 c/mL)	4 (7)	1 (2)	1 (2)	6 (3)	1 (2)
Discontinued for lack of efficacy	2 (3)	1 (2)	1 (2)	4 (2)	3 (5)
Discontinued for other reason while not below threshold	3 (5)	1 (2)	1 (2)	5 (3)	5 (8)
Prior change in ART	0	3 (5)	0	3 (2)	1 (2)
No Virologic Data	**10 (17)**	**9 (15)**	**7 (11)**	**26 (14)**	**13 (21)**
Discontinued due to AE[a]	1 (2)	1 (2)	4 (7)	6 (3)	8 (13)
Discontinued for Other Reasons	8 (13)	8 (13)	3 (5)	19 (10)	4 (6)
Missing data during window but on study	1 (2)	0	0	1 (<1)	1 (2)

a. No deaths occurred during this study.

Summary of Study Outcomes (HIV-1 RNA <50 c/mL) at Week 96 - Snapshot (MSDF) Analysis (ITT-ME Population)

Outcome	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)	EFV 600 mg N=47 n (%)
Virologic Success	**41 (79)**	**45 (85)**	**51 (93)**	**137 (86)**	**39 (83)**
Virologic Non-Response[a]	**7 (13)**	**4 (8)**	**2 (4)**	**13 (8)**	**3 (6)**
Data in window not below threshold (<50 c/mL)	4 (8)	1 (2)	1 (2)	6 (4)	1 (2)
Discontinued for lack of efficacy	1 (2)	0	0	1 (<1)	1 (2)
Discontinued for other reason while not below threshold (<50 c/mL)	2 (4)	1 (2)	1 (2)	4 (3)	1 (2)
Prior change in ART	0	2 (4)	0	2 (1)	0
No Virologic Data	**4 (8)**	**4 (8)**	**2 (4)**	**10 (6)**	**5 (11)**
Discontinued due to AE[b]	1 (2)	0	1 (2)	2 (1)	2 (4)
Discontinued for Other Reasons	2 (4)	4 (8)	1 (2)	7 (4)	2 (4)
Missing data during window but on study	1 (2)	0	0	1 (<1)	1 (2)

a. Virologic failure

No deaths occurred during this study.

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Key Visits and Baseline Plasma HIV-1 RNA - Snapshot (MSDF) Analysis (ITT-E Population)

Baseline Plasma HIV-1 RNA: <100,000 c/mL					
Visit	**CAB 10 mg N=60 n/N (%)**	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	0 / 52	0 / 53	0 / 49	0 / 154	0 / 54
Week 16	49 / 52 (94)	46 / 53 (87)	44 / 49 (90)	139 / 154 (90)	42 / 54 (78)
Week 24	46 / 52 (88)	46 / 53 (87)	44 / 49 (90)	136 / 154 (88)	40 / 54 (74)
Week 48	42 / 52 (81)	42 / 53 (79)	44 / 49 (90)	128 / 154 (83)	38 / 54 (70)
Week 72	38 / 52 (73)	39 / 53 (74)	43 / 49 (88)	120 / 154 (78)	35 / 54 (65)
Week 96	37 / 52 (71)	40 / 53 (75)	43 / 49 (88)	120 / 154 (78)	32 / 54 (59)
Baseline Plasma HIV-1 RNA: ≥100,000 c/mL					
	CAB 10 mg N=60 n/N (%)	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	0 / 8	0 / 7	0 / 12	0 / 27	0 / 8
Week 16	5 / 8 (63)	4 / 7 (57)	9 / 12 (75)	18 / 27 (67)	4 / 8 (50)
Week 24	6 / 8 (75)	5 / 7 (71)	9 / 12 (75)	20 / 27 (74)	6 / 8 (75)
Week 48	6 / 8 (75)	6 / 7 (86)	9 / 12 (75)	21 / 27 (78)	6 / 8 (75)
Week 72	5 / 8 (63)	5 / 7 (71)	9 / 12 (75)	19 / 27 (70)	7 / 8 (88)
Week 96	4 / 8 (50)	5 / 7 (71)	8 / 12 (67)	17 / 27 (63)	7 / 8 (88)

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Key Visits and Background Dual NRTI - Snapshot (MSDF) Analysis (ITT-E Population)

Background Dual NRTI: ABC/3TC					
Actual Visit for MSDF	**CAB 10 mg N=60 n/N (%)**	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	0 / 23	0 / 21	0 / 24	0 / 68	0 / 23
Week 16	20 / 23 (87)	19 / 21 (90)	20 / 24 (83)	59 / 68 (87)	17 / 23 (74)
Week 24	19 / 23 (83)	19 / 21 (90)	21 / 24 (88)	59 / 68 (87)	17 / 23 (74)
Week 48	19 / 23 (83)	15 / 21 (71)	20 / 24 (83)	54 / 68 (79)	16 / 23 (70)
Week 72	18 / 23 (78)	15 / 21 (71)	20 / 24 (83)	53 / 68 (78)	15 / 23 (65)
Week 96	18 / 23 (78)	16 / 21 (76)	20 / 24 (83)	54 / 68 (79)	13 / 23 (57)
Background Dual NRTI: TDF/FTC					
Actual Visit for MSDF	**CAB 10 mg N=60 n/N (%)**	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	0 / 37	0 / 39	0 / 37	0 / 113	0 / 39
Week 16	34 / 37 (92)	31 / 39 (79)	33 / 37 (89)	98 / 113 (87)	29 / 39 (74)
Week 24	33 / 37 (89)	32 / 39 (82)	32 / 37 (86)	97 / 113 (86)	29 / 39 (74)
Week 48	29 / 37 (78)	33 / 39 (85)	33 / 37 (89)	95 / 113 (84)	28 / 39 (72)
Week 72	25 / 37 (68)	29 / 39 (74)	32 / 37 (86)	86 / 113 (76)	27 / 39 (69)
Week 96	23 / 37 (62)	29 / 39 (74)	31 / 37 (84)	83 / 113 (73)	26 / 39 (67)

Note: background dual NRTI at Week 16 or time of IP discontinuation, whichever is earlier.

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Key Visits - OC Analysis (ITT-E Population)

Act. Rel. Time	**CAB 10 mg N=60 n/N (%)**	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	0 / 60	0 / 60	0 / 61	0 / 181	0 / 62
Week 16	54 / 57 (95)	51 / 54 (94)	53 / 57 (93)	158 / 168 (94)	45 / 52 (87)
Week 24	52 / 56 (93)	52 / 53 (98)	53 / 56 (95)	157 / 165 (95)	46 / 48 (96)
Week 48	47 / 51 (92)	49 / 53 (92)	53 / 54 (98)	149 / 158 (94)	43 / 44 (98)
Week 72	43 / 47 (91)	44 / 48 (92)	52 / 52 (100)	139 / 147 (95)	42 / 42 (100)
Week 96	40 / 45 (89)	47 / 48 (98)	51 / 52 (98)	138 / 145 (95)	39 / 40 (98)

Proportion of Subjects with Plasma HIV-1 RNA <400 c/mL Over Time

Proportion of Subjects with Plasma HIV-1 RNA <400 c/mL by Key Visits – Snapshot (MSDF) Analysis (ITT-E Population)

Actual Visit for MSDF	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Baseline	0	0	0	0	0
Week 16	56 (93)	52 (87)	57 (93)	165 (91)	50 (81)
Week 24	56 (93)	52 (87)	56 (92)	164 (91)	49 (79)
Week 48	50 (83)	51 (85)	54 (89)	155 (86)	45 (73)
Week 72	46 (77)	45 (75)	52 (85)	143 (79)	42 (68)
Week 96	45 (75)	46 (77)	52 (85)	143 (79)	40 (65)

Proportion of Subjects with Plasma HIV-1 RNA <400 c/mL by Key Visits - OC Analysis (ITT-E Population)

Visit	CAB 10 mg N=60 n/N (%)	CAB 30 mg N=60 n/N (%)	CAB 60 mg N=61 n/N (%)	CAB Subtotal N=181 n/N (%)	EFV 600 mg N=62 n/N (%)
Baseline	0 / 60	0 / 60	0 / 61	0 / 181	0 / 62
Week 16	56 / 57 (98)	54 / 54 (100)	57 / 57 (100)	167 / 168 (>99)	50 / 52 (96)
Week 24	56 / 56 (100)	53 / 53 (100)	56 / 56 (100)	165 / 165 (100)	48 / 48 (100)
Week 48	50 / 51 (98)	52 / 53 (98)	54 / 54 (100)	156 / 158 (99)	44 / 44 (100)
Week 72	46 / 47 (98)	46 / 48 (96)	52 / 52 (100)	144 / 147 (98)	42 / 42 (100)
Week 96	43 / 45 (96)	48 / 48 (100)	52 / 52 (100)	143 / 145 (99)	40 / 40 (100)

CD4+ Cell Count Change From Baseline:

Summary of Baseline Absolute Value and Change from Baseline in CD4+ Cell Count (cells/mm^3) by Key Visits (ITT-E Population)

Visit	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subgroup N=181	EFV 600 mg N=62
Baseline	**N=60**	**N=60**	**N=61**	**N=181**	**N=62**
Mean (SD)	445.5 (155.60)	444.9 (190.98)	459.0 (170.64)	449.8 (172.16)	456.5 (196.11)
Median~ (IQR)	415.0 ~(342.0, 541.0)	404.0 ~(319.0, 550.5)	420.0 ~(343.0, 548.0)	412.0 ~(333.0, 548.0)	416.5 ~(304.0, 651.0)
Week 16	**57**	**54**	**57**	**168**	**52**
Mean (SD)	159.3 (115.36)	142.2 (145.64)	148.3 (131.81)	150.1 (130.66)	135.5 (153.48)
Median~ (IQR)	137.0 ~(78.0, 235.0)	157.0 ~(89.0, 228.0)	141.0 ~(73.0, 252.0)	140.5 ~(79.5, 236.5)	125.0 ~(48.0, 253.5)
Week 24	**56**	**53**	**56**	**165**	**47**
Mean (SD)	172.5 (112.04)	180.9 (161.43)	204.0 (166.78)	185.9 (148.26)	143.4 (145.18)
Median~ (IQR)	158.0 ~(83.5, 236.5)	196.0 ~(88.0, 281.0)	182.5 ~(104.0, 284.0)	185.0 ~(95.0, 270.0)	159.0 ~(43.0, 212.0)
Week 48	**51**	**53**	**54**	**158**	**44**
Mean (SD)	235.1 (179.89)	241.6 (182.90)	259.0 (154.21)	245.5 (171.81)	262.5 (201.33)
Median~ (IQR)	203.0 ~(126.0, 294.0)	235.0 ~(131.0, 369.0)	240.0 ~(164.0, 370.0)	219.0 ~(141.0, 343.0)	216.0 ~(133.5, 363.0)
Week 72	**47**	**48**	**52**	**147**	**42**
Mean (SD)	232.0 (191.05)	201.4 (206.54)	254.0 (189.26)	229.8 (195.50)	257.1 (216.41)
Median~ (IQR)	181.0 ~(90.0, 339.0)	208.5 ~(94.0, 352.5)	221.5 ~(160.5, 325.5)	205.0 ~(117.0, 339.0)	208.5 ~(94.0, 355.0)
Week 96	**46**	**46**	**52**	**144**	**41**
Mean (SD)	269.4 (204.32)	267.5 (196.27)	286.2 (181.50)	274.8 (192.57)	281.7 (232.90)
Median~ (IQR)	236.5 ~(135.0, 359.0)	249.5 ~(118.0, 348.0)	271.5 ~(150.5, 355.0)	259.5 ~(137.0, 355.0)	289.0 ~(158.0, 415.0)

Note: Baseline values are actual CD4+ Cell Count (cells/mm^3) values.

Safety:

Safety Summary: (Safety Population)

	CAB				EFV
	10 mg N=60 n (%)	30 mg N=60 n (%)	60 mg N=61 n (%)	Subtotal N=181 n (%)	600 mg N=62 n (%)
Adverse Event (AE)					
Any	56 (93)	55 (92)	60 (98)	171 (94)	60 (97)
Grade 2 to 4 AE					
Any	5 (8)	8 (13)	13 (21)	26 (14)	12 (19)
Drug-Related AE					
Any	28 (47)	32 (53)	33 (54)	93 (51)	42 (68)
Serious AE					
Any	7 (12%)	5 (8%)	7 (11%)	19 (10%)	4 (6%)
AE leading to withdrawal / IP Discontinuation					
Any	1 (2)	2 (3)	4 (7)	7 (4)	9 (15)

Summary of Common (>=3% in any arm) Treatment-Emergent Adverse Events by Overall Frequency (Safety Population)

Dictionary-Derived Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Any event	**56 (93)**	**55 (92)**	**60 (98)**	**171 (94)**	**60 (97)**
Upper respiratory tract infection	11 (18)	17 (28)	16 (26)	44 (24)	12 (19)
Diarrhea	14 (23)	14 (23)	15 (25)	43 (24)	12 (19)
Nausea	14 (23)	12 (20)	16 (26)	42 (23)	13 (21)
Headache	13 (22)	13 (22)	14 (23)	40 (22)	7 (11)
Insomnia	5 (8)	7 (12)	11 (18)	23 (13)	15 (24)
Dizziness	7 (12)	7 (12)	3 (5)	17 (9)	18 (29)
Fatigue	8 (13)	8 (13)	8 (13)	24 (13)	11 (18)
Nasopharyngitis	11 (18)	6 (10)	8 (13)	25 (14)	6 (10)
Abnormal dreams	1 (2)	5 (8)	6 (10)	12 (7)	15 (24)
Cough	8 (13)	6 (10)	5 (8)	19 (10)	8 (13)
Back pain	7 (12)	5 (8)	6 (10)	18 (10)	6 (10)
Rash	4 (7)	7 (12)	5 (8)	16 (9)	8 (13)
Bronchitis	5 (8)	7 (12)	6 (10)	18 (10)	4 (6)
Depression	5 (8)	6 (10)	4 (7)	15 (8)	4 (6)
Syphilis	8 (13)	3 (5)	4 (7)	15 (8)	4 (6)
Vomiting	3 (5)	7 (12)	4 (7)	14 (8)	3 (5)
Anxiety	3 (5)	4 (7)	5 (8)	12 (7)	4 (6)
Sinusitis	4 (7)	2 (3)	6 (10)	12 (7)	4 (6)
Abdominal pain	6 (10)	4 (7)	4 (7)	14 (8)	1 (2)
Lymphadenopathy	3 (5)	5 (8)	5 (8)	13 (7)	2 (3)
Gonorrhea	4 (7)	4 (7)	3 (5)	11 (6)	3 (5)
Oropharyngeal pain	3 (5)	6 (10)	3 (5)	12 (7)	2 (3)
Seasonal allergy	4 (7)	4 (7)	4 (7)	12 (7)	1 (2)
Acne	2 (3)	5 (8)	5 (8)	12 (7)	0
Chest pain	1 (2)	3 (5)	5 (8)	9 (5)	3 (5)
Pyrexia	1 (2)	3 (5)	5 (8)	9 (5)	3 (5)
Sinus congestion	4 (7)	5 (8)	1 (2)	10 (6)	2 (3)
Arthralgia	2 (3)	3 (5)	4 (7)	9 (5)	2 (3)
Haemorrhoids	4 (7)	1 (2)	2 (3)	7 (4)	4 (6)
Pharyngitis	4 (7)	1 (2)	4 (7)	9 (5)	2 (3)
Constipation	4 (7)	2 (3)	3 (5)	9 (5)	1 (2)
Decreased appetite	3 (5)	2 (3)	1 (2)	6 (3)	4 (6)
Folliculitis	3 (5)	3 (5)	3 (5)	9 (5)	1 (2)
Gastroenteritis	7 (12)	0	2 (3)	9 (5)	1 (2)
Influenza	1 (2)	2 (3)	5 (8)	8 (4)	2 (3)
Musculoskeletal pain	5 (8)	1 (2)	3 (5)	9 (5)	1 (2)
Pain	0	2 (3)	4 (7)	6 (3)	4 (6)
Nasal congestion	2 (3)	1 (2)	3 (5)	6 (3)	3 (5)

Dictionary-Derived Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Any event	**56 (93)**	**55 (92)**	**60 (98)**	**171 (94)**	**60 (97)**
Toothache	3 (5)	3 (5)	1 (2)	7 (4)	2 (3)
Cellulitis	4 (7)	2 (3)	1 (2)	7 (4)	1 (2)
Dermatitis	3 (5)	1 (2)	2 (3)	6 (3)	2 (3)
Pain in extremity	2 (3)	5 (8)	1 (2)	8 (4)	0
Chlamydial infection	1 (2)	3 (5)	1 (2)	5 (3)	2 (3)
Conjunctivitis	2 (3)	2 (3)	0	4 (2)	3 (5)
Gastritis	3 (5)	2 (3)	1 (2)	6 (3)	1 (2)
Ligament sprain	2 (3)	1 (2)	3 (5)	6 (3)	1 (2)
Night sweats	2 (3)	1 (2)	1 (2)	4 (2)	3 (5)
Paraesthesia	2 (3)	2 (3)	2 (3)	6 (3)	1 (2)
Procedural pain	1 (2)	1 (2)	3 (5)	5 (3)	2 (3)

Summary of Treatment-Emergent Drug-Related Adverse Events (>=5% in any arm) by Overall Frequency (Safety Population)

Preferred Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Any event	**28 (47)**	**32 (53)**	**33 (54)**	**93 (51)**	**42 (68)**
Nausea	8 (13)	10 (17)	13 (21)	31 (17)	9 (15)
Headache	11 (18)	8 (13)	9 (15)	28 (15)	3 (5)
Dizziness	4 (7)	5 (8)	2 (3)	11 (6)	14 (23)
Abnormal dreams	0	4 (7)	5 (8)	9 (5)	13 (21)
Diarrhea	4 (7)	9 (15)	6 (10)	19 (10)	3 (5)
Fatigue	4 (7)	4 (7)	2 (3)	10 (6)	9 (15)
Insomnia	1 (2)	4 (7)	2 (3)	7 (4)	9 (15)
Rash	2 (3)	1 (2)	2 (3)	5 (3)	6 (10)
Vomiting	0	4 (7)	2 (3)	6 (3)	2 (3)
Constipation	1 (2)	1 (2)	3 (5)	5 (3)	0
Dry mouth	0	3 (5)	1 (2)	4 (2)	1 (2)
Depression	0	1 (2)	3 (5)	4 (2)	0
Rash macular	0	0	0	0	3 (5)
Somnolence	0	0	0	0	3 (5)

Summary of Treatment-Emergent Grade 2 to 4 Adverse Events (>=5% in any arm) by Overall Frequency (Safety Population)

Dictionary-Derived Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Any event	**37 (62)**	**42 (70)**	**39 (64)**	**118 (65)**	**37 (60)**
Upper respiratory tract infection	6 (10)	7 (12)	3 (5)	16 (9)	3 (5)
Depression	4 (7)	3 (5)	3 (5)	10 (6)	4 (6)
Insomnia	2 (3)	2 (3)	4 (7)	8 (4)	6 (10)
Headache	2 (3)	3 (5)	6 (10)	11 (6)	2 (3)
Fatigue	2 (3)	5 (8)	4 (7)	11 (6)	1 (2)
Diarrhea	5 (8)	2 (3)	3 (5)	10 (6)	1 (2)
Bronchitis	2 (3)	1 (2)	4 (7)	7 (4)	3 (5)
Nausea	2 (3)	4 (7)	3 (5)	9 (5)	1 (2)
Syphilis	4 (7)	3 (5)	2 (3)	9 (5)	1 (2)
Abdominal pain	4 (7)	3 (5)	1 (2)	8 (4)	0
Back pain	1 (2)	2 (3)	3 (5)	6 (3)	2 (3)
Anxiety	0	2 (3)	1 (2)	3 (2)	3 (5)
Gonorrhea	3 (5)	1 (2)	0	4 (2)	2 (3)
Musculoskeletal pain	3 (5)	0	2 (3)	5 (3)	1 (2)
Blood creatine phosphokinase increased	3 (5)	0	0	3 (2)	2 (3)
Cellulitis	3 (5)	1 (2)	0	4 (2)	1 (2)
Dizziness	1 (2)	1 (2)	0	2 (1)	3 (5)
Sinusitis	0	1 (2)	3 (5)	4 (2)	0
Rash macular	0	0	0	0	3 (5)

Summary of Grade 2-4 Drug-Related Treatment-Emergent Adverse Events (≥3% in any arm) by Overall Frequency (Safety Population)

Dictionary-Derived Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Any event	**5 (8)**	**8 (13)**	**13 (21)**	**26 (14)**	**12 (19)**
Insomnia	1 (2)	2 (3)	0	3 (2)	4 (6)
Nausea	0	2 (3)	3 (5)	5 (3)	1 (2)
Headache	1 (2)	1 (2)	3 (5)	5 (3)	0
Fatigue	0	2 (3)	1 (2)	3 (2)	1 (2)
Rash	0	0	1 (2)	1 (<1)	2 (3)
Rash macular	0	0	0	0	3 (5)
Depression	0	0	2 (3)	2 (1)	0

Summary of Serious Treatment-Emergent Adverse Events by System Organ Class (Safety Population)

System Organ Class Preferred Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
ANY EVENT	**7 (12)**	**5 (8)**	**7 (11)**	**19 (10)**	**4 (6)**
Uncoded					
Any event	0	0	1 (2)	1 (<1)	0
Uncoded[a]	0	0	1 (2)	1 (<1)	0
Infections and infestations					
Any event	4 (7)	2 (3)	4 (7)	10 (6)	1 (2)
Cellulitis	2 (3)	0	0	2 (1)	1 (2)
Pneumonia	1 (2)	1 (2)	0	2 (1)	0
Shigella infection	1 (2)	0	1 (2)	2 (1)	0
Abscess	0	0	1 (2)	1 (<1)	0
Appendiceal abscess	0	0	1 (2)	1 (<1)	0
Appendicitis	0	0	1 (2)	1 (<1)	0
Osteomyelitis	0	0	1 (2)	1 (<1)	0
Pyelonephritis	1 (2)	0	0	1 (<1)	0
Sepsis	1 (2)	0	0	1 (<1)	0
Staphylococcal infection	1 (2)	0	0	1 (<1)	0
Viral infection	0	1 (2)	0	1 (<1)	0
Gastrointestinal disorders					
Any event	1 (2)	1 (2)	1 (2)	3 (2)	1 (2)
Colitis	1 (2)	1 (2)	0	2 (1)	0
Enteritis	0	0	1 (2)	1 (<1)	0
Gastrointestinal haemorrhage	0	0	0	0	1 (2)
Psychiatric disorders					
Any event	1 (2)	0	2 (3)	3 (2)	1 (2)
Mania	0	0	1 (2)	1 (<1)	0
Substance-induced psychotic disorder	0	0	1 (2)	1 (<1)	0
Suicidal ideation	1 (2)	0	0	1 (<1)	0
Suicide attempt	0	0	0	0	1 (2)
Cardiac disorders					
Any event	1 (2)	0	0	1 (<1)	1 (2)
Atrial flutter	1 (2)	0	0	1 (<1)	0
Cardiac arrest	0	0	0	0	1 (2)
Myocardial infarction	0	0	0	0	1 (2)
General disorders and administration site conditions					
Any event	0	1 (2)	0	1 (<1)	1 (2)
Chest pain	0	1 (2)	0	1 (<1)	1 (2)
Musculoskeletal and connective tissue disorders					
Any event	0	0	1 (2)	1 (<1)	0
Musculoskeletal pain	0	0	1 (2)	1 (<1)	0

System Organ Class Preferred Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Any event	0	1 (2)	0	1 (<1)	0
Burkitt's lymphoma	0	1 (2)	0	1 (<1)	0
Nervous system disorders					
Any event	0	1 (2)	0	1 (<1)	0
Headache	0	1 (2)	0	1 (<1)	0
Renal and urinary disorders					
Any event	1 (2)	0	0	1 (<1)	0
Nephrolithiasis	1 (2)	0	0	1 (<1)	0
Respiratory, thoracic and mediastinal disorders					
Any event	0	1 (2)	0	1 (<1)	0
Pulmonary embolism	0	1 (2)	0	1 (<1)	0

a. Uncoded AE for Subject [redacted] was originally listed as a SAE for "[redacted]" which was coded to Abscess Intestinal under the Infections and Infestations SOC following the final SAC. This subject had another serious abscess (same start date) that was coded under the Infection and Infestation SOC (Appendiceal abscess), therefore the Any Event counts under Infections and Infestation are accurate and would not change if this term had coded prior to the final SAC.

Summary of Treatment-Emergent Adverse Events by System Organ Class Leading to Withdrawal/Permanent Discontinuation of Investigational Product (Safety Population)

System Organ Class Preferred Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
ANY EVENT	**1 (2)**	**2 (3)**	**4 (7)**	**7 (4)**	**9 (15)**
Psychiatric disorders					
Panic attack	0	1 (2)	0	1 (<1)	1 (2)
Agitation	0	0	0	0	1 (2)
Anxiety disorder	0	0	1 (2)	1 (<1)	0
Confusional state	0	0	0	0	1 (2)
Substance-induced psychotic disorder	0	0	0	0	1 (2)
Suicide attempt	0	0	0	0	1 (2)
Investigations					
Transaminases increased	0	0	1 (2)	1 (<1)	1 (2)
Electrocardiogram abnormal	1 (2)	0	0	1 (<1)	0
Nervous system disorders					
Dizziness	0	0	0	0	2 (3)
Disturbance in attention	0	0	0	0	1 (2)
Lethargy	0	0	0	0	1 (2)

System Organ Class Preferred Term	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Cardiac disorders					
Palpitations	1 (2)	0	0	1 (<1)	0
Gastrointestinal disorders					
Colitis microscopic	0	0	0	0	1 (2)
Hepatobiliary disorders					
Hepatitis	0	0	1 (2)	1 (<1)	0
Metabolism and nutrition disorders					
Hypertriglyceridaemia	0	0	0	0	1 (2)
Musculoskeletal and connective tissue disorders					
Musculoskeletal pain	0	0	1 (2)	1 (<1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Burkitt's lymphoma	0	1 (2)	0	1 (<1)	0
Renal and urinary disorders					
Incontinence	0	0	0	0	1 (2)

Treatment-Emergent Laboratory Abnormalities for Select Tests (Safety Population)

	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Alanine Amino Transferase (IU/L), n (%)					
Grades 1 to 4	8 (13)	12 (20)	17 (28)	37 (20)	13 (21)
Grades 2 to 4	3 (5)	7 (12)	2 (3)	12 (7)	5 (8)
Grades 3 to 4	0	1 (2)	2 (3)	3 (2)	1 (2)
Grade 1	5 (8)	5 (8)	15 (25)	25 (14)	8 (13)
Grade 2	3 (5)	6 (10)	0	9 (5)	4 (6)
Grade 3	0	0	0	0	0
Grade 4	0	1 (2)	2 (3)	3 (2)	1 (2)
ALK Phos (IU/L), n (%)					
Grades 1 to 4	1 (2)	2 (3)	4 (7)	7 (4)	5 (8)
Grades 2 to 4	0	1 (2)	0	1 (<1)	0
Grades 3 to 4	0	0	0	0	0
Grade 1	1 (2)	1 (2)	4 (7)	6 (3)	5 (8)
Grade 2	0	1 (2)	0	1 (<1)	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Aspartate Amino Transferase (IU/L), n (%)					
Grades 1 to 4	12 (20)	17 (28)	16 (26)	45 (25)	13 (21)
Grades 2 to 4	6 (10)	9 (15)	6 (10)	21 (12)	6 (10)
Grades 3 to 4	2 (3)	1 (2)	3 (5)	6 (3)	4 (6)
Grade 1	6 (10)	8 (13)	10 (16)	24 (13)	7 (11)
Grade 2	4 (7)	8 (13)	3 (5)	15 (8)	2 (3)
Grade 3	2 (3)	0	3 (5)	5 (3)	3 (5)
Grade 4	0	1 (2)	0	1 (<1)	1 (2)
Total Bilirubin (UMOL/L) n (%)					
Grades 1 to 4	8 (13)	3 (5)	8 (13)	19 (10)	0
Grades 2 to 4	2 (3)	1 (2)	2 (3)	5 (3)	0
Grades 3 to 4	0	0	0	0	0
Grade 1	6 (10)	2 (3)	6 (10)	14 (8)	0
Grade 2	2 (3)	1 (2)	2 (3)	5 (3)	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0

Conclusions:

Efficacy:

- CAB, in combination with NRTIs, exhibited rapid HIV-1 RNA virologic suppression in the Induction Phase.
- Response rates (HIV-1 RNA <50 c/mL) were higher at Week 24 of the Induction Phase with CAB compared to the EFV control arm, as a result of the slower decline in HIV-1 RNA and more adverse event (AE) related withdrawals on the EFV arm.

- Following 24 weeks of Induction therapy, CAB plus RPV maintained virologic suppression at a rate similar to EFV plus two NRTIs through 24 weeks of Maintenance (Week 48).
- At Week 96 (72 weeks on maintenance therapy), the proportion of subjects with plasma HIV–1 RNA <50 c/mL, in each of the CAB plus RPV arms was higher than the EFV arm with differences primarily resulting from a higher rate of discontinuations for AEs and a higher rate of virologic non-responders in the EFV group. The Per Protocol (PP) population analysis supported the findings of sustained virologic activity across CAB arms, with numerically higher HIV-1 suppression rates compared to the EFV arm
- Response rates at Week 96 were associated with CAB dose level (60 mg >30 mg >10 mg), driven by both differences in virologic response and non-virologic discontinuations between CAB groups. Both the 10 mg and 30 mg CAB treatment arms had higher rates of no virologic data compared to the 60 mg arm due to discontinuations including protocol deviation, loss to follow-up, investigator discretion, and withdrawal of consent.
- Based on the ITT-ME population, CAB plus RPV maintained viral suppression, during the 72 week Maintenance phase at rates comparable to EFV. The PP-M analysis similarly demonstrated a higher HIV-1 suppression rate at Week 96 for subjects on CAB compared with subjects on EFV.

Safety:

- CAB was generally well tolerated across doses with few AE related withdrawals, treatment limitations or discernible trends in incidence of AEs relative to dose.
- No CAB drug-related SAEs have been reported to date in this study through 96 weeks.
- Two subjects with steatohepatitis receiving CAB 60 mg + ABC/3TC developed asymptomatic treatment-emergent ALT elevations >10x ULN, with normal bilirubin levels, which resolved on withdrawal of study drug.
- With the possible exception of insomnia, there was no apparent dose relationship between AE frequency and CAB dose level.
- Overall rates of graded laboratory abnormalities including ALT elevations were similar between CAB and EFV arms.
- The transition from dual NRTIs to RPV at Week 24 for subjects treated with CAB did not significantly alter the overall frequency of AEs or laboratory abnormalities, with fewer treatment-related AEs reported during the Maintenance Phase compared to the Induction Phase.
- The AE profile of EFV observed in this study was consistent with existing EFV prescribing information.

Virology:

- Overall, there was a low rate of PDVF during the Induction Phase, with 3 of 181 (<2%) of subjects meeting PDVF in the CAB treatment arms and 4 of 62 subjects (6%) with PDVFs in the EFV treatment arm.
- There were no treatment-emergent resistance mutations, nor phenotypic resistance, in any of the subjects with PDVF during the Induction Phase.
- There were five subjects with PDVF during the Maintenance Phase including two on 10 mg CAB + RPV, one on 30 mg CAB + RPV, and two on EFV + TDF/FTC.
- One subject on 10 mg CAB + RPV had treatment-emergent NNRTI resistance mutations K101K/E and E138E/A with accompanying 4.6 FC to RPV at Week 72. Treatment-emergent NNRTI and IN resistance mutations were observed in one subject with PDVF at Week 48 on 10 mg CAB + RPV. This subject had CAB and RPV exposures <50% of the expected concentrations.

PK:

- Plasma CAB C0 increased proportionally with doses of 10 mg, 30 mg, and 60 mg once daily.
- CAB Individual Average C0 was 8.1-, 25-, and 48-fold above the *in vitro* PA-IC90 following 10 mg, 30 mg, and 60 mg once daily, respectively during the Induction Phase, and 8.1-, 24-, and 50-fold above the *in vitro* PA-IC90 during the Maintenance Phase.
- Geometric mean (CVb) RPV Individual Average C0 was 60.5 ng/mL (77), 72.0 ng/mL (40), and 78.0 ng/mL (59), following RPV 25 mg once daily with CAB 10 mg, 30 mg, and 60 mg once daily, respectively. It is unclear why mean RPV concentration are lower following co-administration with CAB 10 mg as compared to higher CAB doses, but it is unlikely that this reflects an impact of CAB on RPV PK.
- No relationship between CAB PK and antiviral response was elucidated.

Dose Selection:

- Efficacy and safety results support selection of CAB 30 mg once daily for further evaluation beyond Week 96 in LAI116482. All CAB treated subjects in the LAI116482 study were transitioned on to CAB 30 mg + RPV, following Week 96. CAB 30 mg will be further evaluated in future HIV-1 treatment studies.

Effective Date: [redacted]-20[redacted]

Synopsis for Study LAI116482 Week 144

Title: A Phase IIb, Dose Ranging Study of Oral GSK1265744 in Combination with Nucleoside Reverse Transcriptase Inhibitors for Induction of HIV-1 Virologic Suppression Followed by an Evaluation of Maintenance of Virologic Suppression when Oral GSK1265744 is combined with Oral Rilpivirine (RPV) in HIV-1 Infected, Antiretroviral Therapy Naive Adult Subjects - Week 144 Results

Investigator(s): This is a multi-center study; 49 investigators screened subjects, 48 sites randomized subjects.

Study center(s): This study was conducted at 49 centers in two countries (41 in the US, 8 in Canada).

Publication(s):

Margolis DA, Brinson CC, Smith GH, de Vente J, Hagins DP, Eron JJ, Griffith SK, St. Clair MH, Stevens MC, Williams PE, Ford SL, Stancil BS, Bomar MM, Hudson KJ, Smith KY, Spreen WR. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis*. 2015 Jul 17. pii: S1473-3099(15)00152-8. doi: 10.1016/S1473-3099(15)00152-8. [October 2015].

Study Period: 06-Aug-2012 (First subject screened) –18-Dec-2015 (Last Subject Week 144); this study is ongoing in an open label phase.

Phase of Development: IIb

Objectives:

Primary Objective:

To select a dose of cabotegravir (CAB, GSK1265744) for further evaluation as part of a two-drug combination antiretroviral therapy (ART) regimen with RPV for 24 weeks, following a 24-week induction period of CAB with two Nucleoside reverse transcriptase inhibitor (NRTIs), in Human Immunodeficiency Virus Type 1 (HIV-1) infected, antiretroviral naïve subjects.

Secondary Objectives:

Overall secondary objectives:

- To evaluate the safety, efficacy and tolerability of 10, 30, and 60 mg of CAB once daily both in combination with two NRTIs and as part of a two-drug combination maintenance ART regimen with RPV, relative to efavirenz (EFV), through Week 96;
- To evaluate the effect of 10, 30, and 60 mg of CAB on selected virologic and immunologic markers of HIV infection over 96 weeks.

Induction Phase – Specific Secondary Objectives:

- To select and confirm a dose of CAB in combination with two NRTIs through Week 24 for induction of virologic suppression;
- To evaluate the antiviral activity, safety, and tolerability of 10, 30, and 60 mg of CAB once daily relative to EFV, all in combination with two NRTIs, through Week 24;
- To characterize the pharmacokinetic (PK) parameters of CAB and to explore exposure-response relationships (e.g., the relationship between CAB plasma exposure at Weeks 2 and 12 and virologic response or occurrence of adverse events (AEs) through Week 24);
- To assess the development of viral resistance to CAB and other on-study ART in subjects experiencing virologic failure through Week 24;
- To evaluate the effect of various demographic factors and adherence on exposure-response parameters of CAB through Week 24.

Maintenance Phase – Specific Secondary Objectives:

- To evaluate the ability of a two drug ART regimen, consisting of CAB plus RPV, to maintain virologic suppression through Week 96 in subjects who achieved plasma HIV-1 Ribonucleic acid (RNA) <50 c/mL by Week 24 in the Induction Phase with dual NRTI background ART;
- To evaluate the effect of 10, 30, and 60 mg of CAB and RPV on selected virologic and immunologic markers of HIV-1 infection from Week 24 through Week 96;
- To evaluate the safety and tolerability of 10, 30, and 60 mg of CAB and RPV from Week 24 through Week 96;
- To characterize the PK parameters of CAB and RPV and to explore exposure-response relationships (e.g., the relationship between CAB and RPV plasma exposure at Weeks 26 and 36 and virologic response or occurrence of AEs from Week 24 through Week 96);
- To assess the development of viral resistance to CAB and RPV in subjects experiencing virologic failure from Week 24 through Week 96;
- To evaluate the effect of various demographic factors and adherence on exposure-response parameters of CAB and RPV from Week 24 through Week 96.

Methodology: This Phase IIb study in HIV-1 infected, ART-naive adult subjects consisted of two parts, an Induction Phase and a Maintenance Phase. The Induction Phase consisted of a 24-week dose-ranging evaluation of CAB at blinded doses of 10 mg, 30 mg and 60 mg once daily and a contemporary control arm of open-label EFV 600 mg once daily. The background dual NRTI for all arms was either abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) fixed dose combination (FDC) tablets, as chosen by the Investigator. Randomization was stratified by screening viral load and choice of background NRTIs. CAB once daily blinded doses in combination with

background NRTIs were evaluated on the basis of antiviral activity, safety and PK over 24 weeks. Subjects randomized to a CAB containing arm, who successfully completed 24 weeks on study and demonstrated virologic suppression (defined as having a plasma HIV-1 RNA <50 c/mL before Week 24, with no signs of virologic rebound) were eligible for the Maintenance Phase of this study. During the Maintenance Phase, the background NRTIs were discontinued and the subject's ART regimen was simplified to their randomized dose of CAB in combination with RPV 25 mg once daily for an additional 72 weeks. The Maintenance Phase evaluated the ability of this two drug ART regimen to maintain virologic suppression through Week 48, Week 72 and Week 96. Subjects randomized to the EFV arm continued on their randomized regimen through Week 96, after which time they will be discontinued from the study. At Week 96, All subjects randomized to a GSK1265744-containing regimen and who successfully completed 96 weeks of treatment continue to have access to CAB (at the sponsor selected dose of 30 mg) and RPV 25 mg via the Open-Label Phase.

Number of subjects: The study planned to randomize approximately 200 subjects. A total of 244 subjects were randomized and 243 subjects received at least one dose of investigational product (IP).

Diagnosis and main criteria for inclusion:

The main <u>Inclusion</u> criteria included:

- HIV-1 infected subjects ≥ 18 years of age;
- HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 c/mL;
- CD4+ cell count ≥200 cells/mm^3 (or higher as local guidelines dictate);
- ART-naive defined as having ≤ 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection (Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor was exclusionary).

The main <u>Exclusion</u> criteria included:

- Women who were pregnant or breastfeeding;
- Any evidence of an active Centers for disease control and prevention (CDC) Category C disease;
- Moderate to severe hepatic impairment;
- Any subject who posed a significant suicide risk;
- History of ongoing or clinically relevant hepatitis within the previous 6 months; anticipated need for Hepatitis C Virus (HCV) therapy;
- History of liver cirrhosis with or without hepatitis viral co-infection;
- Ongoing or clinically relevant pancreatitis;
- History of cardiac diseases: myocardial infarction, congestive heart failure, documented hypertrophic cardiomyopathy, sustained ventricular tachycardia;

- Personal or known family history of prolonged QT syndrome;
- Any evidence of primary resistance or any historical resistance;
- Estimated creatinine clearance <50 mL/min;
- Alanine aminotransferase (ALT) ≥5 times upper limit of normal (ULN);
- Alanine aminotransferase (ALT) ≥ 3xULN and bilirubin ≥ 1.5xULN (with >35% direct bilirubin).

Treatment administration:

Investigational Product (IP) in this study included CAB, matching placebo, RPV, and EFV. Background antiretrovirals (ABC/3TC, TDF/FTC, protocol-permitted switch agents) were not considered Investigational Product. Subjects and Investigators on the CAB arms were blinded to CAB dose assignment. To blind treatment of CAB doses, subjects on the 10 and 30 mg CAB treatment arms received matching placebo tablets once daily together with the CAB dose.

During the Induction Phase, CAB was taken orally as 10 mg, 30 mg, or 60 mg tablets once daily in combination with ABC/3TC or TDF/FTC, with a meal.

In the Maintenance Phase, subjects randomized to CAB took once daily with a meal, plus RPV 25 mg instead of ABC/3TC or TDF/FTC.

In the Open-Label Phase, all subjects randomized to CAB were switched to CAB 30 mg and continued to receive RPV 25 mg.

Subjects randomized to EFV took one 600 mg tablet orally once daily in combination with ABC/3TC or TDF/FTC. ABC/3TC and TDF/FTC could be taken with or without food while EFV was recommended to be taken on an empty stomach at bedtime.

Investigational Product	Strength and Packaging	Batch Numbers
CAB	10 mg tablets; 34 tablets per bottle	[redacted]
	30 mg tablets; 34 tablets per bottle	[redacted]
CAB Placebo to Match (PTM)	PTM CAB; 34 tablets per bottle	[redacted]
EFV	600 mg tablets; 30 tablet per bottle	[redacted]
RPV	25 mg tablets; 30 tablets per bottle	[redacted]

Criteria for evaluation:

Primary Efficacy Endpoint:

The primary endpoint is the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 based on Intent-to-Treat-Exposed (ITT-E) population using the Missing, Switch, or Discontinuation equals Failure (MSDF) algorithm. Dose selection was based primarily on antiviral activity and tolerability in conjunction with immunologic, safety, virologic resistance and PK measures.

Overall Secondary Endpoints:

Proportion of subjects with plasma HIV-1 RNA <400 and <50 c/mL over time by visit using the MSDF and Observed algorithm;

Absolute values and change from baseline in plasma HIV-1 RNA by visit;

Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death);

Absolute values and changes from baseline in CD4+ cell counts by visit;

Incidence of treatment-emergent genotypic and phenotypic resistance to CAB, RPV and other on-study ART for protocol-defined virologic failures;

Medication adherence to IP based on pill counts by visit.

Induction Phase – Specific Secondary Endpoint:

The proportion of subjects with HIV-1 RNA <50 c/mL at Week 16 and Week 24 based on ITT-E population using the MSDF algorithm. Dose selection for induction was based primarily on antiviral activity and tolerability in conjunction with immunologic, safety, virologic resistance and PK measures at Week 16 and confirmed at Week 24.

Maintenance Phase – Specific Secondary Endpoints:

The proportion of subjects with HIV-1 RNA <50 c/mL from Week 24 through Week 96 by visit for the ITT-Maintenance Exposed (ME) population (MSDF);

Incidence of AEs and laboratory abnormalities over time from Week 24 through Week 96, maintenance safety population.

Statistical methods:

The sample size of 50 subjects per arm was chosen to ensure a high probability that a dosage arm with truly poor response was not selected for further study, while allowing for the formal consideration of other factors in dose selection should efficacy be similar across dosage arms.

The primary efficacy endpoint was the response rate at Week 48 (proportion of subjects with plasma HIV-1 RNA <50 c/mL). The efficacy decision criteria were based on an observed difference of >8% between the CAB dosage arms (i.e., a difference of more than 4 responders in 50 subjects).

With 50 subjects per arm, and assuming true response rates of 85% and 75%, respectively in 2 dosage arms, there was at least 55% chance that the superior dose would be selected (i.e., the observed difference in the two dosage arms would be greater than 8%), while the chance of incorrectly selecting the inferior dose was <1% (i.e., the observed difference in the two dosage arms would be less than -8%). The chance of not being able to make a selection between the 2 doses was 44% (i.e., the observed difference in the two dosage arms would be between -8% and 8%).

The ITT-E population was the primary population used for the efficacy analyses. The ITT-E population consists of all randomized subjects who received at least one dose of IP. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received.

The ITT-Maintenance Exposed (ITT-ME) population consists of all randomized who received at least one dose of IP during the Maintenance Phase of the study. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received. The ITT-ME population was the secondary population for some efficacy analyses.

The Per Protocol (PP) population consists of subjects in the ITT-E population with the exception of major protocol violators. The PP population was a secondary population for efficacy purposes. The PP Population could have been used for a supporting analysis of the primary endpoint comparisons only. Such a supporting analysis would not be performed if the PP Population comprises more than 95% of the ITT-E Population.

The Per Protocol Maintenance (PP-M) population consists of subjects in the ITT-ME population with the exception of major protocol violators. The PP-M population was a secondary population for efficacy purposes.

The Safety population was the primary population used for the safety analyses. The Safety Population consists of all randomized subjects who were exposed to IPs with the exception of any subjects with documented evidence of not having consumed any amount of IP. Subjects were analyzed according to the actual treatments received. Subjects were not excluded from this population as a result of changes to the background regimen.

The Maintenance Safety Population consists of all randomized subjects who were exposed to IP during the Maintenance Phase of the study with the exception of any subjects with documented evidence of not having consumed any amount of IP during the Maintenance Phase of the study. Subjects were analyzed according to the actual treatments received. Subjects were not excluded from this population as a result of changes to the background regimen. The Maintenance Safety Population was an additional population for safety analyses.

The PK Summary Population includes all subjects who received CAB or RPV, had intensive and/or limited/sparse PK sampling during the study, and provided evaluable CAB or RPV plasma concentration data. Subjects in this population were included in listings.

Efficacy analyses performed included summaries of the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 48 and 96 were summarized using the Snapshot and observed algorithm. Additional summaries by stratification subgroups were also performed.

Other efficacy analyses performed included summaries of the proportion of subjects with plasma HIV-1 RNA <400 c/mL at Week 48 and 96, absolute values and changes from Baseline in CD4+ counts and HIV-1 RNA over time, and the incidence of disease progression (HIV-associated conditions, AIDS and death).

The occurrence of protocol-defined virologic failures (PDVF) was summarized by visit for each treatment group. Viral genotyping and phenotyping analyses were conducted to explore the relationship between treatment with CAB and EFV and the evolution of HIV-1 resistance. The incidence of treatment-emergent genotypic and phenotypic resistance to integrase inhibitors (INIs) at time of PDVF were summarized by treatment group.

The following AEs were summarized overall and by treatment group: all AEs, drug-related AEs, AEs by grade, fatal and non-fatal serious adverse events (SAEs), and AEs leading to withdrawals.

SAEs were summarized on-therapy. Mean values and changes from Baseline for laboratory parameters and vital signs were summarized by treatment group. Treatment-emergent laboratory toxicity grades were also summarized by treatment group.

Pharmacokinetic Analytical Methods:

The following CAB PK parameters were estimated for subjects in the intensive PK sampling group at Week 2: area under the plasma drug concentration-time curve from pre-dose to the end of the dosing interval at steady state (AUC (0-τ)), maximum plasma drug concentration (Cmax), pre-dose plasma drug concentration (C0), concentration at the end of a dosing interval (Cτ), time at which Cmax was observed (tmax), and Apparent clearance following oral dosing (CL/F). CAB C0 was estimated from pre-dose concentrations for all subjects in the Sparse PK Concentration Population and also Weeks 12 and 26 and 36 of the PK Summary Population. RPV C0 was estimated from pre-dose concentrations for all subjects in the Sparse PK Concentration Population during the Maintenance Phase of the study. An individual average C0 (which includes Cτ for intensive PK group) was created for each phase of the study.

Pharmacokinetic data were presented in graphical and/or tabular form and summarized descriptively.

Derived PK parameters were listed. For all parameters except tmax, the following summary statistics were calculated for each treatment group: median, maximum, minimum, arithmetic mean, standard deviation, coefficient of variation on arithmetic mean, geometric mean, coefficient of variation on geometric mean, 95% confidence interval for the geometric mean and standard deviation of logarithmically transformed data. For tmax, median, maximum, minimum, arithmetic mean, and standard deviation were calculated.

PK parameters were summarized by treatment, Baseline plasma HIV-1 RNA (≤100,000, >100,000 c/mL) and background dual NRTI (ABC/3TC, TDF/FTC, or other), and overall.

Dose proportionality of CAB PK parameters (Week 2: AUC (0-τ), Cmax, C0, and Cτ) was assessed using the power model: $y = \alpha \times dose^{\beta}$.

Log-transformed PK parameter individual subject C0 average from the Induction Phase was compared with Maintenance Phase for each treatment with SAS PROC MIXED model.

Pearson's correlations and p-values between dose-normalized CAB PK parameters (AUC (0-τ), Cmax, C0, individual subject average C0) and age, weight, height, body mass index, body surface area (BSA), gender, and race (African-American vs. others) were calculated.

PK/PD analyses including exposure-antiviral activity, exposure-immunology, and exposure-toxicity analyses were performed using Pearson's correlations.

Summary:

At this time LAI116482 is ongoing; results presented throughout this clinical study report are based on the last subject through Week 144 (Data cut-off date: Last Subject Last Visit Week 144: [[redacted]20[redacted]]; Database release: [20Mar2016]; Statistical analysis complete: [10Nov2016]).

The treatment dosing regimen (all oral administration) assignments used in this study were:

Induction Phase:

- CAB 10 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg
- CAB 30 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg
- CAB 60 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg
- EFV 600 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg

Maintenance Phase:

- CAB 10 mg once daily + RPV 25 mg once daily
- CAB 30 mg once daily + RPV 25 mg once daily
- CAB 60 mg once daily + RPV 25 mg once daily
- EFV 600 mg once daily + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg

Open-Label Phase:

- CAB 30 mg once daily + RPV 25 mg once daily

After the statistical analysis was completed, the Sponsor became aware of GCP noncompliance issues at one site (Investigator ID [redacted], Site [redacted]) in [redacted] where 11 subjects were enrolled in this study. The study team was notified of this issue on 29 APR 2016, and in conjunction with ViiV Healthcare, the Sponsor team agreed to conduct a sensitivity analysis of the primary and select other endpoints to assess the impact of efficacy when removing these subjects from the database. In addition, the safety analysis was re-run to ensure all AEs were properly accounted for and reported in the database.

The primary GCP concerns at Site [redacted] in this study were as follows:

- Failure to provide new information to study subjects and to give the subjects the opportunity to re-consent.
- Apparent falsification of subject signatures on informed consent documents.
- Protocol noncompliance including deficiencies in source documentation and under-reporting of AEs: Study monitors were given incomplete access to medical records during the study. A complete review of the medical records post hoc for subjects at this site identified several unreported AEs.

- Inadequacies in Principal Investigator oversight, which contributed to the noncompliance concerns outlined in this section.
- Failure to pay subject stipends according to the Institutional Review Board (IRB)-approved informed consent form (ICF).
- Apparent falsification of some suicide assessment (eC-SSRS) data, as discrepancies were noted for the time and date stamps relative to subject visit dates.

The US FDA was notified of GCP noncompliance issues at this site.

Study Population Results

Subject Disposition

At the time of this Week 144 analysis, 71% (129/181) receiving CAB were ongoing.

Table 1 Summary of Subject Accountability: Study Conclusion Record (ITT-E Population)

	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	EFV 600 mg N=62	Total N=243
Completion Status, n (%)					
Completed	0	3 (5)	1 (2)	41 (66)	45 (19)
Withdrawal	23 (38)	14 (23)	11 (18)	21 (34)	69 (28)
Ongoing at time of analysis	37 (62)	43 (72)	49 (80)	0	129 (53)
Primary[a]/subreason[b] for withdrawal, n (%)					
Adverse event	**2 (3)**	**2 (3)**	**4 (7)**	**9 (15)**	**17 (7)**
Lack of efficacy	**8 (13)**	**3 (5)**	**2 (3)**	**6 (10)**	**19 (8)**
Insufficient viral load response	3 (5)	0	1 (2)	1 (2)	5 (2)
Protocol defined virologic failure	5 (8)	3 (5)	1 (2)	5 (8)	14 (6)
Protocol deviation	**2 (3)**	**1 (2)**	**1 (2)**	**0**	**4 (2)**
Non-compliance with IP treatment	2 (3)	0	0	0	2 (<1)
Lost to follow-up	**6 (10)**	**2 (3)**	**2 (3)**	**4 (6)**	**14 (6)**
Investigator discretion	**0**	**2 (3)**	**0**	**1 (2)**	**3 (1)**
Withdrew consent	**5 (8)**	**4 (7)**	**2 (3)**	**1 (2)**	**12 (5)**
Burden of travel or lack of access to travel	1 (2)	1 (2)	1 (2)	0	3 (1)
Subject homeless	0	1 (2)	0	0	1 (<1)
Subject relocated	3 (5)	2 (3)	1 (2)	0	6 (2)

Data Source: Table 6.2

b. Subjects can have only one primary reason for withdrawal.

Percentages for subreasons may sum to more or less than 100%. Subjects may have more than one subreason underneath a single primary reason. Subjects are not required to indicate subreasons.

Demographics and Baseline Characteristics

Demographic characteristics were well balanced across treatment arms. The majority of subjects across all four arms were white (62%) and male (96%). The mean age was 35.1 years. Further demographic details can be found in the LAI116482 Week 96 CSR [GlaxoSmithKline Document Number 2014N216014_00].

Efficacy Results

Plasma HIV-1 RNA <50 c/mL at Week 144

At Week 144, 58% (CAB 10 mg arm), 67% (CAB 30 mg arm) and 77% (CAB 60 mg arm) of subjects randomized to oral CAB dosing maintained virologic suppression (HIV-1 <50 c/mL). At the Week 96 timepoint, all EFV subjects were discontinued from the study. Subjects randomized to one of the three oral CAB dosing arms were transitioned to the Sponsor selected regimen of CAB 30 mg + RPV 25 mg once the last subject completed the Week 96 visit and the study was unblinded. The transition took place between Weeks 108 and 120 (Table 2, Figure 1).

Table 2 Proportion (95% CI) of Subjects with Plasma HIV-1 RNA <50 c/mL at Key Visits- Snapshot (MSDF) Analysis (ITT-E Population)

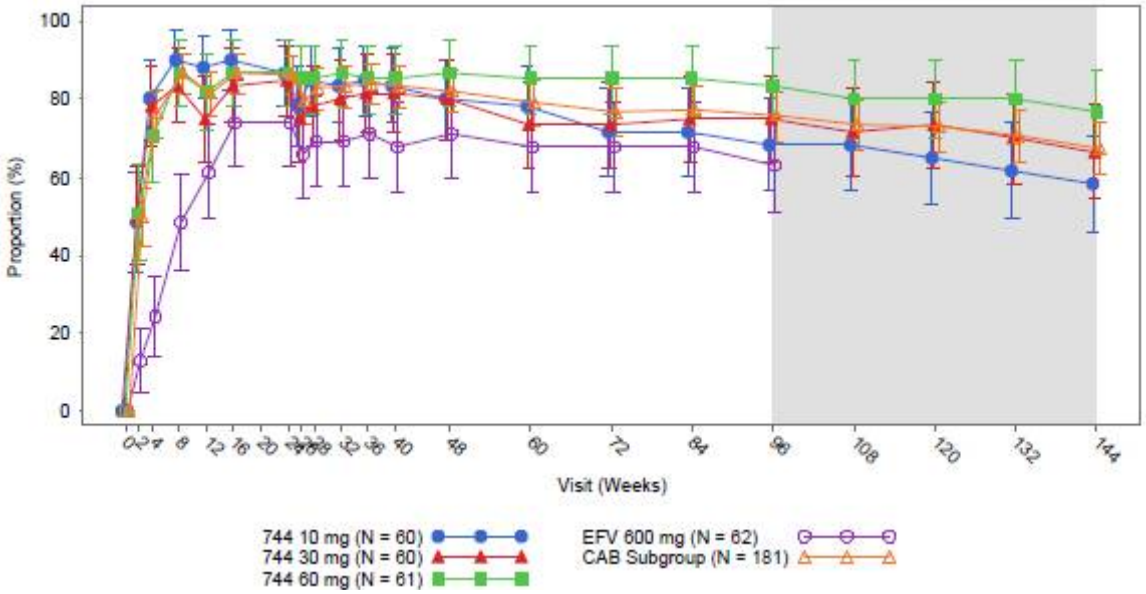
Visit		CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subtotal N=181	EFV 600 mg N=62
Week 16	n (%)	54 (90)	50 (83)	53 (87)	157 (87)	46 (74)
	95%CI Proportion	(82, 98)	(74, 93)	(78, 95)	(82, 92)	(63, 85)
Week 24	n (%)	52 (87)	51 (85)	53 (87)	156 (86)	46 (74)
	95%CI Proportion	(78, 95)	(76, 94)	(78, 95)	(81, 91)	(63, 85)
Week 48	n (%)	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)
	95%CI Proportion	(70, 90)	(70, 90)	(78, 95)	(77, 88)	(60, 82)
Week 72	n (%)	43 (72)	44 (73)	52 (85)	139 (77)	42 (68)
	95%CI Proportion	(60, 83)	(62, 85)	(76, 94)	(71, 83)	(56, 79)
Week 96	n (%)	41 (68)	45 (75)	51 (84)	137 (76)	39 (63)
	95%CI Proportion	(57, 80)	(64, 86)	(74, 93)	(69, 82)	(51, 75)
Week 144	n (%)	35 (58)	40 (67)	47 (77)	122 (67)	-
	95%CI Proportion	(46, 71)	(55, 79)	(66, 88)	(61, 74)	-
Week 144 without site [redacted]	n (%)	32 (58)	38 (69)	43 (78)	113 (68)	-
	95% CI Proportion	(45, 71)	(57, 81)	(67, 89)	(61, 76)	-

Data Source: Table 7.2 and Table 7.102
95% CIs are normal approximation confidence intervals.

A sensitivity analysis was conducted on the proportion of subjects with plasma HIV 1 RNA <50 c/mL which excluded 11 subjects from the analysis due to suspected violations of GCP. These 11 subjects had been randomly assigned and treated at Investigator ID [redacted], Site [redacted]. At Week 144, the GCP sensitivity analysis revealed 58%, 69% and 78% of the subjects had virologic success in the CAB 10 mg, CAB 30 mg and CAB 60 mg arms, respectively (Source: post-hoc Table 7.102), which except for a slightly higher success rate for the CAB 30 mg and 60 mg arms, were identical to those of the complete ITT-E population analysis. At Week 96, there was little to no change to the snapshot response rates for the GCP sensitivity analysis compared to the primary analysis

(Week 96: 68%, 75% and 84% for the ITT-E population and 67%, 76% and 85% for the GCP sensitivity analysis; Data Source: Table 7.2 and post-hoc Table 7.102). Accordingly, this sensitivity analysis demonstrates that the data issues identified at this site had minimal to no impact to the key efficacy endpoint analyses.

Figure 1 Proportion (95% CI) of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit – Snapshot (MSDF) Analysis (ITT-E Population)



Data Source: Figure 7.1
Note: 95% CIs are normal approximation confidence intervals. At week 96, EFV arm completed study participation and those in 744 (CAB)arms who chose to enter the open label extension phase were all switched to oral CAB 30 mg + oral RPV 25 mg (shaded area).

Table 3 Summary of Study Outcomes (<50 copies/mL) at Week 144 - Snapshot (MSDF) Analysis (ITT-E Population)

Outcome	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)
Virologic Success	**35 (58)**	**40 (67)**	**47 (77)**	**122 (67)**
Virologic Non-response[a]	**8 (13)**	**8 (13)**	**2 (3)**	**18 (10)**
Data in window not below threshold (<50 c/mL)	2 (3)	3 (5)	0	5 (3)
Discontinued for lack of efficacy	2 (3)	1 (2)	1 (2)	4 (2)
Discontinued for other reason while not below threshold	4 (7)	1 (2)	1 (2)	6 (3)
Prior change in ART	0	3 (5)	0	3 (2)
No Virologic Data	**17 (28)**	**12 (20)**	**12 (20)**	**41 (23)**
Discontinued due to AE[b]	2 (3)	2 (3)	4 (7)	8 (4)
Discontinued for Other Reasons	14 (23)	8 (13)	5 (8)	27 (15)
Missing data during window but on study	1 (2)	2 (3)	3 (5)	6 (3)

Data Source: Table 7.3

a. Virologic failure

No deaths occurred during this study.

Plasma HIV-1 RNA Response by Baseline HIV-1 RNA

For subjects with RNA levels <100,000 c/mL at Baseline, 106/154 (69%) subjects receiving CAB remained suppressed at Week 144. Forty (82%) of 49 in the 60 mg group, 36 (68%) of 53 in the 30 mg group, and 30 (58%) of 52 in the 10 mg group had sustained viral suppression after 144 weeks on study.

Of subjects who had ≥100,000 c/mL at Baseline (high viral load), 16/27 (59%) of subjects receiving CAB remained suppressed at Week 144. Subjects on CAB with a high viral load were discontinued due to both virologic and non-virologic reasons. For subjects who had a high viral load (HIV-1 RNA of at least 100,000 c/mL) at Baseline, 7 (58%) of 12 in the 60 mg group, 4 (57%) of 7 in the 30 mg group, and 5 (63%) of 8 in the 10 mg group had sustained viral suppression at Week 144.

Table 4 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit and Baseline Plasma HIV-1 RNA - Snapshot (MSDF) Analysis (ITT-E Population)

Baseline Plasma HIV-1 RNA: <100,000 c/mL					
Visit	**CAB 10 mg N=60 n/N (%)**	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	**0 / 52**	**0 / 53**	**0 / 49**	**0 / 154**	**0 / 54**
Week 2	28 / 52 (54)	30 / 53 (57)	31 / 49 (63)	89 / 154 (58)	8 / 54 (15)
Week 4	46 / 52 (88)	44 / 53 (83)	43 / 49 (88)	133 / 154 (86)	15 / 54 (28)
Week 8	49 / 52 (94)	48 / 53 (91)	45 / 49 (92)	142 / 154 (92)	29 / 54 (54)
Week 12	47 / 52 (90)	43 / 53 (81)	41 / 49 (84)	131 / 154 (85)	36 / 54 (67)
Week 16	49 / 52 (94)	46 / 53 (87)	44 / 49 (90)	139 / 154 (90)	42 / 54 (78)
Week 24	46 / 52 (88)	46 / 53 (87)	44 / 49 (90)	136 / 154 (88)	40 / 54 (74)
Week 26	41 / 52 (79)	40 / 53 (75)	43 / 49 (88)	124 / 154 (81)	35 / 54 (65)
Week 28	45 / 52 (87)	43 / 53 (81)	44 / 49 (90)	132 / 154 (86)	36 / 54 (67)
Week 32	44 / 52 (85)	43 / 53 (81)	44 / 49 (90)	131 / 154 (85)	36 / 54 (67)
Week 36	45 / 52 (87)	43 / 53 (81)	44 / 49 (90)	132 / 154 (86)	37 / 54 (69)
Week 40	44 / 52 (85)	44 / 53 (83)	45 / 49 (92)	133 / 154 (86)	36 / 54 (67)
Week 48	42 / 52 (81)	42 / 53 (79)	44 / 49 (90)	128 / 154 (83)	38 / 54 (70)
Week 60	41 / 52 (79)	40 / 53 (75)	44 / 49 (90)	125 / 154 (81)	35 / 54 (65)
Week 72	38 / 52 (73)	39 / 53 (74)	43 / 49 (88)	120 / 154 (78)	35 / 54 (65)
Week 84	37 / 52 (71)	40 / 53 (75)	43 / 49 (88)	120 / 154 (78)	35 / 54 (65)
Week 96	37 / 52 (71)	40 / 53 (75)	43 / 49 (88)	120 / 154 (78)	32 / 54 (59)
Week 108	36 / 52 (69)	38 / 53 (72)	42 / 49 (86)	116 / 154 (75)	
Week 120	35 / 52 (67)	39 / 53 (74)	42 / 49 (86)	116 / 154 (75)	
Week 132	32 / 52 (62)	37 / 53 (70)	42 / 49 (86)	111 / 154 (72)	
Week 144	30 / 52 (58)	36 / 53 (68)	40 / 49 (82)	106 / 154 (69)	
Baseline Plasma HIV-1 RNA: ≥100,000 c/mL					
	CAB 10 mg N=60 n/N (%)	**CAB 30 mg N=60 n/N (%)**	**CAB 60 mg N=61 n/N (%)**	**CAB Subtotal N=181 n/N (%)**	**EFV 600 mg N=62 n/N (%)**
Baseline	**0 / 8**	**0 / 7**	**0 / 12**	**0 / 27**	**0 / 8**
Week 2	1 / 8 (13)	0 / 7	0 / 12	1 / 27 (4)	0 / 8
Week 4	2 / 8 (25)	3 / 7 (43)	0 / 12	5 / 27 (19)	0 / 8
Week 8	5 / 8 (63)	2 / 7 (29)	8 / 12 (67)	15 / 27 (56)	1 / 8 (13)
Week 12	6 / 8 (75)	2 / 7 (29)	9 / 12 (75)	17 / 27 (63)	2 / 8 (25)
Week 16	5 / 8 (63)	4 / 7 (57)	9 / 12 (75)	18 / 27 (67)	4 / 8 (50)
Week 24	6 / 8 (75)	5 / 7 (71)	9 / 12 (75)	20 / 27 (74)	6 / 8 (75)
Week 26	6 / 8 (75)	5 / 7 (71)	9 / 12 (75)	20 / 27 (74)	6 / 8 (75)
Week 28	6 / 8 (75)	4 / 7 (57)	8 / 12 (67)	18 / 27 (67)	7 / 8 (88)
Week 32	6 / 8 (75)	5 / 7 (71)	9 / 12 (75)	20 / 27 (74)	7 / 8 (88)
Week 36	6 / 8 (75)	6 / 7 (86)	8 / 12 (67)	20 / 27 (74)	7 / 8 (88)
Week 40	6 / 8 (75)	5 / 7 (71)	7 / 12 (58)	18 / 27 (67)	6 / 8 (75)
Week 48	6 / 8 (75)	6 / 7 (86)	9 / 12 (75)	21 / 27 (78)	6 / 8 (75)
Week 60	6 / 8 (75)	4 / 7 (57)	8 / 12 (67)	18 / 27 (67)	7 / 8 (88)
Week 72	5 / 8 (63)	5 / 7 (71)	9 / 12 (75)	19 / 27 (70)	7 / 8 (88)
Week 84	6 / 8 (75)	5 / 7 (71)	9 / 12 (75)	20 / 27 (74)	7 / 8 (88)
Week 96	4 / 8 (50)	5 / 7 (71)	8 / 12 (67)	17 / 27 (63)	7 / 8 (88)
Week 108	5 / 8 (63)	5 / 7 (71)	7 / 12 (58)	17 / 27 (63)	
Week 120	4 / 8 (50)	5 / 7 (71)	7 / 12 (58)	16 / 27 (59)	
Week 132	5 / 8 (63)	5 / 7 (71)	7 / 12 (58)	17 / 27 (63)	
Week 144	5 / 8 (63)	4 / 7 (57)	7 / 12 (58)	16 / 27 (59)	

Data Source: Table 7.14

Plasma HIV-1 RNA Response over Time

The proportion of subjects with plasma HIV-1 RNA <50 c/mL using MSDF analysis for the ITT-E Population increased steeply in all CAB treatment groups from Baseline to Week 4, then tended to plateau starting at Week 8 onward. There was a slight decline between Week 24 and Week 36, but in general subjects maintained suppression through the primary analysis performed at Week 48. The advantage in virologic response for subjects treated with CAB was sustained for an additional 72 weeks following discontinuation of their background NRTIs and switch to the two-drug maintenance regimen (CAB plus RPV). All CAB treatment groups after switch to the sponsor selected CAB 30 mg tablet for the open label period of the study continued to show good response at Week 144.

Table 5 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit - Snapshot (MSDF) Analysis (ITT-E Population)

Visit	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)	EFV 600 mg N=62 n (%)
Baseline	0	0	0	0	0
Week 2	29 (48)	30 (50)	31 (51)	90 (50)	8 (13)
Week 4	48 (80)	47 (78)	43 (70)	138 (76)	15 (24)
Week 8	54 (90)	50 (83)	53 (87)	157 (87)	30 (48)
Week 12	53 (88)	45 (75)	50 (82)	148 (82)	38 (61)
Week 16	54 (90)	50 (83)	53 (87)	157 (87)	46 (74)
Week 24	52 (87)	51 (85)	53 (87)	156 (86)	46 (74)
Week 26	47 (78)	45 (75)	52 (85)	144 (80)	41 (66)
Week 28	51 (85)	47 (78)	52 (85)	150 (83)	43 (69)
Week 32	50 (83)	48 (80)	53 (87)	151 (83)	43 (69)
Week 36	51 (85)	49 (82)	52 (85)	152 (84)	44 (71)
Week 40	50 (83)	49 (82)	52 (85)	151 (83)	42 (68)
Week 48	48 (80)	48 (80)	53 (87)	149 (82)	44 (71)
Week 60	47 (78)	44 (73)	52 (85)	143 (79)	42 (68)
Week 72	43 (72)	44 (73)	52 (85)	139 (77)	42 (68)
Week 84	43 (72)	45 (75)	52 (85)	140 (77)	42 (68)
Week 96	41 (68)	45 (75)	51 (84)	137 (76)	39 (63)
Week 108	41 (68)	43 (72)	49 (80)	133 (73)	
Week 120	39 (65)	44 (73)	49 (80)	132 (73)	
Week 132	37 (62)	42 (70)	49 (80)	128 (71)	
Week 144	35 (58)	40 (67)	47 (77)	122 (67)	

Data Source: Table 7.8

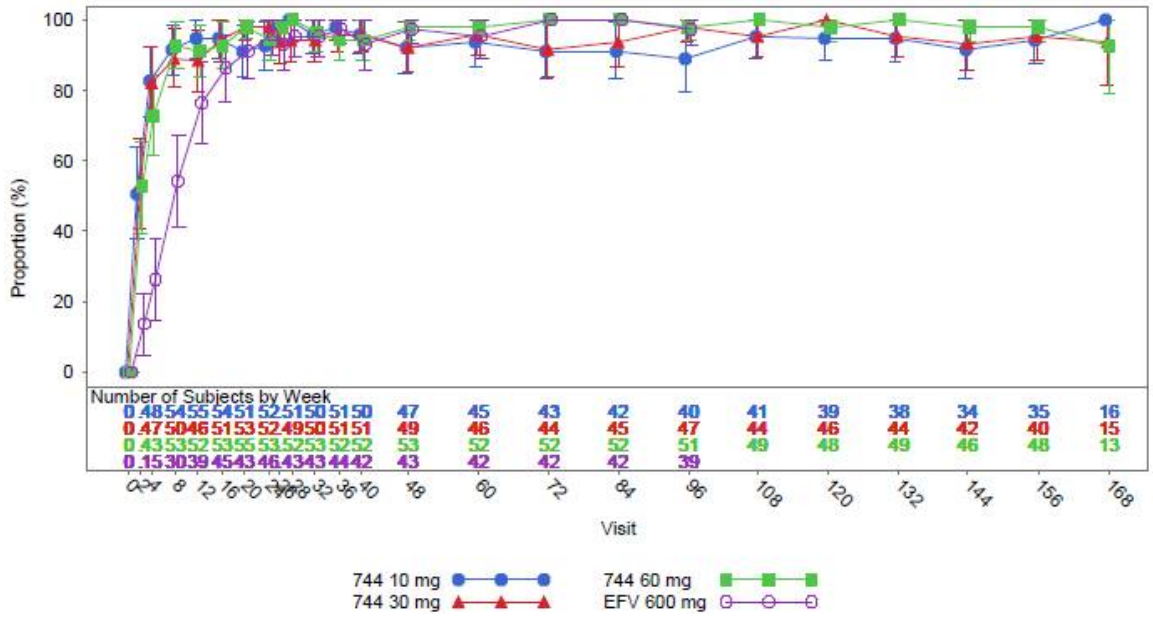
The proportion of subjects with plasma HIV-1 RNA <50 c/mL using the observed case (OC) analysis for the ITT-E Population also demonstrated a more rapid response for subjects on the CAB treatment arms through Week 12. By Week 16, the majority (>85%) of subjects across all treatment arms remaining on study were suppressed (HIV-1 RNA <50 c/mL) with a high response rate persisting through Week 144.

Table 6 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit - OC Analysis (ITT-E Population)

Act. Rel. Time	CAB 10 mg N=60 n/N (%)	CAB 30 mg N=60 n/N (%)	CAB 60 mg N=61 n/N (%)	CAB Subtotal N=181 n/N (%)	EFV 600 mg N=62 n/N (%)
Baseline	0 / 60	0 / 60	0 / 61	0 / 181	0 / 62
Week 2	29 / 57 (51)	30 / 56 (54)	31 / 59 (53)	90 / 172 (52)	8 / 59 (14)
Week 4	48 / 58 (83)	47 / 57 (82)	43 / 59 (73)	138 / 174 (79)	15 / 57 (26)
Week 8	54 / 59 (92)	50 / 56 (89)	53 / 57 (93)	157 / 172 (91)	30 / 55 (55)
Week 12	55 / 58 (95)	46 / 52 (88)	52 / 57 (91)	153 / 167 (92)	39 / 51 (76)
Week 16	54 / 57 (95)	51 / 54 (94)	53 / 57 (93)	158 / 168 (94)	45 / 52 (87)
Week 20	51 / 56 (91)	53 / 54 (98)	55 / 56 (98)	159 / 166 (96)	43 / 47 (91)
Week 24	52 / 56 (93)	52 / 53 (98)	53 / 56 (95)	157 / 165 (95)	46 / 48 (96)
Week 26	47 / 48 (98)	47 / 50 (94)	52 / 53 (98)	146 / 151 (97)	41 / 44 (93)
Week 28	51 / 51 (100)	49 / 52 (94)	52 / 52 (100)	152 / 155 (98)	43 / 45 (96)
Week 32	50 / 52 (96)	50 / 53 (94)	53 / 55 (96)	153 / 160 (96)	43 / 45 (96)
Week 36	51 / 52 (98)	51 / 53 (96)	52 / 55 (95)	154 / 160 (96)	44 / 45 (98)
Week 40	50 / 52 (96)	51 / 53 (96)	52 / 55 (95)	153 / 160 (96)	42 / 45 (93)
Week 48	47 / 51 (92)	49 / 53 (92)	53 / 54 (98)	149 / 158 (94)	43 / 44 (98)
Week 60	45 / 48 (94)	46 / 48 (96)	52 / 53 (98)	143 / 149 (96)	42 / 44 (95)
Week 72	43 / 47 (91)	44 / 48 (92)	52 / 52 (100)	139 / 147 (95)	42 / 42 (100)
Week 84	42 / 46 (91)	45 / 48 (94)	52 / 52 (100)	139 / 146 (95)	42 / 42 (100)
Week 96	40 / 45 (89)	47 / 48 (98)	51 / 52 (98)	138 / 145 (95)	39 / 40 (98)
Week 108	41 / 43 (95)	44 / 46 (96)	49 / 49 (100)	134 / 138 (97)	
Week 120	39 / 41 (95)	46 / 46 (100)	48 / 49 (98)	133 / 136 (98)	
Week 132	38 / 40 (95)	44 / 46 (96)	49 / 49 (100)	131 / 135 (97)	
Week 144	34 / 37 (92)	42 / 45 (93)	46 / 47 (98)	122 / 129 (95)	

Data Source: Table 7.12

Figure 2 Proportion of Subjects with HIV-1 RNA <50 c/mL (OC Analysis; ITT-E Population)



Data Source: Figure 7.2
Note: Number of subjects at week 2 were 57, 56, 59, and 59, respectively. Number of subjects at week 26 were 48, 50, 53, and 44, respectively.

CD4+ Cell Count Change from Baseline-(ITT-E)

The median increase in CD4+ cell count from Baseline was 185.0 cells/µL (IQR 95.0–270.0) in the CAB groups by Week 24. After 24 weeks of maintenance therapy (Week 48), the median increase in CD4+ cell count from Baseline was 219.0 cells/µL (141.0–343.0) for subjects on the CAB arms. By Week 96, the median increase in CD4+ cell count from Baseline was 259.5 cells/µL (137.0–355.0) for subjects receiving CAB. By Week 144, the median increase in CD4+ cell count from Baseline was 299 cells/uL (151.0-465.5) in the remaining CAB groups.

Table 7 Summary of Baseline Absolute Value and Change from Baseline in CD4+ Cell Count (cells/mm^3) by Visit (ITT-E Population)

Visit	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subgroup N=181	EFV 600 mg N=62
Baseline	**N=60**	**N=60**	**N=61**	**N=181**	**N=62**
Mean (SD)	445.5 (155.60)	444.9 (190.98)	459.0 (170.64)	449.8 (172.16)	456.5 (196.11)
Median~ (IQR)	415.0 ~(342.0, 541.0)	404.0 ~(319.0, 550.5)	420.0 ~(343.0, 548.0)	412.0 ~(333.0, 548.0)	416.5 ~(304.0, 651.0)
Week 2	**N=57**	**N=56**	**N=59**	**N=172**	**N=59**
Mean (SD)	92.6 (112.44)	79.5 (118.15)	91.7 (127.92)	88.0 (119.23)	24.8 (138.47)
Median~ (IQR)	90.0 ~(31.0, 146.0)	101.5 ~(-17.5, 150.5)	88.0 ~(10.0, 149.0)	89.0 ~(10.5, 149.5)	26.0 ~(-35.0, 83.0)
Week 4	**N=58**	**N=57**	**N=59**	**N=174**	**N=57**
Mean (SD)	136.4 (157.36)	76.9 (107.01)	88.2 (110.01)	100.6 (128.81)	46.0 (106.35)
Median~ (IQR)	113.0 ~(59.0, 173.0)	77.0 ~(14.0, 145.0)	93.0 ~(25.0, 151.0)	92.5 ~(24.0, 151.0)	48.0 ~(-3.0, 98.0)
Week 8	**N=58**	**N=56**	**N=57**	**N=171**	**N=55**
Mean (SD)	129.9 (123.47)	117.8 (132.19)	90.5 (148.25)	112.8 (135.20)	65.6 (120.25)
Median~ (IQR)	136.5 ~(59.0, 177.0)	120.5 ~(39.5, 198.0)	88.0 ~(4.0, 177.0)	123.0 ~(35.0, 178.0)	59.0 ~(22.0, 144.0)
Week 12	**N=58**	**N=53**	**N=57**	**N=168**	**N=51**
Mean (SD)	140.5 (142.86)	140.8 (165.02)	145.2 (142.24)	142.2 (149.11)	103.4 (125.39)
Median~ (IQR)	115.5 ~(40.0, 221.0)	153.0 ~(72.0, 207.0)	150.0 ~(64.0, 231.0)	146.5 ~(57.5, 223.5)	93.0 ~(21.0, 182.0)
Week 16	**57**	**54**	**57**	**168**	**52**
Mean (SD)	159.3 (115.36)	142.2 (145.64)	148.3 (131.81)	150.1 (130.66)	135.5 (153.48)
Median~ (IQR)	137.0 ~(78.0, 235.0)	157.0 ~(89.0, 228.0)	141.0 ~(73.0, 252.0)	140.5 ~(79.5, 236.5)	125.0 ~(48.0, 253.5)
Week 20	**56**	**54**	**56**	**166**	**49**
Mean (SD)	165.2 (146.90)	153.8 (150.40)	182.6 (142.18)	167.4 (146.08)	149.0 (117.44)
Median~ (IQR)	172.5 ~(49.0, 262.0)	163.5 ~(84.0, 257.0)	185.0 ~(71.0, 281.0)	169.0 ~(73.0, 271.0)	160.0 ~(70.0, 252.0)
Week 24	**56**	**53**	**56**	**165**	**47**
Mean (SD)	172.5 (112.04)	180.9 (161.43)	204.0 (166.78)	185.9 (148.26)	143.4 (145.18)
Median~ (IQR)	158.0 ~(83.5, 236.5)	196.0 ~(88.0, 281.0)	182.5 ~(104.0, 284.0)	185.0 ~(95.0, 270.0)	159.0 ~(43.0, 212.0)
Week 26	**48**	**50**	**53**	**151**	**45**
Mean (SD)	186.4 (153.99)	177.7 (146.84)	194.7 (149.66)	186.4 (149.29)	166.4 (145.11)

Visit	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subgroup N=181	EFV 600 mg N=62
Median~ (IQR)	172.0 ~(74.5, 241.5)	152.0 ~(104.0, 298.0)	167.0 ~(97.0, 292.0)	165.0 ~(97.0, 279.0)	174.0 ~(45.0, 246.0)
Week 28	**49**	**52**	**52**	**153**	**45**
Mean (SD)	205.0 (164.91)	188.1 (132.08)	193.3 (154.43)	195.3 (149.97)	178.2 (150.25)
Median~ (IQR)	203.0 ~(116.0, 266.0)	192.0 ~(95.5, 273.5)	154.5 ~(96.0, 265.0)	183.0 ~(103.0, 266.0)	175.0 ~(115.0, 245.0)
Week 32	**52**	**53**	**55**	**160**	**45**
Mean (SD)	191.4 (151.79)	205.2 (145.53)	209.9 (157.56)	202.3 (151.03)	197.4 (170.48)
Median~ (IQR)	177.0 ~(110.5, 274.0)	215.0 ~(139.0, 294.0)	190.0 ~(89.0, 309.0)	201.0 ~(113.0, 286.5)	186.0 ~(82.0, 269.0)
Week 36	**52**	**53**	**55**	**160**	**45**
Mean (SD)	192.0 (165.97)	213.0 (144.89)	265.0 (169.42)	224.1 (162.50)	185.2 (152.91)
Median~ (IQR)	189.0 ~(82.0, 297.0)	219.0 ~(121.0, 300.0)	269.0 ~(136.0, 349.0)	223.5 ~(118.5, 304.0)	181.0 ~(77.0, 285.0)
Week 40	**52**	**53**	**55**	**160**	**45**
Mean (SD)	203.6 (171.74)	212.8 (180.38)	212.3 (114.67)	209.6 (156.79)	221.5 (188.99)
Median~ (IQR)	189.0 ~(89.0, 251.5)	206.0 ~(92.0, 303.0)	197.0 ~(118.0, 309.0)	195.0 ~(109.0, 290.0)	204.0 ~(63.0, 331.0)
Week 48	**51**	**53**	**54**	**158**	**44**
Mean (SD)	235.1 (179.89)	241.6 (182.90)	259.0 (154.21)	245.5 (171.81)	262.5 (201.33)
Median~ (IQR)	203.0 ~(126.0, 294.0)	235.0 ~(131.0, 369.0)	240.0 ~(164.0, 370.0)	219.0 ~(141.0, 343.0)	216.0 ~(133.5, 363.0)
Week 60	**48**	**47**	**53**	**148**	**44**
Mean (SD)	217.7 (152.92)	269.4 (188.34)	266.1 (156.03)	251.5 (166.56)	263.8 (181.15)
Median~ (IQR)	215.5 ~(111.5, 303.0)	275.0 ~(130.0, 398.0)	251.0 ~(156.0, 371.0)	242.5 ~(133.5, 363.5)	268.5 ~(144.0, 363.0)
Week 72	**47**	**48**	**52**	**147**	**42**
Mean (SD)	232.0 (191.05)	201.4 (206.54)	254.0 (189.26)	229.8 (195.50)	257.1 (216.41)
Median~ (IQR)	181.0 ~(90.0, 339.0)	208.5 ~(94.0, 352.5)	221.5 ~(160.5, 325.5)	205.0 ~(117.0, 339.0)	208.5 ~(94.0, 355.0)
Week 84	**46**	**48**	**52**	**146**	**42**
Mean (SD)	261.5 (171.65)	287.0 (207.10)	278.1 (166.11)	275.8 (181.27)	279.4 (191.30)
Median~ (IQR)	243.5 ~(142.0, 389.0)	276.5 ~(169.5, 410.5)	255.0 ~(178.0, 353.0)	257.0 ~(166.0, 389.0)	258.5 ~(157.0, 395.0)
Week 96	**46**	**46**	**52**	**144**	**41**
Mean (SD)	269.4 (204.32)	267.5 (196.27)	286.2 (181.50)	274.8 (192.57)	281.7 (232.90)
Median~ (IQR)	236.5 ~(135.0, 359.0)	249.5 ~(118.0, 348.0)	271.5 ~(150.5, 355.0)	259.5 ~(137.0, 355.0)	289.0 ~(158.0, 415.0)
Week 108	**43**	**46**	**49**	**138**	**0**
Mean (SD)	296.2 (215.21)	304.3 (195.30)	288.4 (184.61)	296.1 (196.75)	-
Median~ (IQR)	248.0 ~(143.0, 398.0)	269.0 ~(185.0, 442.0)	259.0 ~(146.0, 412.0)	263.0 ~(158.0, 415.0)	-
Week 120	**41**	**46**	**49**	**136**	**0**
Mean (SD)	266.1 (173.09)	279.3 (181.10)	307.2 (225.39)	285.4 (195.37)	-
Median~ (IQR)	263.0 ~(177.0, 378.0)	250.5 ~(184.0, 385.0)	276.0 ~(155.0, 430.0)	264.0 ~(175.5, 401.0)	-
Week 132	**40**	**46**	**49**	**135**	**0**
Mean (SD)	297.1 (167.59)	305.2 (184.98)	313.2 (168.30)	305.7 (172.78)	-
Median~ (IQR)	296.0 ~(193.0, 440.0)	292.0 ~(195.0, 402.0)	313.0 ~(209.0, 382.0)	304.0 ~(196.0, 402.0)	-
Week 144	**37**	**45**	**46**	**128**	**0**
Mean (SD)	330.7 (225.42)	308.9 (224.63)	322.4 (224.57)	320.0 (223.24)	-
Median~	302.0	273.0	327.5	299.0	-

Visit	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	CAB Subgroup N=181	EFV 600 mg N=62
(IQR)	~(169.0, 410.0)	~(146.0, 504.0)	~(144.0, 492.0)	~(151.0, 465.5)	

Data Source: Table 7.20
Note: Baseline values are actual CD4+ Cell Count (cells/mm^3) values.

Safety Results

The data in this section address the secondary objective to evaluate the safety and tolerability of 10, 30, and 60 mg of CAB once daily in combination with two NRTIs through Week 24 and as part of a two-drug combination maintenance ART regimen with RPV, through Week 144. The results are from the first Phase IIb study administering oral CAB to antiretroviral naïve HIV-1 positive subjects. This study is currently ongoing; results presented here are through the cutoff date of [redacted]20[redacted]– date of database release.

A sensitivity analysis was conducted to exclude 11 subjects from Investigator ID [redacted], Site [redacted] due to suspected violations of GCP. Accordingly, this sensitivity analysis demonstrated that the data issues identified at this site had minimal to no impact to the key safety endpoint analyses.

Adverse Events

There were no new trends/signals through Week 144 identified for subjects continuing in to the open label phase of the study. The most commonly reported AEs among subjects receiving CAB at Week 144 were upper respiratory tract infection (21%), diarrhea (11%), and bronchitis (8%).

Table 8 Summary of Common (>=3% Overall) Maintenance Treatment-Emergent Adverse Events by Overall Frequency (Safety Maintenance Population)

Dictionary-Derived Term	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
Any event	38 (73)	49 (92)	50 (91)	137 (86)
Upper respiratory tract infection	9 (17)	13 (25)	12 (22)	34 (21)
Diarrhoea	5 (10)	7 (13)	5 (9)	17 (11)
Bronchitis	4 (8)	3 (6)	6 (11)	13 (8)
Fatigue	4 (8)	5 (9)	3 (5)	12 (8)
Depression	5 (10)	2 (4)	3 (5)	10 (6)
Back pain	3 (6)	2 (4)	4 (7)	9 (6)
Insomnia	3 (6)	2 (4)	5 (9)	10 (6)
Nasopharyngitis	2 (4)	4 (8)	2 (4)	8 (5)
Nausea	0	3 (6)	8 (15)	11 (7)
Syphilis	5 (10)	4 (8)	1 (2)	10 (6)
Gonorrhoea	4 (8)	4 (8)	3 (5)	11 (7)
Pharyngitis	4 (8)	2 (4)	3 (5)	9 (6)
Rash	1 (2)	6 (11)	2 (4)	9 (6)
Seasonal allergy	1 (2)	3 (6)	4 (7)	8 (5)
Cough	3 (6	2 (4)	1 (2)	6 (4)
Lymphadenopathy	2 (4)	1 (2)	4 (7)	7 (4)
Anogenital warts	2 (4)	1 (2)	4 (7)	7 (4)
Folliculitis	1 (2)	2 (4)	3 (5)	6 (4)
Headache	2 (4)	3 (6)	2 (4)	7 (4)

Data Source: Table 8.21
Note: Common adverse events are those with >=3% overall incidence.

Drug-Related AEs

At Week 144, the most frequent drug-related AEs, as assessed by the investigator, that occurred in the CAB treatment group were headache, nausea and abnormal dreams, all at 3%.

Table 9 Summary of Maintenance Treatment-Emergent Drug-Related Adverse Events (>=3% in any arm) by Overall Frequency (Safety Maintenance Population)

Preferred Term	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
Any event	8 (15)	12 (23)	10 (18)	30 (19)
Headache	2 (4)	2 (4)	1 (2)	5 (3)
Nausea	0	0	4 (7)	4 (3)
Abnormal dreams	1 (2)	0	3 (5)	4 (3)
Fatigue	0	2 (4)	0	2 (1)
Depression	1 (2)	0	2 (4)	3 (2)
Diarrhoea	0	2 (4)	0	2 (1)
Memory impairment	0	2 (4)	0	2 (1)

Data Source: Table 8.78

AEs Leading to Withdrawal of Investigational Product

The proportion of AEs leading to withdrawal through Week 144 was low across all CAB arms (3% of all patients). All individually reported AE preferred terms resulting in withdrawal had an incidence of 1 subject in any arm.

Table 10 Summary of Maintenance Treatment Emergent Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product (Safety Maintenance Population)

System Organ Class Preferred Term	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
Any event	1 (2)	2 (4)	1 (2)	4 (3)
Psychiatric disorders				
Any event	0	0	1 (2)	1 (<1)
Anxiety disorder	0	0	1 (2)	1 (<1)
Investigations				
Any event	1 (2)	0	0	1 (<1)
Electrocardiogram abnormal	1 (2)	0	0	1 (<1)
Transaminases increased	0	0	0	0
Infections and infestations				
Any event	0	1 (2)	0	1 (<1)
Acute hepatitis C	0	1 (2)	0	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	0	1 (2)	0	1 (<1)
Burkitt's lymphoma	0	1 (2)	0	1 (<1)

Data Source: Table 8.25

Serious Adverse Events

Post-Baseline through Week 144, 15 (9%) of CAB subjects reported a SAE. None of these events were considered drug-related.

Table 11 Summary of Serious Maintenance Treatment Emergent Adverse Events by System Organ Class (Safety Maintenance Population)

System Organ Class Preferred Term	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
ANY EVENT	5 (10)	5 (9)	5 (9)	15 (9)
Infections and infestations				
Any event	2 (4)	2 (4)	3 (5)	7 (4)
Cellulitis	1 (2)	0	0	1 (<1)
Pneumonia	1 (2)	1 (2)	0	2 (1)
Shigella infection	1 (2)	0	0	1 (<1)
Abscess	0	0	1 (2)	1 (<1)
Abscess intestinal	0	0	1 (2)	1 (<1)
Appendiceal abscess	0	0	1 (2)	1 (<1)
Appendicitis	0	0	1 (2)	1 (<1)
Osteomyelitis	0	0	1 (2)	1 (<1)
Sepsis	1 (2)	0	0	1 (<1)
Staphylococcal infection	1 (2)	0	0	1 (<1)
Viral infection	0	1 (2)	0	1 (<1)
Gastrointestinal disorders				
Any event	**1 (2)**	**1 (2)**	**1 (2)**	**3 (2)**
Colitis	1 (2)	1 (2)	0	2 (1)
Enteritis	0	0	1 (2)	1 (<1)
Gastrointestinal hemorrhage	0	0	0	0
Psychiatric disorders				
Any event	**1 (2)**	**0**	**2 (4)**	**3 (2)**
Mania	0	0	1 (2)	1 (<1)
Substance-induced psychotic disorder	0	0	1 (2)	1 (<1)
Suicidal ideation	1 (2)	0	0	1 (<1)
Cardiac disorders				
Any event	**1 (2)**	**0**	**0**	**1 (<1)**
Atrial flutter	1 (2)	0	0	1 (<1)
General disorders and administration site conditions				
Any event	**0**	**1 (2)**	**0**	**1 (<1)**
Chest pain	0	1 (2)	0	1 (<1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Any event	**0**	**1 (2)**	**0**	**1 (<1)**
Burkitt's lymphoma	0	1 (2)	0	1 (<1)
Nervous system disorders				
Any event	**0**	**1 (2)**	**0**	**1 (<1)**
Headache	0	1 (2)	0	1 (<1)
Respiratory, thoracic and mediastinal disorders				
Any event	**0**	**1 (2)**	**0**	**1 (<1)**
Pulmonary embolism	0	1 (2)	0	1 (<1)

Data Source: Table 8.24

Deaths

No deaths had occurred in this study at the time of the Week 144 analysis.

Suspected Abacavir Hypersensitivity

There were no suspected abacavir hypersensitivity reactions reported in this study at the time of this analysis.

Clinical Laboratory Evaluations

Clinical chemistry laboratory parameters of special interest were defined prior to the start of the study as those of specific clinical relevance to the study (ALT, aspartate aminotransferase [AST], Creatine Kinase, Creatinine, Total Bilirubin and Total Neutrophils). The rate of any grade lab abnormality of special interests was 53% in the CAB subjects. This was driven by a higher rate of Grade 1 and Grade 2 abnormalities. Grade 1 to Grade 4 ALT, AST and Creatine Kinase occurred at a frequency of, 17%, 17% and 19%, respectively.

Table 12 Summary of Maximum Maintenance Treatment Emergent Laboratory Toxicities Parameters of Special Interests (Safety Maintenance Population)

	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
ALL PARAMETERS				
Grades 1 to 4	27 (52)	24 (45)	33 (60)	84 (53)
Grades 2 to 4	10 (19)	13 (25)	14 (25)	37 (23)
Grades 3 to 4	7 (13)	6 (11)	4 (7)	17 (11)
Grade 1	17 (33)	11 (21)	19 (35)	47 (29)
Grade 2	3 (6)	7 (13)	10 (18)	20 (13)
Grade 3	3 (6)	2 (4)	1 (2)	6 (4)
Grade 4	4 (8)	4 (8)	3 (5)	11 (7)
Alanine Amino Transferase (IU/L)				
Grades 1 to 4	7 (13)	12 (23)	8 (15)	27 (17)
Grades 2 to 4	2 (4)	4 (8)	1 (2)	7 (4)
Grades 3 to 4	0	1 (2)	0	1 (<1)
Grade 1	5 (10)	8 (15)	7 (13)	20 (13)
Grade 2	2 (4)	3 (6)	1 (2)	6 (4)
Grade 3	0	0	0	0
Grade 4	0	1 (2)	0	1 (<1)
Aspartate Amino Transferase (IU/L)				
Grades 1 to 4	7 (13)	12 (23)	8 (15)	27 (17)
Grades 2 to 4	4 (8)	6 (11)	3 (5)	13 (8)
Grades 3 to 4	1 (2)	1 (2)	0	2 (1)
Grade 1	3 (6)	6 (11)	5 (9)	14 (9)
Grade 2	3 (6)	5 (9)	3 (5)	11 (7)
Grade 3	1 (2)	0	0	1 (<1)
Grade 4	0	1 (2)	0	1 (<1)
Creatine Kinase (IU/L)				
Grades 1 to 4	11 (21)	6 (11)	14 (25)	31 (19)

	CAB 10 mg N=52 n (%)	CAB 30 mg N=53 n (%)	CAB 60 mg N=55 n (%)	CAB Subtotal N=160 n (%)
Grades 2 to 4	5 (10)	5 (9)	7 (13)	17 (11)
Grades 3 to 4	5 (10)	4 (8)	3 (5)	12 (8)
Grade 1	6 (12)	1 (2)	7 (13)	14 (9)
Grade 2	0	1 (2)	4 (7)	5 (3)
Grade 3	2 (4)	2 (4)	2 (4)	6 (4)
Grade 4	3 (6)	2 (4)	1 (2)	6 (4)
Creatinine (UMOL/L)				
Grades 1 to 4	0	0	1 (2)	1 (<1)
Grades 2 to 4	0	0	0	0
Grades 3 to 4	0	0	0	0
Grade 1	0	0	1 (2)	1 (<1)
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Total Bilirubin (UMOL/L)				
Grades 1 to 4	7 (13)	3 (6)	8 (15)	18 (11)
Grades 2 to 4	1 (2)	2 (4)	2 (4)	5 (3)
Grades 3 to 4	0	0	0	0
Grade 1	6 (12)	1 (2)	6 (11)	13 (8)
Grade 2	1 (2)	2 (4)	2 (4)	5 (3)
Grade 3	0	0	0	0
Grade 4	0	0	0	0
Total Neutrophils (Total ANC - Total Absolute Neutrophil Count) (GI/L)				
Grades 1 to 4	6 (12)	5 (9)	8 (15)	19 (12)
Grades 2 to 4	2 (4)	2 (4)	4 (7)	8 (5)
Grades 3 to 4	2 (4)	1 (2)	1 (2)	4 (3)
Grade 1	4 (8)	3 (6)	4 (7)	11 (7)
Grade 2	0	1 (2)	3 (5)	4 (3)
Grade 3	1 (2)	0	0	1 (<1)
Grade 4	1 (2)	1 (2)	1 (2)	3 (2)

Data Source: Table 8.38

Note: Lipid parameters only summarised on fasting data.

Note: This table summarizes the maximum grade seen during the maintenance phase of the study that was higher than the grade the subject had when they entered the maintenance phase at Week 24.

Urinalysis

There were no clinically significant trends in urinalysis results between CAB arms and EFV or between CAB dosing arms.

Electrocardiograms (ECG)

ECGs were collected at Baseline, Day 1 and Weeks 2, 4, 12, 24, 26, 28, 36, 48, 60, 72, 84, 96, 108, 120, 132 and 144. Most subjects had a change from Baseline in QTcB or QTcF ≤30 msec. Four CAB subjects had an isolated ECG on study with a QTcB or QTcF change from Baseline >60 msec. None of the observed QTc changes were subsequently confirmed by triplicate ECG and no subject discontinued therapy as a result of a change in QTc intervals.

Table 13 Summary of Change from Baseline in QTc Values (Safety Population)

	CAB 10 mg N=60 n (%)	CAB 30 mg N=60 n (%)	CAB 60 mg N=61 n (%)	CAB Subtotal N=181 n (%)
Maximum On-treatment change QTcB (msec)				
n	42	50	44	136
≤30	30 (71)	34 (68)	31 (70)	95 (70)
>30 to ≤60	10 (24)	15 (30)	12 (27)	37 (27)
>60	2 (5)	1 (2)	1 (2)	4 (3)
Maximum On-treatment change QTcF (msec)				
N	42	50	44	136
≤30	37 (88)	41 (82)	32 (73)	110 (81)
>30 to ≤60	3 (7)	8 (16)	11 (25)	22 (16)
>60	2 (5)	1 (2)	1 (2)	4 (3)

Data Source: Table 8.56

Vital Signs

Vital signs were assessed at Day 1, Weeks 2, 4, 12, 24, 26, 28, 36 48, 60, 72, 84, 96, 108, 120, 132, and 144. No significant patterns of changes in vital signs were identified in any treatment group.

Pregnancies

No pregnancies have occurred prior to this analysis.

Virology

Three subjects met PDVF criteria during the Open Label Phase between Week 96 and Week 144 (Data Source: Table 7.16): two subjects who were originally randomized to CAB 10 mg (Weeks 108 and 132) and one subject to 30 mg (Week 132). The 3 subjects are described below:

The 10 mg CAB + RPV subject that met the definition of PDVF (virologic rebound) at Week 108 had a V151V/I mutation (not a primary INI resistance mutation) with a 1.05-fold change to CAB. The subject had 385 c/mL HIV-1 RNA at Week 108. The confirmatory HIV-1 RNA was 772 c/mL HIV1 RNA.

The 10 mg CAB + RPV subject that met the definition of PDVF (virologic rebound) at Week 132 had treatment-emergent NNRTI mutations K101E and M230M/L with a 12-fold change to RPV. The subject had 836 c/mL HIV-1 RNA at Week 132. The confirmatory HIV-1 RNA was 1727 c/mL HIV-1 RNA.

The 30 mg CAB + RPV subject that met the definition of PDVF (virologic rebound) at Week 132 did not have any treatment-emergent mutations. The subject had 908 c/mL HIV-1 RNA at Week 132. The confirmatory HIV-1 RNA was 211 c/mL HIV-1 RNA.

(Data Source: Listing 7.2, Listing 12.1, Listing 12.2, Listing 12.3, Listing 12.5)

Conclusions:

- Based on the ITT-ME population, CAB plus RPV demonstrated durable virologic suppression through 144 weeks of treatment. Subjects who entered the Open Label phase and switched to CAB 30 mg oral continued to remain virologically suppressed, with few non-virologic discontinuations or virologic failures.
- Overall CAB + RPV has been well tolerated, with few AEs leading to withdrawal, none drug related.
- These data support the selection of CAB 30 mg + RPV 25 mg for future use to support long acting (LA) therapy as either an oral lead-in and/or bridging supply.
- The results continue to support the evaluation of all-injectable regimens of CAB LA + RPV LA as maintenance therapy.

Effective Date: [redacted]

Synopsis for Study LAI116482 End of Study

Title: A Phase IIb, Dose Ranging Study of Oral GSK1265744 in Combination with Nucleoside Reverse Transcriptase Inhibitors for Induction of HIV-1 Virologic Suppression Followed by an Evaluation of Maintenance of Virologic Suppression when Oral GSK1265744 is combined with Oral Rilpivirine (RPV) in HIV-1 Infected, Antiretroviral Therapy Naive Adult Subjects – End of Study Report Report

Investigator(s): This is a multi-center study; 49 investigators screened subjects, 48 sites randomized subjects.

Study center(s): This study was conducted at 49 centers in two countries (41 in the US, 8 in Canada).

Publication(s): Margolis DA, Brinson CC, Smith GH, de Vente J, Hagins DP, Eron JJ, Griffith SK, St. Clair MH, Stevens MC, Williams PE, Ford SL, Stancil BS, Bomar MM, Hudson KJ, Smith KY, Spreen WR. Cabotegravir plus rilpivirine, once a day, after induction with cabotegravir plus nucleoside reverse transcriptase inhibitors in antiretroviral-naive adults with HIV-1 infection (LATTE): a randomised, phase 2b, dose-ranging trial. *Lancet Infect Dis*. 2015 Jul 17. pii: S1473-3099(15)00152-8. doi: 10.1016/S1473-3099(15)00152-8.

Study Period: 06Aug2012 (First subject screened) – 15Jan2019 (Last subject Week 324)

Phase of Development: IIb

Objectives:

Primary Objective:

To select a dose of cabotegravir (CAB, GSK1265744) for further evaluation as part of a two-drug combination antiretroviral therapy (ART) regimen with RPV for 24 weeks, following a 24 week induction period of CAB with two NRTIs (Nucleoside reverse transcriptase inhibitor), in HIV-1- (Human Immunodeficiency Virus Type 1) infected, antiretroviral naïve subjects.

Secondary Objectives:

Overall secondary objectives:

- To evaluate the safety, efficacy and tolerability of 10, 30, and 60 mg of CAB once daily both in combination with two NRTIs and as part of a two drug combination maintenance ART regimen with RPV, relative to efavirenz (EFV), through Week 96;
- To evaluate the effect of 10, 30, and 60 mg of CAB on selected virologic and immunologic markers of HIV infection over 96 weeks.

Induction Phase – Specific Secondary Objectives:

- To select and confirm a dose of CAB in combination with two NRTIs through Week 24 for induction of virologic suppression;
- To evaluate the antiviral activity, safety, and tolerability of 10, 30, and 60 mg of CAB once daily relative to EFV, all in combination with two NRTIs, through Week 24;
- To characterize the pharmacokinetic (PK) parameters of CAB and to explore exposure-response relationships (e.g., the relationship between CAB plasma exposure at Weeks 2 and 12 and virologic response or occurrence of adverse events [AEs] through Week 24);
- To assess the development of viral resistance to CAB and other on-study ART in subjects experiencing virologic failure through Week 24;
- To evaluate the effect of various demographic factors and adherence on exposure-response parameters of CAB through Week 24.

Maintenance Phase – Specific Secondary Objectives:

- To evaluate the ability of a two drug ART regimen, consisting of CAB plus RPV, to maintain virologic suppression through Week 96 in subjects who achieved plasma HIV-1 RNA (Ribonucleic acid) <50 c/mL by Week 24 in the Induction Phase with dual nucleoside reverse transcriptase inhibitor (NRTI) background ART;
- To evaluate the effect of 10, 30, and 60 mg of CAB and RPV on selected virologic and immunologic markers of HIV-1 infection from Week 24 through Week 96;
- To evaluate the safety and tolerability of 10, 30, and 60 mg of CAB and RPV from Week 24 through Week 96;
- To characterize the PK parameters of CAB and RPV and to explore exposure-response relationships (e.g., the relationship between CAB and RPV plasma exposure at Weeks 26 and 36 and virologic response or occurrence of adverse events [AEs] from Week 24 through Week 96);

- To assess the development of viral resistance to CAB and RPV in subjects experiencing virologic failure from Week 24 through Week 96;
- To evaluate the effect of various demographic factors and adherence on exposure-response parameters of CAB and RPV from Week 24 through Week 96.

Methodology: This Phase IIb study in human immunodeficiency virus type 1 (HIV-1) infected, antiretroviral therapy (ART)-naive adult subjects consists of two parts, an Induction Phase and a Maintenance Phase. The Induction Phase consists of a 24-week dose-ranging evaluation of GSK1265744 at blinded doses of 10 mg, 30 mg and 60 mg once-daily and a contemporary control arm of open-label efavirenz (EFV) 600 mg once daily. The background dual nucleoside reverse transcriptase inhibitor (NRTI) ART for all arms will be either abacavir/lamivudine (ABC/3TC) or tenofovir/emtricitabine (TDF/FTC) fixed dose combination (FDC) tablets, as chosen by the Investigator. Randomization will be stratified by screening viral load and choice of background NRTIs. GSK1265744 once-daily blinded doses in combination with background NRTIs will be evaluated on the basis of antiviral activity, safety and pharmacokinetics (PK) over 24 weeks. Subjects randomized to a GSK1265744 containing arm, who successfully complete 24 weeks on study and demonstrate virologic suppression (defined as having a plasma HIV-1 RNA <50 c/mL before Week 24, with no signs of virologic rebound) will become eligible for the Maintenance Phase of this study. During the Maintenance Phase, the background NRTIs will be discontinued and the subject's ART regimen will be simplified to their randomized dose of GSK1265744 in combination with rilpivirine 25 mg once-daily for an additional 72 weeks. The Maintenance phase will evaluate the ability of this two drug ART regimen to maintain virologic suppression through Week 48, Week 72 and Week 96. Subjects randomized to the EFV arm will continue on their randomized regimen through Week 96.

Number of subjects: The study planned to randomize approximately 200 subjects. A total of 244 subjects were randomized and 243 subjects received at least one dose of investigational product (IP).

Diagnosis and main criteria for inclusion:

The main Inclusion criteria included:

- HIV-1 infected subjects ≥18 years of age;
- HIV-1 infection as documented by Screening plasma HIV-1 RNA ≥1000 c/mL;
- CD4+ cell count ≥200 cells/mm^3 (or higher as local guidelines dictate);
- ART-naive defined as having ≤10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection (Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor was exclusionary).

Treatment administration: Investigational Product (IP) in this study included CAB, matching placebo, RPV, and EFV. Background antiretrovirals (ABC/3TC, TDF/FTC, protocol-permitted switch agents) were not considered Investigational Product. Subjects and Investigators on the CAB arms were blinded to CAB dose assignment. To blind

treatment of CAB doses, subjects on the 10 and 30 mg CAB treatment arms received matching placebo tablets once daily together with the CAB dose.

During the Induction Phase, CAB was taken orally as 10 mg, 30 mg, or 60 mg tablets once daily in combination with ABC/3TC or TDF/FTC, with a meal.

In the Maintenance Phase, subjects randomized to CAB took once daily with a meal, plus RPV 25 mg instead of ABC/3TC or TDF/FTC.

In the Open-Label Phase, all subjects randomized to CAB were switched to the Sponsor selected dose of CAB 30 mg and will continue to receive RPV 25 mg.

Subjects randomized to EFV taken one 600 mg tablet orally once daily in combination with ABC/3TC or TDF/FTC. ABC/3TC and TDF/FTC could be taken with or without food while EFV was recommended to be taken on an empty stomach at bedtime.

Criteria for evaluation:

Primary Efficacy Endpoint:

The primary endpoint is the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 based on ITT-E (Intent-to-Treat-Exposed) population using the Missing, Switch, or Discontinuation equals Failure (MSDF) algorithm. Dose selection will be based primarily on antiviral activity and tolerability in conjunction with immunologic, safety, virologic resistance and PK measures.

Overall Secondary Endpoints:

Proportion of subjects with plasma HIV-1 RNA <400 and <50 c/mL over time by visit using the MSDF and Observed algorithm;

Absolute values and change from baseline in plasma HIV-1 RNA by visit;

Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome (AIDS) and death);

Absolute values and changes from baseline in CD4+ cell counts by visit;

Incidence of treatment-emergent genotypic and phenotypic resistance to CAB, RPV and other on-study ART for protocol-defined virologic failures;

Medication adherence to IP based on pill counts by visit.

Induction Phase – Specific Secondary Endpoint:

The proportion of subjects with HIV-1 RNA <50 c/mL at Week 16 and Week 24 based on ITT-E population using the MSDF algorithm. Dose selection for induction will be based primarily on antiviral activity and tolerability in conjunction with immunologic, safety, virologic resistance and PK measures at Week 16 and confirmed at Week 24.

Maintenance Phase – Specific Secondary Endpoints:

The proportion of subjects with HIV-1 RNA <50 c/mL from Week 24 through Week 96 by visit for the ITT-ME population (MSDF);

Incidence of AEs and laboratory abnormalities over time from Week 24 through Week 96, maintenance safety population.

Statistical methods: The sample size of 50 subjects per arm was chosen to ensure a high probability that a dosage arm with truly poor response was not selected for further study, while allowing for the formal consideration of other factors in dose selection should efficacy be similar across dosage arms.

The primary efficacy endpoint is the response rate at Week 48 (proportion of subjects with plasma HIV-1 RNA <50 c/mL). The efficacy decision criteria were based on an observed difference of >8% between the CAB dosage arms (i.e., a difference of more than 4 responders in 50 subjects).

With 50 subjects per arm, and assuming true response rates of 85% and 75%, respectively in 2 dosage arms, there was at least 55% chance that the superior dose would be selected (i.e., the observed difference in the two dosage arms would be greater than 8%), while the chance of incorrectly selecting the inferior dose was <1% (i.e., the observed difference in the two dosage arms is less than -8%). The chance of not being able to make a selection between the 2 doses was 44% (i.e., the observed difference in the two dosage arms would be between -8% and 8%).

The ITT-E population is the primary population used for the efficacy analyses. The ITT-E population consists of all randomized subjects who received at least one dose of IP. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received.

The ITT-Maintenance Exposed (ITT-ME) population consists of all randomized who received at least one dose of IP during the Maintenance Phase of the study. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received. The ITT-ME population is the secondary population for some efficacy analyses.

The Per Protocol (PP) population consists of subjects in the ITT-E population with the exception of major protocol violators. The PP population was a secondary population for efficacy purposes. The PP Population could have been used for a supporting analysis of the primary endpoint comparisons only. Such a supporting analysis would not be performed if the PP Population comprises more than 95% of the ITT-E Population.

The Per Protocol Maintenance (PP-M) population consists of subjects in the ITT-ME population with the exception of major protocol violators. The PP-M population was a secondary population for efficacy purposes.

The Safety population is the primary population used for the safety analyses. The Safety Population consists of all randomized subjects who were exposed to investigational products with the exception of any subjects with documented evidence of not having

consumed any amount of investigational product. Subjects were analyzed according to the actual treatments received. Subjects were not excluded from this population as a result of changes to the background regimen.

The Maintenance Safety Population consists of all randomized subjects who were exposed to investigational products during the Maintenance Phase of the study with the exception of any subjects with documented evidence of not having consumed any amount of investigational product during the Maintenance Phase of the study. Subjects were analyzed according to the actual treatments received. Subjects were not excluded from this population as a result of changes to the background regimen. The Maintenance Safety Population is an additional population for safety analyses.

The PK Summary Population includes all subjects who received CAB or RPV, had intensive and/or limited/sparse PK sampling during the study, and provided evaluable CAB or RPV plasma concentration data. Subjects in this population were included in listings.

Efficacy analyses performed included summaries of the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Weeks 48 and 96 were summarized using the Snapshot and observed algorithm. Additional summaries by stratification subgroups were also performed.

Other efficacy analyses performed included summaries of the proportion of subjects with plasma HIV-1 RNA <400 c/mL at Week 48 and 96, absolute values and changes from Baseline in CD4+ counts and HIV-1 RNA over time, and the incidence of disease progression (HIV-associated conditions, AIDS and death).

The occurrence of protocol-defined virologic failures was summarized by visit for each treatment group. Viral genotyping and phenotyping analyses were conducted to explore the relationship between treatment with CAB and EFV and the evolution of HIV-1 resistance. The incidence of treatment-emergent genotypic and phenotypic resistance to integrase inhibitors (INIs) at time of protocol defined virologic failure (PDVF) were summarized by treatment group.

The following AEs were summarized overall and by treatment group: all AEs, drug-related AEs, AEs by grade, fatal and non-fatal SAEs (serious adverse events), and AEs leading to withdrawals.

SAEs were summarized on-therapy. Mean values and changes from Baseline for laboratory parameters and vital signs were summarized by treatment group. Treatment-emergent laboratory toxicity grades were also summarized by treatment group.

Summary:

Summary of Subject Accountability: Study Conclusion Record (ITT-E Population)

	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	EFV 600 mg N=62	Total N=243
Completion Status, n (%)					
Completed	30 (50)	36 (60)	44 (72)	41 (66)	151 (62)
Withdrawal	30 (50)	24 (40)	17 (28)	21 (34)	92 (38)
Primary[a]/subreason[b] for withdrawal, n (%)					
Adverse event	**4 (7)**	**3 (5)**	**5 (8)**	**9 (15)**	**21 (9)**
Lack of efficacy	**9 (15)**	**3 (5)**	**2 (3)**	**6 (10)**	**20 (8)**
Insufficient viral load response	3 (5)	0	1 (2)	1 (2)	5 (2)
Protocol defined virologic failure	6 (10)	3 (5)	1 (2)	5 (8)	15 (6)
Protocol deviation	**3 (5)**	**2 (3)**	**1 (2)**	**0**	**6 (2)**
Prohibited medication use	0	1 (2)	0	0	1 (<1)
Non-compliance with IP treatment	3 (5)	0	0	0	3 (1)
Study closed/terminated	**1 (2)**	**0**	**0**	**0**	**1 (<1)**
Lost to follow-up	**8 (13)**	**6 (10)**	**6 (10)**	**4 (6)**	**24 (10)**
Investigator discretion	**0**	**3 (5)**	**1 (2)**	**1 (2)**	**5 (2)**
Withdrew consent	**5 (8)**	**7 (12)**	**2 (3)**	**1 (2)**	**15 (6)**
Subject relocated	3 (5)	5 (8)	1 (2)	0	9 (4)
Subject homeless	0	1 (2)	0	0	1 (<1)
Burden of travel or lack of access to travel	1 (2)	1 (2)	1 (2)	0	3 (1)

b. Subjects can have only one primary reason for withdrawal.

Percentages for subreasons may sum to more or less than 100%. Subjects may have more than one subreason underneath a single primary reason. Subjects are not required to indicate subreasons.

Summary of Demographic Characteristics (ITT-E Population)

Demographic Characteristic	CAB 10 mg N=60	CAB 30 mg N=60	CAB 60 mg N=61	EFV 600 mg N=62	Total N=243
Age (yrs), n (%)					
Mean	34.0	34.4	36.2	35.6	35.1
SD	9.91	10.24	10.15	12.30	10.68
Median	32.0	32.5	36.0	32.5	33.0
Min.	19	20	19	18	18
Max.	54	57	56	70	70
Sex, n (%)					
Female	3 (5)	2 (3)	4 (7)	1 (2)	10 (4)
Male	57 (95)	58 (97)	57 (93)	61 (98)	233 (96)
Ethnicity, n (%)					
Hispanic/Latino	9 (15)	16 (27)	14 (23)	12 (19)	51 (21)
Not Hispanic/Latino	51 (85)	44 (73)	47 (77)	50 (81)	192 (79)
Race, n (%)					
African American/African Heritage	21 (35)	17 (28)	18 (30)	20 (32)	76 (31)
American Indian or Alaskan Native	0	0	2 (3)	2 (3)	4 (2)
Asian - Central/South Asian Heritage	1 (2)	1 (2)	1 (2)	0	3 (1)
Asian - Japanese/East Asian Heritage/South East Asian Heritage	0	1 (2)	2 (3)	0	3 (1)
White	37 (62)	39 (65)	36 (59)	39 (63)	151 (62)
African American/African Heritage & Asian & White	0	0	1 (2)	0	1 (<1)
African American/African Heritage & Native Hawaiian or Other Pacific Islander	0	0	1 (2)	0	1 (<1)
African American/African Heritage & White	0	2 (3)	0	0	2 (<1)
American Indian or Alaskan Native & White	1 (2)	0	0	0	1 (<1)
Asian & White	0	0	0	1 (2)	1 (<1)

SD = Standard Deviation

Efficacy:

There were few virologic failures using the Snapshot (MSDF) algorithm through Week 312 in the CAB groups. This result at Week 312 was driven primarily by discontinuations for other reason while not below threshold (CAB 10 mg: 5 [8%]; CAB 30 mg: 2 [3%]; CAB 60 mg: 3[5%]) and discontinued for lack of efficacy (CAB 10 mg: 4 [7%]; CAB 30 mg: 2 [3%]; CAB 60 mg: 1 [2%]).

Summary of Study Outcomes (HIV-1 RNA <50 c/mL) at Week 312 - Snapshot (MSDF) Analysis (ITT-E Population)

Outcome	CAB 10 mg (N=60) n (%)	CAB 30 mg (N=60) n (%)	CAB 60 mg (N=61) n (%)	CAB Subtotal (N=181) n (%)
Virologic Success	**31 (52)**	**31 (52)**	**43 (70)**	**105 (58)**
Virologic Failure	**9 (15)**	**7 (12)**	**4 (7)**	**20 (11)**
Data in window not below threshold	0	1 (2)	0	1 (<1)
Discontinued for lack of efficacy	4 (7)	2 (3)	1 (2)	7 (4)
Discontinued for other reason while not below threshold	5 (8)	2 (3)	3 (5)	10 (6)
Prior change in ART	0	2 (3)	0	2 (1)
No Virologic Data	**20 (33)**	**22 (37)**	**14 (23)**	**56 (31)**
Discontinued due to AE or Death	4 (7)	3 (5)	5 (8)	12 (7)
Discontinued for Other Reasons	16 (27)	18 (30)	9 (15)	43 (24)
Missing data during window but on study	0	1 (2)	0	1 (<1)

In the study outcomes for the ITT-ME population, there were few virologic failures using the Snapshot (MSDF) algorithm through Week 312 in the CAB groups. Virologic failures at Week 312 was driven primarily by discontinuations for other reason while not below threshold (CAB 10 mg: 4 [8%]; CAB 30 mg: 1 [2%]; CAB 60 mg: 3 [5%]) and discontinued for lack of efficacy (CAB 10 mg: 3 [6%]; CAB 30 mg: 1 [2%]; CAB 60 mg: 0).

Summary of Study Outcomes (HIV-1 RNA <50 c/mL) at Week 312 - Snapshot (MSDF) Analysis (ITT-ME Population)

Outcome	CAB 10 mg (N=52) n (%)	CAB 30 mg (N=53) n (%)	CAB 60 mg (N=55) n (%)	CAB Subtotal (N=160) n (%)
Virologic Success	**31 (60)**	**31 (58)**	**43 (78)**	**105 (66)**
Virologic Failure	**7 (13)**	**5 (9)**	**3 (5)**	**15 (9)**
Data in window not below threshold	0	1 (2)	0	1 (<1)
Discontinued for lack of efficacy	3 (6)	1 (2)	0	4 (3)
Discontinued for other reason while not below threshold	4 (8)	1 (2)	3 (5)	8 (5)
Prior change in ART	0	2 (4)	0	2 (1)
No Virologic Data	**14 (27)**	**17 (32)**	**9 (16)**	**40 (25)**
Discontinued due to AE or Death	4 (8)	2 (4)	2 (4)	8 (5)
Discontinued for Other Reasons	10 (19)	14 (26)	7 (13)	31 (19)
Missing data during window but on study	0	1 (2)	0	1 (<1)

Secondary Efficacy Analysis:

The virologic response for subjects treated with CAB was sustained for an additional 288 weeks following discontinuation of their background NRTIs and switch to the two-drug maintenance regimen (CAB plus RPV). All CAB treatment groups followed a similar pattern, with a decline in response rates attributable to no data in the Week 312 snapshot window.

At Week 312, the mean change from Baseline in plasma HIV-1 RNA was -2.72 $\log_{10}$ c/mL (SD: 0.57) for subjects in all CAB groups. The change from Baseline from Week 2 forward was similar within each CAB arm and sustained through Week 312.

At Week 312, the mean change in CD4+ cell count for the CAB 30 mg group was numerically higher than the 10 mg and 60 mg arms. The median increase in CD4+ cell count from Baseline was 393.0 cells/μL (250.0, 491.0) for subjects in the CAB group.

There was a low number of subjects with post-baseline HIV-1 associated conditions across all treatment arms. One out of 16 reported events (Candidiasis, oropharyngeal) had onset during the Open-label phase. Two subjects experienced disease progression (Herpes simplex and Burkitt's lymphoma) from CDC class A to CDC Class C. Two subjects experienced disease progression from CDC class A, B or C to death.

Safety:

The rate of treatment-related AEs of any grade through Week 312 reported for subjects receiving CAB was 52% (95/181). Of the 95 treatment-related AEs, only 34 occurred between Week 96 and Week 312. The safety data provided contributes to the solid safety profile of CAB in HIV positive subjects.

The most commonly reported AEs among subjects receiving CAB were upper respiratory tract infection, diarrhea, nausea, and headache with Week 312 rates only being marginally higher than those at Week 96. When grouped by System Organ Class (SOC), events in the infections and infestations, gastrointestinal disorders, and psychiatric disorders were the most commonly reported in the CAB group. The individual terms within these SOCs did not suggest a particular diagnosis which would implicate CAB as a possible causative agent.

For subjects on CAB, treatment-related AEs decreased from 46% during the 24-week Induction Phase to 21% during the Maintenance and Open-label Phases. Only nausea (7%), headache (6%) and abnormal dreams (5%) were reported as treatment-related AEs with a frequency ≥5% in any treatment group (headache: CAB 30 mg; other AEs: CAB 60 mg) during the Maintenance and Open-label Phases. Serious adverse events (SAEs) occurred in 36 (20%) CAB-treated subjects. Two subjects had a total of three drug-related SAEs (suicidal ideation, depression, and seizure). SAEs of cellulitis, appendicitis, pneumonia, shigella infection, suicide attempt, major depression, suicidal ideation, colitis and systemic inflammatory response syndrome were each reported in more than one subject treated with CAB during the Maintenance and Open-label Phases.

There were four subjects with AEs leading to discontinuation of IP during the Open-label Phase. Suicidal ideation and behavior were intensively monitored in this study with overall rates of suicidality being very low across all study arms. Between Week 96 and Week 312, only two subjects receiving CAB + RPV withdrew due to an AE (chest discomfort and suicidal ideation/depression) that was considered drug-related.

The bilirubin elevations on CAB arms consisted of a low rate of Grade 1 or Grade 2 elevations. There was one Grade 3 elevation of bilirubin. There were no Grade 4 elevations of bilirubin to date and there have been no clinical cases of jaundice. The mild, non-progressive bilirubin elevations in a small subset of subjects may reflect the properties of CAB as a substrate for UGT1A1. No subjects met liver stopping criteria in the Open Label Phase of the study.

Changes in lipid parameters were small with no evidence of a clinically significant impairment of the lipid profile across all arms through Week 312.

No clinically significant patterns of changes in vital signs or ECGs were identified in any group.

Virology:

After Week 96, two subjects developed both treatment emergent NNRTI and IN-resistant mutations. One subject randomized to CAB 10 mg had treatment-emergent NNRTI resistance mutation K101E with an accompanying 21 FC to RPV and IN-resistant mutations E138K, G140A and Q148R with an accompanying 116 FC to CAB. The subject was virally suppressed through Week 108 followed by an extended period of intermittent/low-level viremia. Another subject who was randomized to CAB 60 mg, had treatment-emergent NNRTI Resistance mutations K101K/E and E138E/K with 1.77 FC to RPV and IN-resistant mutations G140S and Q148R with 9.84 FC to CAB. This subject had suspected virologic failure at Week 216 that wasn't confirmed. This subject had a second suspected virologic failure at Week 264 that was confirmed at Week 276.

Conclusions:

Efficacy

- Based on the ITT-ME population, CAB plus RPV provided durable viral suppression during the Maintenance and Open-label Phases of the study.

- Response rates observed at Week 312 were associated with differences in non-virologic discontinuations. The virologic response rates at Week 312 were similar to the response rates observed at Week 96.

Safety

- CAB plus RPV was generally well tolerated, with few AEs leading to discontinuation or discernible trends in incidence of AEs relative to randomized CAB dose.

- Reported SAEs remained low in the Maintenance and Open-label Phases.

- There were three CAB drug-related SAEs as determined by the investigator reported between Week 96 and Week 312.

- There were two deaths reported in the Open-label Phase (gastrointestinal bleed and cardiac arrest while undergoing elective shoulder surgery). No deaths were considered related to study treatment

Virology

- The rate of PDVFs was low in subjects treated with CAB plus RPV. A majority of PDVFs occurred in subjects randomized to the CAB 10 mg arm. Three subjects developed treatment-emergent IN-resistance mutations and three subjects developed treatment-emergent NNRTI resistance mutations.

Effective Date: [redacted]

Synopsis for Study 200056

Synopsis for Study 200056 Week 96

Name of company: ViiV Healthcare and the GlaxoSmithKline group of companies

Name of finished product: Not available/ known at the time of this report

Name of active substance: Cabotegravir

Study Number: 200056

Title: A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 For the Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects: Week 96 - Secondary Endpoint

Investigator(s): This is a multi-center study; 50 investigators screened subjects, 54 sites randomized subjects.

Study center(s): This study is being conducted at 50 centers in 5 countries (19 in United States, 8 in Canada, 9 in Spain, 9 in France, 9 in Germany).

Publication(s): None at the time of this report

Study Period: 28-Apr-2014 (First subject screened) - 10-Nov-2016 (Last Subject Last Visit Week 96)

Phase of Development: IIb

Objectives: The overall objective of this study was to select an intramuscular (IM) dosing regimen of Cabotegravir (CAB) Long Acting (LA) plus Rilpivirine (RPV) LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of the two IM dosing regimens, relative to CAB 30 mg plus abacavir (ABC)/lamivudine (3TC) orally once daily.

Secondary objectives

- To evaluate the antiviral activity, tolerability, and safety of CAB 30 mg plus ABC/3TC 600/300 mg orally once daily through the Induction and Maintenance Periods.
- To evaluate the efficacy, tolerability, and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks, relative to CAB 30 mg plus ABC/3TC 600/300 mg orally once daily, through Week 96 of the Maintenance Period.
- To characterize CAB LA and RPV LA Pharmacokinetics (PK) and to explore PK-Pharmacodynamic (PD) relationships.

- To assess the development of viral resistance in subjects experiencing protocol defined virologic failure (PDVF).
- To explore the effect of various demographic Baseline characteristics and adherence on virologic response of CAB and RPV over time.
- To evaluate the treatment satisfaction for subjects on the long-acting injectable regimens with those on the oral regimen through Week 96 of the Maintenance Period.
- To evaluate the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 32 of the Maintenance Period.
- To evaluate medication adherence over time.

Methodology: Study 200056 was a Phase IIb, randomized, multicentre, parallel group, open-label, three-part study conducted in Human Immunodeficiency Virus (HIV-1) infected, Antiretroviral (ARV) Treatment (ART)-naive adults. This study consisted of a Screening Period, Induction Period, Maintenance Period, Extension Period and a Long-term Follow-up Period (withdrawn IM dosing regimen subjects only).

Induction Period

Following the 28-day Screening Period, eligible subjects were enrolled into the study and began a 20 week Induction Period utilizing an oral regimen of CAB 30 mg once daily plus ABC/3TC 600/300 mg once daily.

Subjects initiated treatment on their first day (Week -20) on study and were seen every 4 weeks for study treatment dispensing and safety and efficacy assessments.

At Week (-4), the treatment regimen was modified to add RPV 25 mg once daily for the remainder of the Induction Period.

Eligibility for the Maintenance Period

Subjects who demonstrated tolerability to the Induction Period regimen and with an undetectable HIV-1 Ribonucleic Acid (RNA) (<50 c/mL) at the Week (-4) visit were eligible to enter the Maintenance Period. A single repeat to determine eligibility may have been allowed ONLY after consultation with the medical monitor. Subjects with HIV-1 RNA ≥400 c/mL at Week (-4) were not eligible to enter the Maintenance Period, were not allowed a repeat to determine eligibility and were therefore withdrawn from the study.

Maintenance Period

At Day 1, the Maintenance Period began. Eligible subjects were randomized 2:2:1 to receive an IM regimen of CAB LA 400 mg + RPV LA 600 mg every 4 weeks for 96 weeks, an IM regimen of CAB LA 600 mg + RPV LA 900 mg every 8 weeks for 96 weeks, or continued on the oral Induction Period regimen of CAB 30 mg + ABC/3TC 600/300 mg once daily for 96 weeks (or 104 weeks if continuing on to the Extension

Period). Subject randomization was stratified by subjects' HIV-1 RNA prior to Week (-8) (<50 copies/millilitre [c/mL], yes or no).

On the first day of the Maintenance Period (Day 1), subjects received their last dose of the Induction regimen (CAB+ABC/3TC+RPV) in the clinic and initiated either IM injections or was dispensed the oral regimen depending on the randomization arm. Add-on RPV treatment was discontinued for all subjects after Day 1.

Visits for subjects on the oral dosing arm were expected to occur as projected according to the Baseline visit. There is a (+ or -) 3 day visit window, from the projected visit date. However, the number of tablets dispensed was considered when scheduling the next visit. Visits in Long Term Follow Up were to occur as projected from the last injection with a (+ or -) 3 day visit window, from the projected visit date.

All subjects were seen approximately every 4 weeks for safety, efficacy and PK assessments through Week 32. After Week 32, subjects continued to be seen as per the Time and Events Schedule for dosing, safety, efficacy and PK assessments through Week 96 (or Week 100 for the oral arm if continuing on to the Extension Period).

Some visits that are not aligned with dosing were conducted by telephone interview. This allows for safety assessments to be conducted at all visits, but limited clinic visits for non-dosing visits.

Extension Period

Both IM dosing regimen (Q8W and Q4W) were continued to be evaluated in the Extension period.

Entering from the CAB LA + RPV LA Arms

All subjects who successfully complete 96 weeks of CAB LA + RPV LA treatment in the Maintenance Period were continued with their current IM dosing regimen of CAB LA and RPV LA in the Extension Period until:

- study treatment was locally approved and commercially available,
- the subject no longer derived clinical benefit,
- the subject met a protocol-defined reason for discontinuation
- until development of either CAB LA or RPV LA was terminated.

Subjects remained on their current regimen after Week 96 and continued to receive their Maintenance Period IM dosing regimen for the remainder of study participation. Safety and efficacy assessments was conducted every 16 weeks. Dosing visits will occur according to the selected dosing regimen.

Entering from the CAB 30 mg + ABC/3TC Arm

All subjects who successfully complete 96 weeks of CAB 30 mg + ABC/3TC treatment in the Maintenance Period will have the option to continue study participation by switching to an optimized IM dosing regimen of their choice (either Q8W or Q4W) of CAB LA + RPV LA in the Extension Period. Subjects not choosing to switch to an optimized long acting regimen will complete their study participation at Week 96.

Subjects who choose to continue on to the Extension Period will be assessed for eligibility to begin their selected CAB LA + RPV LA regimen. Subjects will continue on their Maintenance regimen (CAB 30 mg + ABC/3TC) while eligibility is being confirmed. RPV will not be added to their Maintenance regimen prior to the switch to optimized IM dosing. Subjects were given RPV during the last 4 weeks of the Induction Period to evaluate safety and tolerability before being randomized to continue in the Maintenance Period and thus further evaluation is not necessary.

Participants with a Week 96 HIV-1 RNA <50 c/mL, will continue their oral regimen (CAB 30 mg + ABC/3TC) until Week 100. In order to qualify to receive CAB LA + RPV LA injections at Week 100, the HIV-1 RNA results from the Week 96 visit must be undetectable (<50 c/mL; a single repeat HIV-1 RNA test may be allowed prior to Week 100 following consultation with the Medical Monitor).

If the Optimized Q4W IM Dosing Regimen is Selected by the Subject

At visit Week 100, participants will return to the clinic, take the last dose of their oral regimen (CAB 30 mg + ABC/3TC 600/300 mg), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second and third injections (CAB LA 400 mg + RPV LA 600 mg) were administered at Week 104 and Week 108. There will be a one week dosing window for the second and third IM injections such that the second injections occur within the window of Week 103 to Week 104, but not later than Week 104, and the third injections occur within the window of Week 107 to Week 108, but no later than Week 108. Subsequent injections (CAB LA 400 mg + RPV LA 600 mg) will occur every 4 weeks thereafter, from the projected visit date, with a (+ or -) 7 day dosing window being allowed (but not preferred). Following the Week 108 injection, the interval between injection visits should be limited to a maximum of 5 weeks. The Medical Monitor must be contacted if the length of time between injections exceeds, or is projected to exceed, 5 weeks.

If the Optimized Q8W IM Dosing Regimen is Selected by the Subject

At visit Week 100, subjects returned to the clinic, took the last dose of their oral (CAB 30 mg + ABC/3TC 600/300 mg), and receive the first CAB LA (600 mg) + RPV LA (900 mg) injections (within 2 hours of the final oral dose of CAB + ABC/3TC). The second loading injections will be administered at Week 104 (CAB LA 600 mg + RPV LA 900 mg, with subsequent injections (CAB LA 600 mg + RPV LA 900 mg) occurring every 8 weeks thereafter. The dosing window for the second injection allows administration between Week 103 and Week 104, but preferably not later than Week 104. Starting at the Week 112 injection, the interval between injection visits should be limited

to a maximum of 9 weeks. If the length of time between injections exceeds, or is projected to exceed 9 weeks, the Medical Monitor must be contacted to discuss individual subject case management. After Week 112, a dosing window (±7 days) for injections is allowed, but not preferred.

Subjects will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of either CAB LA or RPV LA is terminated.

Safety and efficacy assessments will be conducted as per the Time and Events Schedule in the protocol.

Subjects not eligible to enter the Extension Period will end their study participation and will complete the Withdrawal Visit. Sites may be reimbursed for up to a one-month supply of ARV medication to facilitate transition to non-study ART for subjects that do not qualify for the Extension Period.

Long-term Follow-Up Period IM Regimens

Any subject who receives at least a single dose of CAB LA and/or RPV LA and discontinues the CAB LA + RPV LA regimen for any reason must remain on suppressive highly active antiretroviral therapy (HAART) for at least 52 weeks after the last dose of CAB LA and/or RPV LA in order to prevent selective pressure on HIV and the potential for selection of resistant mutants. This period is considered study participation and subjects will be followed on study during this time.

In the Long-Term Follow-Up Period, subjects will receive oral HAART and be followed for 52 weeks after the last dose of CAB LA and/or RPV LA. In order to assure that subjects have access to HAART during the Long-Term Follow-Up Period, GlaxoSmithKline (GSK) may supply HAART regionally or reimbursement will be provided during this period.

Follow Up Visit

A Follow up visit may be conducted approximately 4 weeks after the last dose of Investigational Product (IP) and is required only if the subject has ongoing adverse events (AEs) or lab abnormalities at the last on-study visit.

Number of subjects: There were 309 subjects who enrolled into the study and a total of 288 subjects (93%) completed the Induction period with CAB 30 mg+ 2 Nucleoside reverse transcriptase inhibitor (NRTIs). 286 subjects qualified for and were included on Day 1 into the Maintenance Period.

Diagnosis and main criteria for inclusion:

Notable inclusion criteria:

- Male or female subjects at least 18 years old that were HIV-1 positive (HIV-1 RNA ≥1000 c/mL)
- Women of childbearing potential were enrolled if they agreed to use adequate contraception for the life of the study and at least 52 weeks after withdrawal from an IM regimen.
- CD4+ cell count ≥200 cells/mm^3 (or higher as local guidelines dictate).
- Antiretroviral therapy (ART) naive (no more than 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection. Any previous exposure to an HIV integrase inhibitor (INI) or NNRTI was exclusionary).

Notable exclusion criteria:

- Any evidence of primary resistance based on the presence of any major resistance-associated mutation in the Screening result or, if known, any historical resistance test result.
- Subjects with known moderate to severe hepatic impairment.
- History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic Hepatitis B Virus (HBV) infection (Hepatitis B Virus Surface Antigen [HBsAg] positive). Asymptomatic individuals with chronic Hepatitis C Virus (HCV) infection were not excluded, however Investigators carefully assessed if therapy specific for HCV infection was required; subjects who were anticipated to require such therapy were excluded.
- History of liver cirrhosis with or without hepatitis viral co-infection.
- Current or anticipated need for chronic anti-coagulation.
- Any verified Grade 4 laboratory abnormality.
- Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, precluded the subject's participation in the study of an investigational compound.
- Subject had estimated creatinine clearance <50 mL/min via Cockcroft-Gault method.
- Alanine aminotransferase (ALT) ≥5 times upper limit of normal (ULN). Subjects with ALT > 2xULN but <5xULN participated in the study if, in the opinion of the Investigator and GSK medical monitor, the lab abnormality did not interfere with the study procedures or compromise subject safety.
- ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).
- Subjects who were Human Leukocyte Antigen (*HLA)-B*5701* positive and were unable to use an alternative NRTI backbone (subjects who were HLA-B*5701 positive were enrolled if they use an alternative NRTI backbone that did not contain abacavir).

- Any clinically significant finding on Screening or Baseline electrocardiograph (ECG).
- Tattoo or other dermatologic condition over gluteus region.
- Need for chronic anticoagulants.

Treatment administration:

Investigational Product	Strength and Packaging	Batch Numbers
CAB	30 mg tablets; 34 tablets per bottle	[redacted]
CAB LA	200 mg/mL injectable suspension; 2 mL per vial	[redacted]
RPV	25 mg tablets; 30 tablets per bottle	[redacted]
RPV LA	300 mg/mL injectable suspension; 2 mL per vial	[redacted]
ABC/3TC	600 mg ABC/300 mg 3TC fixed dose combination (FDC) tablets; 30 tablets per bottle	[redacted]

Induction Period (Week -20 through Day 1)	
Week -20 to Week (-4) (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Week (-4) to Day 1 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal • Take Day 1 doses in the clinic
Maintenance Period (Day 1 to Week 96*)	
CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 4 – 2nd loading dose (1 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injections (No RPV LA)

Week 8 to Week 88 (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Week 4 to Week 92 (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
CAB 30 mg + ABC/3TC once daily	
Day 1	Receive last dose of Induction regimen
Day 2 to Week 96 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
If continuing to Extension Period:	
Week 96 to Week 100 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Extension Period (Week 96 plus+)	
CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks:	
Week 96 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
If switching from Oral Arm:	
Week 100 – loading dose (3 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 2 X 2 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 – 2nd loading dose (1 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 112 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks:	
Week 96 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
If switching from Oral Arm:	
Week 100 – loading dose (3 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Week 104 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection

+until locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of CAB or RPV is terminated

Criteria for evaluation:

Primary endpoints

- The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 32 based on intent-to-treat-maintenance exposed (ITT-ME) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm.
- Proportion of subjects with PDVFs over time.
- Incidence and severity of AEs and laboratory abnormalities over time.

Secondary endpoints

- Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.
- Absolute values and change from Baseline in plasma HIV-1 RNA.
- Absolute values and changes from Baseline in CD4+ cell counts.
- Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).
- Incidence and severity of AEs and laboratory abnormalities over time.
- Absolute values and changes in laboratory parameters over time.
- Proportion of subjects with PDVFs over time.
- Plasma PK parameters for CAB LA and RPV LA (Ctrough and concentrations post dose [~Cmax]) during the Maintenance Period.
- Plasma CAB and RPV trough concentrations to determine when steady state is achieved for each CAB LA and RPV LA regimen.
- Relationship between plasma PK parameters and plasma HIV-1 RNA, CD4+ cell counts and/or occurrence of AEs through Week 48 of the Maintenance Period was explored.
- Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study ART.
- Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status and Change (HIVTSQ(s) and HIVTSQ(c)) over time.
- Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.

Statistical methods: The study was designed to evaluate the efficacy and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg IM every 8 weeks, relative to CAB 30 mg once daily plus ABC/3TC once daily, through Week 32 of the Maintenance Period.

To claim positive outcome, the following hypotheses were tested:

Null Hypothesis (H_0): Response rate for CAB LA plus RPV LA two-drug regimen ≤ CAB plus ABC/3TC -10%

Alternative Hypothesis (H_1): Response rate for CAB LA plus RPV LA two-drug regimen > CAB plus ABC/3TC -10%

The sample size of 45 subjects in the oral treatment arm and 90 subjects each in the IM treatment arms were chosen to ensure a high probability that a long-acting two drug treatment with truly poor response relative to CAB once daily plus ABC/3TC once daily will not be studied further, while allowing for formal considerations of other factors should efficacy be similar between the treatment arms. It is assumed that 85% subjects enrolled will be suppressed at Week (-16), approximately 265 subjects will be enrolled in order to have 225 subjects randomized at Day 1.

The study was designed to test the comparability of CAB LA plus RPV LA two-drug regimen to CAB 30 mg once daily plus ABC/3TC. The primary comparison of interest was performed using a Bayesian probability model. If the posterior probability that the difference was greater than -10% was large (i.e., ≥90%), then sufficient statistical evidence had been provided for the positive outcome. A response rate of 82% in the CAB LA plus RPV LA two-drug regimen (compared with an CAB plus ABC/3TC response rate of 92%) would result in a rejection of the null hypothesis with a probability of approximately 0.064 (type I error). The given sample size was unlikely to select a random sample that would falsely conclude that CAB LA plus RPV LA two-drug regimen was comparable with CAB plus ABC/3TC if the response rates were truly 82% versus 92%, respectively. If the CAB LA plus RPV LA two-drug regimen yielded a response rate of greater than 92%, then there was a high probability of rejecting the null hypothesis and correctly concluding that CAB LA plus RPV LA two-drug regimen was at least as good as CAB plus ABC/3TC.

Incorporation of prior beliefs and information about population parameters was a required part of any Bayesian probability model. The assumptions made will help to provide a more reliable estimate when the prior beliefs were combined with the observed data than the data alone as long as the beliefs were reasonable. Therefore, the trial utilized a Beta (23, 2) distribution with the mean response rate being 92%, with 97.5th percentile of 99% and 2.5th percentile of 78%. Furthermore, a non- informative prior belief was assumed for the response rate for CAB LA plus RPV LA two-drug regimen. Therefore, the trial will conservatively utilize a Beta (1, 1) distribution.

The intent-to-treat exposed population (ITT-E) population consisted of all enrolled subjects who received at least one dose of IP during the induction period. The ITT-E population was used for efficacy analyses of induction period data (Week -20 to Day 1).

The ITT-ME population consisted of all randomized subjects who received at least one dose of IP during the Maintenance Period of the study. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received. The ITT-ME population was the primary population for efficacy analyses.

The per protocol maintenance exposed population (PP-ME) population consisted of subjects in the ITT-ME population with the exception of major protocol violators (these were defined in the RAP of this study). The PP-ME population was a secondary population for efficacy purposes.

The PK Population included all subjects who received CAB and / or RPV and underwent PK sampling during the study, and provided evaluable CAB and /or RPV plasma concentration data. Subjects in this population were included in the PK analysis.

The Safety Population consisted of all enrolled subjects who were exposed to IP with the exception of any subjects with documented evidence of not having consumed any amount of IP. Subjects were analyzed according to the actual treatments received. The safety population was the primary population for safety analyses of induction period data.

The Safety Maintenance Population consisted of all subjects who entered the Maintenance period and received at least one dose of IP. Subjects were analyzed according to the actual treatments received. The safety maintenance population was the primary population for safety analyses of maintenance period data.

The primary efficacy analysis data set were based on the ITT-ME population. The efficacy dataset included missing, switch, or discontinuation equals failure (MSDF) (also referred to as Snapshot), for the proportion of subjects with plasma HIV-1 RNA less than the pre-defined threshold (e.g., <200 c/mL and <50. The primary efficacy analysis was performed at Week 32 based on the proportion of subjects in the ITT-ME population with plasma HIV-1 RNA <50 c/mL using a MSDF approach identical to the current Food and Drug Administration (FDA) definition of the Snapshot algorithm. The primary comparison of interest compared the response rate of each IM dosing arm to the oral control arm using the Bayesian probability model described above. The probability of (Response rate for IM arm > Response rate for Oral arm -10%) was calculated.

The Safety Long-Term Follow-up Population consists of all subjects receiving at least one dose of CAB LA and/or RPV LA who have discontinued IP/withdrawn from maintenance period and have a least one Long-Term Follow-up period clinic visit. Subjects will be analysed according to the actual treatments received during the maintenance period. This population will be used to produce additional safety displays of long-term follow-up period data.

Comparability between the Q8W and Q4W response rates was also assessed using a Bayesian Probability model. This analysis assumed a non-informative Beta (1,1) prior distribution for each IM regimen response rate. The posterior probability that the absolute treatment difference was less than 10% was calculated. A posterior probability >90% was pre-specified as the weight of statistical evidence necessary to conclude that the two IM dosing regimens are equivalent in terms of maintenance of virologic suppression.

An Independent Data Monitoring Committee (IDMC) reviewed interim analysis results at Day 1 (all subjects completing the induction period) and Week 24 (~50% of subjects completing Week 24 of the Maintenance Period). All available data was included in the interim analyses, including data beyond the designated time point except for the Day 1 analysis, which only included data from the Induction Period. The purpose of these planned analyses was to evaluate the efficacy, safety and tolerability at early time points in the study, with the possibility to discontinue a suboptimal regimen before all subjects transitioned to the Maintenance Period of the study. The sponsor was blinded to the Week 24 interim analysis. Continuous monitoring of PDVF was also performed.

This interim analysis schedule did not require an adjustment for multiplicity since there was no possibility of a false positive finding at any of the interim analyses conducted before Week 32, and since the Week 48 and 96 analyses will be used to further characterise the long-term safety and efficacy profile of CAB. As no hypothesis was being tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity was performed.

Summary:

Summary of Study Populations

			Randomized Treatment				
Population, n (%)	**No Treatment (N=76)**	**Induction Oral CAB (N=309)**	**Q8W IM (N=115)**	**Q4W IM (N=115)**	**Oral CAB (N=56)**	**Optimized Q8W (N=34)**	**Optimized Q4W (N=10)**
All Subjects Screened	76 (100)	309 (100)	115 (100)	115 (100)	56 (100)	-	-
Randomized	-	-	115 (100)	115 (100)	56 (100)	-	-
Intent-to-Treat Exposed	-	309 (100)	115 (100)	115 (100)	56 (100)	-	-
Intent-to Treat Maintenance Exposed	-	-	115 (100)	115 (100)	56 (100)	-	-
Per Protocol Maintenance Exposed	-	-	113 (98)	110 (96)	56 (100)	-	-
Safety	-	309 (100)	115 (100)	115 (100)	56 (100)	-	-
Safety Maintenance	-	-	115 (100)	115 (100)	56 (100)	-	-
Safety Long Term Follow up	-	-	6 (5)	9 (8)	-	-	-
PK Population	-	-	115 (100)	115 (100)	56 (100)	-	-
PDVF Genotypic	-	1 (<1)	2 (2)	-	1 (2)	-	-
PDVF Phenotypic	-	1 (<1)	2 (2)	-	1 (2)	-	-
Extension Switch Population	-	-	-	-	-	34 (100)	10 (100)

Summary of Demographic Characteristics – Week 96 (ITT-ME)

Demographic Characteristic	Q8W IM N=115	Q4W IM N=115	Oral CAB N=56	Total N=286
Age (yrs)				
Mean	36.4	36.8	35.6	36.4
Standard Deviation (SD)	10.95	9.70	10.18	10.29
Median	35.0	36.0	35.0	35.0
Min	20	19	19	19
Max	64	62	56	64
Sex, n (%)				
Female	8 (7)	6 (5)	10 (18)	24 (8)
Male	107 (93)	109 (95)	46 (82)	262 (92)
Weight (kg)				
Mean	75.6	75.6	74.8	75.5
Standard Deviation (SD)	12.33	12.62	16.90	13.40
Median	74.0	73.0	71.2	73.3
Min	52	51	48	48
Max	108	117	139	139
Body Mass Index (kg/m^2)				
Mean	24.60	24.44	24.86	24.58
Standard Deviation (SD)	3.802	3.418	6.543	4.332
Median	23.81	24.05	23.29	23.81
Min	18.8	16.9	18.8	16.9
Max	34.9	36.7	61.7	61.7
Ethnicity, n (%)				
Hispanic / Latino	15 (13)	19 (17)	12 (21)	46 (16)
Not Hispanic / Latino	100 (87)	96 (83)	44 (79)	240 (84)
Race, n (%)				
White	93 (81)	94 (82)	39 (70)	226 (79)
African American / African Heritage	17 (15)	12 (10)	15 (27)	44 (15)
American Indian or Alaskan Native	0	8 (7)	1 (2)	9 (3)
Asian	2 (2)	1 (<1)	1 (2)	4 (1)
Central/South Asian Heritage	0	1 (<1)	0	1 (<1)
Japanese/East Asian Heritage/South East Asian Heritage	2 (2)	0	1 (2)	3 (1)
Native Hawaiian or Other Pacific Islander	1 (<1)	0	0	1 (<1)
African American / African Heritage & White	2 (2)	0	0	2 (<1)

Summary of Subject Accountability: Maintenance Period Conclusion Record (ITT-ME Population)

	Q8W IM (N=115)	Q4W IM (N=115)	CAB 30 mg (N=56)	Total (N=286)
Completion Status, n (%)				
Completed Maintenance Period	110 (96)	101 (88)	47 (84)	258 (90)
Prematurely discontinued Maintenance Period	5 (4)	14 (12)	9 (16)	28 (10)
Ongoing at time of analysis	0	0	0	0
Primary[a]/subreason[b] for withdrawal, n (%)				
Adverse Event	1 (<1)	8 (7)	1 (2)	10 (3)
Lack of efficacy	1 (<1)	0	1 (2)	2 (<1)
Protocol defined virologic failure	1 (<1)	0	1 (2)	2 (<1)
Protocol deviation	0	2 (2)	0	2 (<1)
Prohibited medication use	0	1 (<1)	0	1 (<1)
Pregnancy	0	1 (<1)	0	1 (<1)
Subject reached protocol-defined stopping criteria	0	1 (<1)	1 (2)	2 (<1)
Subject met the GSK defined Liver Chemistry Stopping Criteria	0	1 (<1)	1 (2)	2 (<1)
Lost to follow-up	0	0	1 (2)	1 (<1)
Physician decision	1 (<1) [c]	0	0	1 (<1)
Withdrawal by subject	2 (2)	3 (3)	5 (9)	10 (3)
Subject relocated	0	2 (2)	2 (4)	4 (1)
Intolerability of injections	1 (<1)	0	0	1 (<1)
Frequency of visits	0	1 (<1)	0	1 (<1)
Other	1 (<1)	0	3 (5)	4 (1)

a. Subjects can have only one primary reason for withdrawal.
b. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than one subreason underneath a single primary reason. Subjects are not required to indicate subreasons.
c. Subject experienced suspected PDVF at the time of withdrawal, which was subsequently confirmed.

Week 96 Primary Efficacy Results

Proportion (95% CI) of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 96 - Snapshot (MSDF) Analysis (ITT-ME Population)

Visit		Q8W IM[b] N=115	Q4W IM[c] N=115	CAB 30 mg N=56
Week 96	n (%)	108 (94)	100 (87)	47 (84)
	Difference in Proportions (95% CI)[a]	10% (-0.6, 20.5)	3.0% (-8.4,14.4)	NA

a. Difference in proportions (IM – oral CAB arm)
b. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
c. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Study Outcomes (<50 c/mL) at Week 96 – Snapshot (MSDF) Analysis (ITT-ME Population)

Outcome	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	CAB 30 mg N=56 n (%)	Subtotal IM N=230 n (%)
Virologic Success, n (%)	108 (94)	100 (87)	47 (84)	208 (90)
Virologic Failure, n (%)	5 (4)	0	1 (2)	5 (2)
Data in window not below threshold	2 (2)	0	0	2 (<1)
Discontinued for lack of efficacy	1 (<1)	0	1 (2)	1 (<1)
Discontinued for other reason while not below threshold	2 (2)	0	0	2 (<1)
No Virologic Data	2 (2)	15 (13)	8 (14)	17 (7)
Discontinued due to AE or Death	1 (<1)	9 (8)	2 (4)	10 (4)
Discontinued for Other Reasons	1 (<1)	5 (4)	6 (11)	6 (3)
Missing data during window but on study	0	1 (<1)	0	1 (<1)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Week 96 Secondary Efficacy Results

Week 96 Virology Results

There were three subjects with PDVF, defined as confirmed viral load >200 c/mL, through 96 weeks of maintenance treatment (no additional PDVFs between the Week 48 and Week 96 analysis time points).

An oral treatment group subject had 152,250 c/mL HIV-1 RNA at Baseline. The subject had 18,836 c/mL HIV-1 RNA at Week 8 and 498 c/mL HIV-1 at the confirmatory visit. This subject had no treatment emergent resistance mutation in RT, PRO or IN at PDVF.

A Q8W IM arm subject had 81,487 c/mL HIV-1 RNA at Baseline. This subject had 427 c/mL HIV-1 RNA at Week 4 and 5316 c/mL at Week 8. Baseline, Week 4, and Week 8 RT and PRO genotypes and phenotypes are all wild type and unchanged. Baseline and Week 4 IN genotypes are unchanged. Week 8 IN genotype has the addition of R269R/G which is not an INI resistance mutation. Baseline, Week 4, and Week 8 IN phenotypes are all susceptible to all INIs.

Another Q8W IM arm subject had a viral load of 444,489 c/mL HIV-1RNA at Baseline. This subject had 463 c/mL HIV-1 RNA at Week 48 and 205 c/mL at the confirmatory visit seven days later. At the time of PDVF this subject had treatment emergent NNRTI resistance K103N, E138G, and K238T with high level phenotypic resistance to delavirdine (>MAX), efavirenz (EFV) (48 fold change [FC]), nevirapine (>MAX), as well as phenotypic resistance to rilpivirine (3.34 FC). The fold change to etravirine (1.91 FC) was below the lower cutoff. The Week 48 Integrase genotype had the treatment emergent integrase resistance mutation Q148R with accompanying resistance to raltegravir (29 FC), elvitegravir (138 FC), and cabotegravir (5.06 FC). The Week 48 sample was not resistant to dolutegravir (DTG) (1.38 FC).

Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL by Visit (Maintenance)-Snapshot (MSDF) Analysis (ITT-ME Population)

Visit	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	CAB 30 mg N=56 n (%)	Subtotal IM N=230 n (%)
Day 1	109/115 (95)	114/115 (>99)	55/56 (98)	223/230 (97)
Week 4	112/115 (97)	113/115 (98)	52/56 (93)	225/230 (98)
Week 8	113/115 (98)	111/115 (97)	53/56 (95)	224/230 (97)
Week 12	110/115 (96)	112/115 (97)	55/56 (98)	222/230 (96)
Week 16	112/115 (97)	110/115 (96)	50/56 (89)	222/230 (97)
Week 20	112/115 (97)	112/115 (97)	51/56 (91)	224/230 (97)
Week 24	110/115 (96)	107/115 (93)	51/56 (91)	217/230 (94)
Week 28	104/115 (90)	106/115 (92)	48/56 (86)	210/230 (91)
Week 32	109/115 (95)	108/115 (94)	51/56 (91)	217/230 (94)
Week 36	109/115 (95)	104/115 (90)	49/56 (88)	213/230 (93)
Week 40	106/115 (92)	105/115 (91)	48/56 (86)	211/230 (92)
Week 44	107/115 (93)	104/115 (90)	49/56 (88)	211/230 (92)
Week 48	106/115 (92)	105/115 (91)	50/56 (89)	211/230 (92)
Week 56	108/115 (94)	104/115 (90)	47/56 (84)	212/230 (92)
Week 64	109/115 (95)	103/115 (90)	48/56 (86)	212/230 (92)
Week 72	109/115 (95)	103/115 (90)	49/56 (88)	212/230 (92)
Week 80	109/115 (95)	100/115 (87)	47/56 (84)	209/230 (91)
Week 88	109/115 (95)	99/115 (86)	47/56 (84)	208/230 (90)
Week 96	108/115 (94)	100/115 (87)	47/56 (84)	208/230 (90)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Proportion of Subjects with Plasma HIV-1 RNA <200 c/mL by Visit (Maintenance) – Snapshot (MSDF) Analysis (ITT-ME Population)

Actual Visit For MSDF	Q8W IM[a] N=115 n/N (%)	Q4W IM[b] N=115 n/N (%)	Oral CAB 30 mg N=56 n/N (%)	IM Subtotal N=230 n/N (%)
Day 1	115/115 (100)	115/115 (100)	55/56 (98)	230/230 (100)
Week 4	114/115 (>99)	115/115 (100)	54/56 (96)	229/230 (>99)
Week 8	114/115 (>99)	114/115 (>99)	53/56 (95)	228/230 (>99)
Week 12	112/115 (97)	114/115 (>99)	55/56 (98)	226/230 (98)
Week 16	113/115 (98)	113/115 (98)	52/56 (93)	226/230 (98)
Week 20	113/115 (98)	112/115 (97)	52/56 (93)	225/230 (98)
Week 24	111/115 (97)	109/115 (95)	52/56 (93)	220/230 (96)
Week 28	108/115 (94)	109/115 (95)	51/56 (91)	217/230 (94)
Week 32	112/115 (97)	109/115 (95)	51/56 (91)	221/230 (96)
Week 36	112/115 (97)	107/115 (93)	50/56 (89)	219/230 (95)
Week 40	111/115 (97)	106/115 (92)	48/56 (86)	217/230 (94)
Week 44	109/115 (95)	105/115 (91)	50/56 (89)	214/230 (93)
Week 48	111/115 (97)	106/115 (92)	50/56 (89)	217/230 (94)
Week 56	110/115 (96)	104/115 (90)	48/56 (86)	214/230 (93)
Week 64	110/115 (96)	104/115 (90)	49/56 (88)	214/230 (93)
Week 72	110/115 (96)	103/115 (90)	49/56 (88)	213/230 (93)
Week 80	110/115 (96)	101/115 (88)	47/56 (84)	211/230 (92)
Week 88	110/115 (96)	99/115 (86)	47/56 (84)	209/230 (91)
Week 96	110/115 (96)	100/115 (87)	47/56 (84)	210/230 (91)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Baseline Absolute Value and Change from Baseline in Plasma HIV-1 RNA (log10 c/mL) by Visit (Maintenance) (ITT-ME Population)

HIV-1 RNA Change from Baseline, log_{10} c/mL	Q8W IM[a] N=115	Q4W IM[b] N=115	Oral CAB 30 mg N=56
Baseline/Week -20	**n=115**	**n=115**	**n=56**
Mean (SD)	4.40 (0.627)	4.45 (0.708)	4.34 (0.589)
Median (IQR)	4.42 (4.1, 4.8)	4.46 (4.0, 5.0)	4.29 (4.0, 4.7)
Change from Baseline			
Day 1	**n=115**	**n=115**	**n=56**
Mean (SD)	-2.80 (0.614)	-2.86 (0.705)	-2.74 (0.584)
Median (IQR)	-2.83 (-3.2, -2.5)	-2.87 (-3.4, -2.4)	-2.69 (-3.1, -2.4)
Week 4	**n=115**	**n=115**	**n=56**
Mean (SD)	-2.80 (0.621)	-2.86 (0.708)	-2.65 (0.776)
Median (IQR)	-2.83 (-3.2, -2.4)	-2.87 (-3.4, -2.4)	-2.69 (-3.2, -2.4)
Week 8	**n=115**	**n=115**	**n=54**
Mean (SD)	-2.79 (0.638)	-2.85 (0.693)	-2.68 (0.632)
Median (IQR)	-2.83 (-3.2, -2.4)	-2.87 (-3.4, -2.4)	-2.69 (-3.1, -2.4)
Week 12	**n=112**	**n=114**	**n=55**
Mean (SD)	-2.79 (0.611)	-2.84 (0.699)	-2.74 (0.588)
Median (IQR)	-2.82 (-3.2, -2.5)	-2.85 (-3.4, -2.4)	-2.69 (-3.2, -2.4)
Week 16	**n=113**	**n=114**	**n=52**
Mean (SD)	-2.79 (0.610)	-2.85 (0.721)	-2.76 (0.573)
Median (IQR)	-2.83 (-3.2, -2.5)	-2.85 (-3.4, -2.4)	-2.73 (-3.2, -2.4)
Week 20	**n=113**	**n=112**	**n=52**
Mean (SD)	-2.79 (0.610)	-2.86 (0.716)	-2.74 (0.562)
Median (IQR)	-2.81 (-3.2, -2.5)	-2.85 (-3.4, -2.4)	-2.70 (-3.1, -2.4)
Week 24	**n=111**	**n=110**	**n=52**
Mean (SD)	-2.80 (0.611)	-2.88 (0.707)	-2.74 (0.561)
Median (IQR)	-2.83 (-3.2, -2.5)	-2.88 (-3.4, -2.5)	-2.70 (-3.1, -2.4)
Week 28	**n=110**	**n=109**	**n=51**
Mean (SD)	-2.76 (0.588)	-2.88 (0.699)	-2.72 (0.580)
Median (IQR)	-2.82 (-3.2, -2.4)	-2.89 (-3.4, -2.5)	-2.69 (-3.2, -2.4)
Week 32	**n=111**	**n=108**	**n=50**
Mean (SD)	-2.78 (0.610)	-2.88 (0.709)	-2.73 (0.561)
Median (IQR)	-2.83 (-3.2, -2.4)	-2.86 (-3.4, -2.5)	-2.70 (-3.1, -2.4)
Week 36	**n=112**	**n=107**	**n=50**
Mean (SD)	-2.78 (0.616)	-2.88 (0.713)	-2.74 (0.574)
Median (IQR)	-2.83 (-3.2, -2.5)	-2.89 (-3.4, -2.5)	-2.70 (-3.2, -2.4)
Week 40	**n=111**	**n=106**	**n=48**
Mean (SD)	-2.77 (0.612)	-2.88 (0.710)	-2.77 (0.569)
Median (IQR)	-2.81 (-3.2, -2.4)	-2.88 (-3.4, -2.5)	-2.70 (-3.2, -2.4)
Week 44	**n=110**	**n=105**	**n=50**
Mean (SD)	-2.79 (0.612)	-2.88 (0.707)	-2.74 (0.576)
Median (IQR)	-2.83 (-3.2, -2.5)	-2.87 (-3.4, -2.5)	-2.70 (-3.2, -2.4)
Week 48	**n=112**	**n=104**	**n=50**
Mean (SD)	-2.76 (0.596)	-2.88 (0.708)	-2.74 (0.583)
Median (IQR)	-2.82 (-3.2, -2.5)	-2.85 (-3.4, -2.5)	-2.70 (-3.2, -2.4)
Week 56	**n=110**	**n=104**	**n=48**
Mean (SD)	-2.77 (0.608)	-2.88 (0.709)	-2.73 (0.586)
Median (IQR)	-2.81 (-3.2, -2.4)	-2.85 (-3.4, -2.5)	-2.70 (-3.1, -2.4)
Week 64	**n=110**	**n=104**	**n=49**
Mean (SD)	-2.78 (0.605)	-2.88 (0.716)	-2.73 (0.599)
Median (IQR)	-2.82 (-3.2, -2.4)	-2.85 (-3.4, -2.5)	-2.71 (-3.2, -2.4)
Week 72	**n=110**	**n=103**	**n=49**

HIV-1 RNA Change from Baseline, log_{10} c/mL	**Q8W IM[a] N=115**	**Q4W IM[b] N=115**	**Oral CAB 30 mg N=56**
Mean (SD)	-2.78 (0.605)	-2.88 (0.712)	-2.74 (0.589)
Median (IQR)	-2.82 (-3.2, -2.4)	-2.82 (-3.4, -2.5)	-2.71 (-3.2, -2.4)
Week 80	**n=110**	**n=101**	**n=47**
Mean (SD)	-2.77 (0.605)	-2.87 (0.716)	-2.76 (0.595)
Median (IQR)	-2.81 (-3.2, -2.4)	-2.82 (-3.4, -2.5)	-2.75 (-3.2, -2.4)
Week 88	**n=110**	**n=99**	**n=47**
Mean (SD)	-2.78 (0.605)	-2.87 (0.711)	-2.77 (0.582)
Median (IQR)	-2.82 (-3.2, -2.4)	-2.79 (-3.4, -2.5)	-2.75 (-3.2, -2.4)
Week 96	**n=110**	**n=100**	**n=47**
Mean (SD)	-2.77 (0.602)	-2.89 (0.713)	-2.77 (0.582)
Median (IQR)	-2.82 (-3.2, -2.4)	-2.85 (-3.5, -2.5)	-2.75 (-3.2, -2.4)

Note: Baseline values are actual Plasma HIV-1 RNA (log_{10} c/mL) values.

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks

b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Change from Baseline in CD4+ Cell Count (cells/mm3) by Visit (Maintenance) (ITT-ME Population)

CD4+ Change from Baseline, cells/mm^3	Q8W IM[a] N=115	Q4W IM[b] N=115	CAB 30 mg N=56
Baseline/Week -20	**N=115**	**N=115**	**N=56**
Mean (SD)	486.6 (184.44)	503.9 (187.86)	539.5 (165.57)
Median (IQR)	449.0 (343.0, 618.0)	499.0 (359.0, 624.0)	517.5 (416.5, 630.0)
Day 1	**N=115**	**N=115**	**N=56**
Mean (SD)	179.2 (176.06)	176.4 (204.48)	227.4 (167.90)
Median (IQR)	162.0 (64.0, 271.0)	156.0 (78.0, 270.0)	254.0 (133.0, 326.0)
Week 4	**N=115**	**N=115**	**N=56**
Mean (SD)	209.7 (209.84)	221.4 (221.64)	263.3 (199.04)
Median (IQR)	178.0 (88.0, 314.0)	199.0 (110.0, 296.0)	242.0 (124.5, 396.5)
Week 8	**N=114**	**N=115**	**N=54**
Mean (SD)	198.9 (207.79)	212.8 (220.73)	282.5 (174.82)
Median (IQR)	161.5 (83.0, 288.0)	199.0 (86.0, 303.0)	275.5 (181.0, 349.0)
Week 24	**N=111**	**N=110**	**N=52**
Mean (SD)	212.5 (181.03)	238.7 (200.90)	314.8 (222.09)
Median (IQR)	190.0 (94.0, 313.0)	213.0 (114.0, 350.0)	277.0 (150.0, 432.0)
Week 32	**N=112**	**N=108**	**N=50**
Mean (SD)	264.4 (247.84)	263.7 (217.74)	346.1 (219.59)
Median (IQR)	226.0 (107.5, 330.0)	241.5 (138.0, 347.5)	304.0 (176.0, 515.0)
Week 48	**N=112**	**N=104**	**N=50**
Mean (SD)	285.8 (232.20)	266.3 (230.54)	388.7 (239.96)
Median (IQR)	248.0 (151.5, 346.5)	258.0 (132.5, 355.0)	307.0 (199.0, 566.0)
Week 56	**N=110**	**N=104**	**N=48**
Mean (SD)	292.4 (238.00)	310.2 (272.07)	427.4 (286.57)
Median (IQR)	255.5 (153.0, 407.0)	282.5 (168.0, 428.5)	380.0 (239.5, 581.0)
Week 72	**N=110**	**N=103**	**N=49**
Mean (SD)	290.6 (230.80)	304.5 (225.22)	375.7 (247.43)
Median (IQR)	265.5 (129.0, 388.0)	283 (168.0, 410.0)	341.0 (202.0, 525.0)
Week 80	**N=108**	**N=101**	**N=48**
Mean (SD)	291.9 (200.14)	283.6 (215.37)	374.3 (236.73)
Median (IQR)	258.0 (148.5, 367.5)	266.0 (152.0, 445.0)	327.5 (214.0, 487.5)
Week 96	**N=109**	**N=100**	**N=47**
Mean (SD)	257.5 (192.25)	270.6 (210.99)	369.9 (226.60)
Median (IQR)	239.0 (111.0, 359.0)	225.5 (144.5, 393.0)	317.0 (214.0, 505.0)

Note: Baseline values are actual CD4+ Cell Count (cells/mm^3) values

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks

b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of HIV-1 Associated Conditions Progression of HIV Disease (Maintenance Period) (ITT-ME Population)

Category Condition	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	Oral CAB 30 mg N=56 n (%)	IM Subtotal N=230 n (%)
Did subject experience disease progression to Centers for Disease Control and Prevention (CDC) Class C or death?	4 (3)	1 (<1)	0	5 (2)
If yes, number of subjects progressing				
from Baseline CDC Class A to CDC Class C	4 (3)	0	0	4 (2)
from Baseline CDC Class B to CDC Class C	0	0	0	0

Category **Condition**	**Q8W IM[a]** **N=115** **n (%)**	**Q4W IM[b]** **N=115** **n (%)**	**Oral CAB 30 mg** **N=56** **n (%)**	**IM Subtotal** **N=230** **n (%)**
from Baseline CDC Class C to new CDC Class C	0	0	0	0
from Baseline CDC Class A, B or C to Death	0	1 (<1)	0	1 (<1)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Week 96 Safety Results

Summary of All Common Post-Baseline Emergent Adverse Events by Overall Frequency (Safety Maintenance Population)

Preferred Term	Q8W IM[a] (N=115) n (%)	Q4W IM[b] (N=115) n (%)	CAB 30 mg (N=56) n (%)	Subtotal-IM (N=230) n (%)
Any event	115 (100)	115 (100)	54 (96)	230 (100)
Injection site pain	110 (96)	112 (97)	0	222 (97)
Nasopharyngitis	35 (30)	39 (34)	22 (39)	74 (32)
Injection site nodule	29 (25)	36 (31)	0	65 (28)
Injection site swelling	29 (25)	34 (30)	0	63 (27)
Diarrhoea	27 (23)	32 (28)	11 (20)	59 (26)
Injection site pruritus	25 (22)	33 (29)	0	58 (25)
Headache	29 (25)	27 (23)	14 (25)	56 (24)
Injection site induration	29 (25)	25 (22)	0	54 (23)
Injection site warmth	23 (20)	21 (18)	0	44 (19)
Upper respiratory tract infection	23 (20)	13 (11)	7 (13)	36 (16)
Injection site bruising	20 (17)	14 (12)	0	34 (15)
Nausea	16 (14)	18 (16)	9 (16)	34 (15)
Injection site erythema	13 (11)	19 (17)	0	32 (14)
Pyrexia	16 (14)	16 (14)	3 (5)	32 (14)
Gastroenteritis	14 (12)	15 (13)	6 (11)	29 (13)
Fatigue	14 (12)	14 (12)	4 (7)	28 (12)
Syphilis	17 (15)	11 (10)	6 (11)	28 (12)
Back pain	15 (13)	13 (11)	10 (18)	28 (12)
Insomnia	12 (10)	13 (11)	4 (7)	25 (11)
Bronchitis	12 (10)	12 (10)	6 (11)	24 (10)
Cough	11 (10)	13 (11)	7 (13)	24 (10)
Influenza	6 (5)	16 (14)	2 (4)	22 (10)
Arthralgia	12 (10)	10 (9)	4 (7)	22 (10)
Anogenital warts	9 (8)	11 (10)	2 (4)	20 (9)
Anxiety	10 (9)	10 (9)	4 (7)	20 (9)
Pharyngitis	12 (10)	8 (7)	5 (9)	20 (9)
Rash	9 (8)	8 (7)	2 (4)	17 (7)
Dizziness	9 (8)	8 (7)	3 (5)	17 (7)
Respiratory tract infection	6 (5)	11 (10)	6 (11)	17 (7)
Asthenia	7 (6)	10 (9)	9 (16)	17 (7)
Gonorrhoea	10 (9)	6 (5)	0	16 (7)
Myalgia	9 (8)	7 (6)	1 (2)	16 (7)
Abdominal pain	9 (8)	7 (6)	4 (7)	16 (7)
Depression	7 (6)	9 (8)	5 (9)	16 (7)
Rhinitis	7 (6)	8 (7)	3 (5)	15 (7)
Influenza like illness	4 (3)	10 (9)	1 (2)	14 (6)
Dyspepsia	6 (5)	8 (7)	2 (4)	14 (6)
Tonsillitis	7 (6)	7 (6)	4 (7)	14 (6)
Oral herpes	4 (3)	9 (8)	2 (4)	13 (6)
Herpes zoster	4 (3)	8 (7)	0	12 (5)
Seasonal allergy	8 (7)	4 (3)	0	12 (5)
Vomiting	5 (4)	7 (6)	4 (7)	12 (5)
Pain in extremity	6 (5)	5 (4)	2 (4)	11 (5)
Conjunctivitis	8 (7)	3 (3)	3 (5)	11 (5)
Sinusitis	6 (5)	5 (4)	4 (7)	11 (5)
Blood creatine phosphokinase	5 (4)	5 (4)	1 (2)	10 (4%)

Preferred Term	Q8W IM[a] (N=115) n (%)	Q4W IM[b] (N=115) n (%)	CAB 30 mg (N=56) n (%)	Subtotal-IM (N=230) n (%)
increased				
Cellulitis	3 (3)	7 (6)	1 (2)	10 (4)
Gastrooesophageal reflux disease	2 (2)	8 (7)	1 (2)	10 (4)
Haemorrhoids	6 (5)	4 (3)	1 (2)	10 (4)
Rhinitis allergic	7 (6)	3 (3)	1 (2)	10 (4)
Urethritis	3 (3)	7 (6)	1 (2)	10 (4)
Constipation	5 (4)	5 (4)	2 (4)	10 (4)
Oropharyngeal pain	4 (3)	6 (5)	3 (5)	10 (4)
Chlamydial infection	5 (4)	4 (3)	0	9 (4)
Hypertension	5 (4)	4 (3)	0	9 (4)
Injection site discolouration	3 (3)	6 (5)	0	9 (4)
Pruritus	5 (4)	4 (3)	0	9 (4)
Folliculitis	6 (5)	3 (3)	2 (4)	9 (4)
Ligament sprain	3 (3)	5 (4)	0	8 (3)
Proctalgia	6 (5)	2 (2)	0	8 (3)
Hypercholesterolaemia	2 (2)	6 (5)	1 (2)	8 (3)
Pharyngotonsillitis	6 (5)	2 (2)	1 (2)	8 (3)
Skin papilloma	5 (4)	3 (3)	1 (2)	8 (3)
Proctitis	5 (4)	3 (3)	2 (4)	8 (3)
Odynophagia	4 (3)	4 (3)	4 (7)	8 (3)
Contusion	2 (2)	5 (4)	0	7 (3)
Ear infection	3 (3)	4 (3)	0	7 (3)
Flatulence	3 (3)	4 (3)	0	7 (3)
Musculoskeletal pain	4 (3)	3 (3)	0	7 (3)
Nightmare	3 (3)	4 (3)	0	7 (3)
Pain	4 (3)	3 (3)	0	7 (3)
Abdominal discomfort	4 (3)	3 (3)	1 (2)	7 (3)
Abdominal pain upper	6 (5)	1 (<1)	1 (2)	7 (3)
Chest pain	1 (<1)	6 (5)	1 (2)	7 (3)
Fungal skin infection	3 (3)	4 (3)	1 (2)	7 (3)
Subcutaneous abscess	3 (3)	4 (3)	1 (2)	7 (3)
Toothache	5 (4)	2 (2)	1 (2)	7 (3)
Urinary tract infection	3 (3)	4 (3)	2 (4)	7 (3)
Viral infection	3 (3)	4 (3)	3 (5)	7 (3)
Hepatitis C	3 (3)	3 (3)	0	6 (3)
Oropharyngeal gonococcal infection	6 (5)	0	0	6 (3)
Rectal haemorrhage	3 (3)	3 (3)	0	6 (3)
Seborrhoeic dermatitis	3 (3)	3 (3)	0	6 (3)
Tooth abscess	2 (2)	4 (3)	0	6 (3)
Dysuria	3 (3)	3 (3)	1 (2)	6 (3)
Gingivitis	5 (4)	1 (<1)	1 (2)	6 (3)
Catarrh	5 (4)	1 (<1)	3 (5)	6 (3)
Gastritis	2 (2)	4 (3)	3 (5)	6 (3)
Balanoposthitis	3 (3)	2 (2)	0	5 (2)
Erectile dysfunction	1 (<1)	4 (3)	0	5 (2)
Food poisoning	2 (2)	3 (3)	0	5 (2)
Injection site haematoma	3 (3)	2 (2)	0	5 (2)
Irritability	4 (3)	1 (<1)	0	5 (2)
Lymphogranuloma venereum	3 (3)	2 (2)	0	5 (2)
Nasal congestion	3 (3)	2 (2)	0	5 (2)
Pharyngitis streptococcal	2 (2)	3 (3)	0	5 (2)
Tooth infection	2 (2)	3 (3)	0	5 (2)

Preferred Term	Q8W IM[a] (N=115) n (%)	Q4W IM[b] (N=115) n (%)	CAB 30 mg (N=56) n (%)	Subtotal-IM (N=230) n (%)
Vertigo	2 (2)	3 (3)	0	5 (2)
Proctitis gonococcal	4 (3)	1 (<1)	1 (2)	5 (2)
Abdominal distension	4 (3)	1 (<1)	2 (4)	5 (2)
Abnormal dreams	2 (2)	3 (3)	2 (4)	5 (2)
Hordeolum	2 (2)	3 (3)	2 (4)	5 (2)
Vitamin D deficiency	4 (3)	1 (<1)	2 (4)	5 (2)
Rhinorrhoea	3 (3)	2 (2)	3 (5)	5 (2)
Eczema	4 (3)	1 (<1)	6 (11)	5 (2)
Abscess limb	3 (3)	1 (<1)	0	4 (2)
Anal abscess	4 (3)	0	0	4 (2)
Anal chlamydia infection	3 (3)	1 (<1)	0	4 (2)
Decreased appetite	3 (3)	1 (<1)	0	4 (2)
Lymphadenopathy	3 (3)	1 (<1)	0	4 (2)
Pneumonia	1 (<1)	3 (3)	0	4 (2)
Skin lesion	1 (<1)	3 (3)	0	4 (2)
Hyperhidrosis	3 (3)	1 (<1)	1 (2)	4 (2)
Hypoaesthesia	4 (3)	0	1 (2)	4 (2)
Limb injury	3 (3)	1 (<1)	1 (2)	4 (2)
Urticaria	1 (<1)	3 (3)	1 (2)	4 (2)
Anal fissure	4 (3)	0	2 (4)	4 (2)
Anogenital dysplasia	4 (3)	0	2 (4)	4 (2)
Migraine	2 (2)	2 (2)	2 (4)	4 (2)
Sinus congestion	4 (3)	0	2 (4)	4 (2)
Alopecia	0	3 (3)	0	3 (1)
Conjunctivitis allergic	3 (3)	0	0	3 (1)
Genital herpes simplex	3 (3)	0	0	3 (1)
Muscle strain	3 (3)	0	0	3 (1)
Musculoskeletal stiffness	3 (3)	0	0	3 (1)
Oral disorder	0	3 (3)	0	3 (1)
Suicide attempt	3 (3)	0	0	3 (1)
Weight increased	3 (3)	0	0	3 (1)
Acute hepatitis C	0	3 (3)	1 (2)	3 (1)
Ear pain	0	3 (3)	2 (4)	3 (1)
Paraesthesia	2 (2)	1 (<1)	2 (4)	3 (1)
Arthropod bite	1 (<1)	1 (<1)	2 (4)	2 (<1)
Cystitis	0	2 (2)	2 (4)	2 (<1)
Gastroenteritis viral	1 (<1)	1 (<1)	2 (4)	2 (<1)
Depressed mood	2 (2)	0	3 (5)	2 (<1)
Exposure to communicable disease	1 (<1)	0	2 (4)	1 (<1)
Neutropenia	1 (<1)	0	2 (4)	1 (<1)
Onychomycosis	1 (<1)	0	2 (4)	1 (<1)
Tinea pedis	1 (<1)	0	2 (4)	1 (<1)
Vaginal infection	0	1 (<1)	2 (4)	1 (<1)
Anaemia	1 (<1)	0	4 (7)	1 (<1)
Chondropathy	0	0	2 (4)	0
Hypersensitivity	0	0	2 (4)	0
Proteinuria	0	0	2 (4)	0
Rash papular	0	0	2 (4)	0

Note: Common adverse events are those with ≥3% overall incidence in any arm. Includes all post-baseline induction and maintenance period adverse events, as well as long-term follow-up period adverse events for subjects not entering the extension period that occur 35/63 days of last maintenance period IM injection (Q4W/Q8W regimen) up to and including the start date of long-term follow up period antiretroviral therapy.

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Drug-Related Post-Baseline Adverse Events (≥3% in any arm) by Overall Frequency (Safety Maintenance Population)

Preferred Term	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	CAB 30 mg N=56 n (%)	Subtotal IM N=230 n (%)
Any event	110 (96)	113 (98)	21 (38)	223 (97)
Injection site pain	109 (95)	112 (97)	0	221 (96)
Injection site nodule	29 (25)	35 (30)	0	64 (28)
Injection site swelling	29 (25)	34 (30)	0	63 (27)
Injection site pruritus	24 (21)	33 (29)	0	57 (25)
Injection site induration	28 (24)	25 (22)	0	53 (23)
Injection site warmth	22 (19)	21 (18)	0	43 (19)
Injection site bruising	19 (17)	14 (12)	0	33 (14)
Injection site erythema	12 (10)	19 (17)	0	31 (13)
Nausea	8 (7)	12 (10)	5 (9)	20 (9)
Headache	6 (5)	7 (6)	4 (7)	13 (6)
Pyrexia	5 (4)	7 (6)	0	12 (5)
Fatigue	5 (4)	5 (4)	2 (4)	10 (4)
Injection site discolouration	3 (3)	6 (5)	0	9 (4)
Dizziness	4 (3)	4 (3)	1 (2)	8 (3)
Diarrhoea	3 (3)	4 (3)	2 (4)	7 (3)
Dyspepsia	1 (<1)	6 (5)	1 (2)	7 (3)
Influenza like illness	3 (3)	3 (3)	0	6 (3)
Asthenia	2 (2)	3 (3)	3 (5)	5 (2)
Insomnia	0	4 (3)	1 (2)	4 (2)
Injection site haematoma	3 (3)	1 (<1)	0	4 (2)
Nightmare	1 (<1)	3 (3)	0	4 (2)
Arthralgia	3 (3)	0	0	3 (1)
Irritability	3 (3)	0	0	3 (1)

Note: Includes all post-baseline induction period and maintenance period adverse events, as well as long-term follow-up period adverse events for subjects not entering the extension period that occur within 35/63 days of last maintenance period IM injection (Q4W/Q8W regimen) up to and including the start date of long-term follow up period antiretroviral therapy.

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Post-Baseline Serious Adverse Events by Overall Frequency (Safety Maintenance Population)

Preferred Term	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	Oral CAB 30 mg N=56 n (%)	IM Subtotal N=230 n (%)
Any event	13 (11)	13 (11)	9 (16)	26 (11)
Suicide attempt	2 (2)	1 (<1)	0	3 (1)
Anogenital warts	1 (<1)	1 (<1)	0	2 (<1)
Hypertension	1 (<1)	1 (<1)	0	2 (<1)
Abscess limb	1 (<1)	0	0	1 (<1)
Anal abscess	1 (<1)	0	0	1 (<1)
Anal fissure	1 (<1)	0	0	1 (<1)
Asthmatic crisis	1 (<1)	0	0	1 (<1)
Eosinophilic granulomatosis with polyangiitis	0	1 (<1)	0	1 (<1)
Epididymitis	1 (<1)	0	0	1 (<1)
Epilepsy	0	1 (<1)	0	1 (<1)
Fistula	0	1 (<1)	0	1 (<1)
Headache	1 (<1)	0	0	1 (<1)
Hernia	0	1 (<1)	0	1 (<1)
Intervertebral disc protrusion	0	1 (<1)	0	1 (<1)
Meningioma	1 (<1)	0	0	1 (<1)
Mesenteric vein thrombosis	0	1 (<1)	0	1 (<1)
Migraine	1 (<1)	0	0	1 (<1)
Muscular weakness	1 (<1)	0	0	1 (<1)
Myocardial ischaemia	1 (<1)	0	0	1 (<1)
Neck pain	1 (<1)	0	0	1 (<1)
Nephrolithiasis	1 (<1)	0	0	1 (<1)
Orchitis	1 (<1)	0	0	1 (<1)
Overdose	0	1 (<1)	0	1 (<1)
Pain in extremity	1 (<1)	0	0	1 (<1)
Peritonsillar abscess	0	1 (<1)	0	1 (<1)
Portal vein thrombosis	0	1 (<1)	0	1 (<1)
Rib fracture	0	1 (<1)	0	1 (<1)
Rotator cuff syndrome	0	1 (<1)	0	1 (<1)
Splenic vein thrombosis	0	1 (<1)	0	1 (<1)
Umbilical hernia	1 (<1)	0	0	1 (<1)
Depression	0	0	1 (2)	0
Epicondylitis	0	0	1 (2)	0
Gastritis	0	0	1 (2)	0
Gastroenteritis	0	0	1 (2)	0
Hypobarism	0	0	1 (2)	0
Nerve root compression	0	0	1 (2)	0
Ovarian cyst	0	0	1 (2)	0
Pelvic prolapse	0	0	1 (2)	0
Prostatitis	0	0	1 (2)	0
Rhabdomyolysis	0	0	1 (2)	0
Substance abuse	0	0	1 (2)	0

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Deaths

Two deaths were reported in this study through the Week 96 data cut off.

During the Induction Period, a subject had a fatal SAE (road traffic accident, multiple injuries) approximately two months after initiation of study treatment (considered unrelated to study drugs per investigator).

During the Maintenance Period, a 3[redacted]-year-old white male with no known relevant medical history, developed a seizure, resulting in death, which was not considered by the Investigator or Sponsor to be reasonably likely related to IP. The subject was in the Q4W IM arm. Study participation was unremarkable, without any AEs reported through study Week 28 (48 weeks on study). Forty-eight weeks following initial CAB administration and 32 weeks following initial RPV administration, the subject developed acute onset status epilepticus lasting for approximately six hours while alone in his apartment, leading to anoxic brain injury and death. Magnetic resonance imaging showed diffuse cerebral edema without evidence of a focal lesion. Papaverine, a morphine analog often used for erectile dysfunction, was detected on urine and serum spectroscopy. Social history indicated a recent history of frequent [redacted], though no other illicit drugs were detected on urine and serum toxicology screening. An autopsy was not conducted at the family's request. The official cause of death was listed as "brain death following cerebral edema secondary to refractory epilepsy". While an association with IP cannot be fully excluded in this case, the time to onset, lack of any prodromal symptoms, and acute presentation around the time of known or suspected recreational drug use, led to a conclusion that it is not reasonably likely that IP was causally linked with the seizure in this subject.

Summary of Treatment Emergent Adverse Events Leading to Withdrawal/Permanent Discontinuation of Investigational Product (Safety Maintenance Population)

System Organ Class Preferred Term	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	CAB 30 mg N=56 n (%)	Subtotal IM N=230 n (%)
Any event	**2 (2)**	**8 (7)**	**1 (2)**	**10 (4)**
General disorders and administration site conditions, n (%)				
Any event	2 (2)	0	0	2 (<1)
Injection site pain	2 (2)	0	0	2 (<1)
Chills	1 (<1)	0	0	1 (<1)
Injection site induration	1 (<1)	0	0	1 (<1)
Injection site pruritus	1 (<1)	0	0	1 (<1)
Injection site swelling	1 (<1)	0	0	1 (<1)
Pain	1 (<1)	0	0	1 (<1)
Infections and infestations, n (%)				
Any event	0	1 (<1)	1 (2)	1 (<1)
Hepatitis C	0	1 (<1)	0	1 (<1)
Acute hepatitis C	0	0	1 (2)	0
Psychiatric disorders, n (%)				
Any event	0	2 (2)	0	2 (<1)
Adjustment disorder with depressed mood	0	1 (<1)	0	1 (<1)
Psychotic disorder	0	1 (<1)	0	1 (<1)
Blood and lymphatic system disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Splenic vein thrombosis	0	1 (<1)	0	1 (<1)
Cardiac disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Sinus tachycardia	0	1 (<1)	0	1 (<1)
Gastrointestinal disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Mesenteric vein thrombosis	0	1 (<1)	0	1 (<1)
Hepatobiliary disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Portal vein thrombosis	0	1 (<1)	0	1 (<1)
Immune system disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Allergic granulomatous angiitis	0	1 (<1)	0	1 (<1)
Investigations, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Electrocardiogram QT prolonged	0	1 (<1)	0	1 (<1)
Nervous system disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Epilepsy	0	1 (<1)	0	1 (<1)
Skin and subcutaneous tissue disorders, n (%)				
Any event	0	1 (<1)	0	1 (<1)
Rash	0	1 (<1)	0	1 (<1)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Injection Site Reaction Adverse Events (Event Level Summary) – (Safety Maintenance Population)

	Q8W IM[a] N=115	Q4W IM[b] N=115	Subtotal IM N=230
No. of Subjects with Injections	**115**	**115**	**230**
Number of Injections	**3160**	**5419**	**8579**
Number of ISR Events	**1925**	**2435**	**4360**
Any Grade, n (%)			
Grade 1 Events	1543 (80)	2105 (86)	3648 (84)
Grade 2 Events	359 (19)	314 (13)	673 (15)
Grade 3 Events	16 (<1)	14 (<1)	30 (<1)
Grade 4 Events	0	0	0
Not applicable	1 (<1)	0	1 (<1)
Missing	6 (<1)	2 (<1)	8 (<1)
Event Characteristics, n (%)			
Serious	0	0	0
Drug-related	1900 (99)	2420 (>99)	4320 (>99)
Leading to Withdrawal	8 (<1)	0	8 (<1)
Severe or Grade 3 / 4	16 (<1)	14 (<1)	30 (<1)
Fatal	0	0	0
Duration (Days)			
1-7	1718 (89)	2172 (89)	3890 (89)
8-14	133 (7)	162 (7)	295 (7)
>14	51 (3)	78 (3)	129 (3)
Missing	23 (1)	23 (<1)	46 (1)
Mean (SD)	4.4 (8.11)	4.4 (7.79)	4.4 (7.93)
Median (Range)	3.0 (1,176)	3.0 (1, 138)	3.0 (1, 176)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Maximum Maintenance Period Treatment Emergent Clinical Chemistry Toxicities - Week 96 (Safety Maintenance Population)

	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	Oral CAB 30 mg N=56 n (%)	IM Subtotal N=230 n (%)
ALL PARAMETERS, n (%)				
Grades 1 to 4	107 (93)	109 (95)	42 (75)	216 (94)
Grades 2 to 4	67 (58)	63 (55)	26 (46)	130 (57)
Grades 3 to 4	21 (18)	32 (28)	12 (21)	53 (23)
Grade 1	40 (35)	46 (40)	16 (29)	86 (37)
Grade 2	46 (40)	31 (27)	14 (25)	77 (33)
Grade 3	11 (10)	24 (21)	9 (16)	35 (15)
Grade 4	10 (9)	8 (7)	3 (5)	18 (8)

Note: Includes all Treatment Emergent maintenance period toxicities, as well as long-term follow-up period toxicities for subjects not entering the extension phase period that occur within 35/63 days of last maintenance period IM injection (Q4W/Q8W regimen) up to and including the start date of long-term follow up period antiretroviral therapy.
a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary of Maximum Maintenance Period Treatment Emergent Laboratory Toxicities – Select Parameters of Special Interest (Safety Maintenance Population)

	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	Oral CAB 30 mg N=56 n (%)	IM Subtotal N=230 n (%)
Alanine Amino Transferase (IU/L), n (%)				
Grades 1 to 4	22 (19)	17 (15)	10 (18)	39 (17)
Grades 2 to 4	4 (3)	8 (7)	5 (9)	12 (5)
Grades 3 to 4	4 (3)	4 (3)	3 (5)	8 (3)
Grade 1	18 (16)	9 (8)	5 (9)	27 (12)
Grade 2	0	4 (3)	2 (4)	4 (2)
Grade 3	2 (2)	1 (<1)	3 (5)	3 (1)
Grade 4	2 (2)	3 (3)	0	5 (2)
Aspartate Amino Transferase (IU/L), n (%)				
Grades 1 to 4	26 (23)	27 (23)	9 (16)	53 (23)
Grades 2 to 4	12 (10)	12 (10)	4 (7)	24 (10)
Grades 3 to 4	2 (2)	7 (6)	3 (5)	9 (4)
Grade 1	14 (12)	15 (13)	5 (9)	29 (13)
Grade 2	10 (9)	5 (4)	1 (2)	15 (7)
Grade 3	0	6 (5)	2 (4)	6 (3)
Grade 4	2 (2)	1 (<1)	1 (2)	3 (1)
Creatine Kinase (IU/L), n (%)				
Grades 1 to 4	36 (31)	34 (30)	10 (18)	70 (30)
Grades 2 to 4	22 (19)	19 (17)	5 (9)	41 (18)
Grades 3 to 4	11 (10)	12 (10)	4 (7)	23 (10)
Grade 1	14 (12)	15 (13)	5 (9)	29 (13)
Grade 2	11 (10)	7 (6)	1 (2)	18 (8)
Grade 3	5 (4)	7 (6)	3 (5)	12 (5)
Grade 4	6 (5)	5 (4)	1 (2)	11 (5)
Lipase (U/L), n (%)				
Grades 1 to 4	26 (23)	20 (17)	8 (14)	46 (20)
Grades 2 to 4	20 (17)	13 (11)	5 (9)	33 (14)
Grades 3 to 4	6 (5)	4 (3)	4 (7)	10 (4)
Grade 1	6 (5)	7 (6)	3 (5)	13 (6)
Grade 2	14 (12)	9 (8)	1 (2)	23 (10)
Grade 3	4 (3)	4 (3)	3 (5)	8 (3)
Grade 4	2 (2)	0	1 (2)	2 (<1)
Total Bilirubin (µMOL/L), n (%)				
Grades 1 to 4	15 (13)	13 (11)	4 (7)	28 (12)
Grades 2 to 4	6 (5)	5 (4)	0	11 (5)
Grades 3 to 4	0	1 (<1)	0	1 (<1)
Grade 1	9 (8)	8 (7)	4 (7)	17 (7)
Grade 2	6 (5)	4 (3)	0	10 (4)
Grade 3	0	1 (<1)	0	1 (<1)
Grade 4	0	0	0	0

Parameters of special interest included: ALT, AST, total bilirubin, CPK, lipase

Note: Includes all post baseline treatment emergent induction period and maintenance period toxicities, as well as long-term follow up period toxicities for subjects not entering the extension period that occur within 35/63 days of last maintenance period IM injection (Q4W/Q8W regimen) up to and including the start date of long-term follow up period antiretroviral therapy.

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks

b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Summary and Change from Baseline for QTc Values (Safety Maintenance Population)

	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	Oral CAB 30 mg N=56 n (%)	IM Subtotal N=230 n (%)
Maximum Post-baseline QTcB, msec				
n	108	85	16	193
≤450	93 (86)	63 (74)	10 (63)	156 (81)
>450 to ≤480	13 (12)	16 (19)	6 (38)	29 (15)
>480 to ≤500	1 (<1)	4 (5)	0	5 (3)
>500	1 (<1)	2 (2)	0	3 (2)
Maximum Post-baseline change QTcB, msec				
n	115	115	56	230
≤30	77 (67)	73 (63)	42 (75)	150 (65)
>30 to ≤60	35 (30)	31 (27)	14 (25)	66 (29)
>60	3 (3)	11 (10)	0	14 (6)
Maximum Post-baseline QTcF, msec				
n	108	83	14	191
≤450	103 (95)	74 (89)	12 (86)	177 (93)
>450 to ≤480	3 (3)	7 (8)	1 (7)	10 (5)
>480 to ≤500	1 (<1)	2 (2)	1 (7)	3 (2)
>500	1 (<1)	0	0	1 (<1)
Maximum Post-baseline change QTcF, msec				
n	115	115	56	230
≤30	85 (74)	88 (77)	44 (79)	173 (75)
>30 to ≤60	26 (23)	21 (18)	10 (18)	47 (20)
>60	4 (3)	6 (5)	2 (4)	10 (4)

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Vital Signs

No clinically significant patterns of changes in vital signs were identified in any arm.

Pregnancy

Throughout the study, up to Week 96, one pregnancy was reported in a 2[redacted]-year-old female in the Q4W IM arm. The pregnancy was noted at Week 20 of the Maintenance Period, with the last injection being administered at Week 16. The subject initiated ART therapy with tenofovir/emtricibine, and darunavir/ritonavir, and is being followed in the Long-Term Follow-Up period of the study. The subject delivered a normal baby [redacted] on [redacted]2015 at approximately 40 weeks gestation.

Week 96 Health Outcomes Results

High levels of treatment satisfaction were observed across all treatment groups. At Week 96, patients reported very high levels of satisfaction across all three groups via the HIVTSQ(s), with 97% of subjects selecting a score of 5 or 6 on a 6-point satisfaction scale. A similar percentage of subjects in each of the IM arms (99%) reported they would be highly satisfied to continue their current regimen, while a lower percentage

would elect to continue on oral dosing (78%). Subjects who discontinued for any reason before Week 96 did not complete the questionnaire at this timepoint, introducing a small degree of selection bias in the results.

The high levels of satisfaction reported by subjects through 96 weeks of maintenance therapy suggests that LA regimens may be a preferred alternative to oral daily therapy for patients infected with HIV. The acceptability and tolerability will continue to be observed carefully as this will be important to the long-term success of IM dosing.

Conclusions:

Efficacy

Both IM dosing regimens of CAB LA + RPV LA continued to demonstrate comparable antiviral activity compared to daily oral CAB + ABC/3TC through 96 weeks of treatment in virologically suppressed patients.

At Week 96, 94% (Q8W IM arm) and 87% (Q4W IM) of subjects receiving injectable dosing maintained virologic suppression (HIV-1 RNA <50 c/mL) compared to 84% of subjects continuing oral CAB + 2 NRTIs, demonstrating a comparable response overall, across the three dosing arms.

There were no Snapshot virologic failures in the Q4W treatment arm. The Q8W treatment arm exhibited a lower rate of Snapshot virologic failures at Week 96 compared to Week 48. At Week 96, the proportion of subjects who discontinued due to AEs or death or for "Other" reasons while suppressed were higher in the Q4W IM and oral CAB arms (12% and 16%, respectively) and lower in Q8W IM arm (4%).

Four subjects in the Q8W IM arm progressed from Class A to Class C (Kaposi's sarcoma [n=1], Herpes simplex [n=2] and Pneumonia [n=1]) and one subject in Q4W IM arm progressed from a Class A to Death not considered drug-related. No new progressions since the Week 48 analysis.

Safety

CAB LA + RPV LA continues to be well tolerated through Week 96 for both the Q8W and Q4W dosing regimens, as demonstrated by a low discontinuation rate due to AEs, including injection site reaction (ISR) related AEs in either dosing arm, with no significant dose-dependent trends in safety parameters. Only 1 additional subject withdrew due to an AE since the Week 48 analysis.

During the 96-week Maintenance Period, no new drug-related SAEs were reported.

No additional subjects since Week 48 withdrew from the study due to drug induced liver injury.

The majority of ISRs were mild or moderate in severity and resolved within a median of 3 days. There have been no additional withdrawals due to ISRs since Week 32.

During the 96-week Maintenance Period, one death was reported (fatal, non-drug related epilepsy). This event was not assessed as likely related to study product by the Investigator or Sponsor and was reported in the Week 48 analysis.

Virology

There were 3 subjects with PDVF through 96 weeks of maintenance treatment. No additional PDVFs have been identified since the Week 48 analysis.

Health Outcomes

- All treatment groups reported a high level of satisfaction throughout the study with consistently high overall treatment satisfaction scores through Week 96.

Effective Date: [redacted]

Synopsis for Study 200056 Week 160

Name of finished product:	**Name of active substance:**
Not available at the time of this report	GSK1265744(Cabotegravir) and GSK1329758 (Rilpivirine)

Study Number: 200056

Title: A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 for The Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects. Week 160 - Clinical Study Report.

Investigator(s): This is a multi-center study; 50 investigators screened subjects, 50 sites randomized subjects.

Study center(s): This study is being conducted at 50 centers in 5 countries (15 in United States, 8 in Canada, 9 in Spain, 9 in France, 9 in Germany).

Publication(s): Margolis et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. Lancet. 2017 Sep 23;390(10101):1499-1510. doi: 10.1016/S0140-6736(17)31917-7. Epub 2017 Jul 24.

Study Period: 28-Apr-2014 (First subject screened) - 31-Jan-2018 (Last Subject Last Visit Week 160)

Phase of Development: IIb

Objective: The overall objective of this study was to select an intramuscular dosing regimen of Cabotegravir (CAB) Long Acting (LA) plus Rilpivirine (RPV) LA based on a comparison of the Week 32 antiviral activity, tolerability, and safety of the two IM dosing regimens, relative to CAB 30 mg plus abacavir (ABC)/lamivudine (3TC) orally once daily.

Primary Objectives:

- Evaluated the proportion of subjects with Human Immunodeficiency Virus Type 1 (HIV-1) Ribonucleic acid (RNA) <50 c/mL at Maintenance Week 32 based on intent to treat-maintenance exposed (ITT-ME) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm.
- Evaluated the proportion of subjects with protocol defined virologic failures over time.
- Evaluated the incidence and severity of adverse events (AEs) and laboratory abnormalities over time.

Secondary objectives:

- Evaluated the antiviral activity, tolerability, and safety of CAB 30 mg plus ABC/3TC orally once daily through the Induction and Maintenance Periods.
- Evaluated the efficacy, tolerability, and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg every 8 weeks, relative to CAB 30 mg plus ABC/3TC orally once daily, through Week 96 of the Maintenance Period.
- Characterized CAB LA and RPV LA Pharmacokinetics (PK) and explored PK-Pharmacodynamic (PD) relationships.
- Assessed the development of viral resistance in subjects with protocol defined virologic failure (PDVF).
- Explored the effect of various demographic baseline characteristics and adherence on virologic response of CAB and RPV over time.
- Evaluated the treatment satisfaction for subjects on the long-acting injectable regimens compared with those on the oral regimen through Week 96 of the Maintenance Period.
- Evaluated the change in treatment satisfaction for subjects in both the long-acting injectable and oral regimens through Week 32 of the Maintenance Period.
- Evaluated medication adherence over time.

Methodology: Study 200056 was a Phase IIb, randomized, multicentre, parallel group, open-label, three-part study conducted in Human Immunodeficiency Virus (HIV-1) infected, Antiretroviral (ARV) Treatment (ART)-naive adults. This study consisted of a Screening Period, Induction Period, Maintenance Period, Extension Period and a Long-term Follow-up Period (withdrawn IM dosing regimen subjects only). A subject was considered to have completed the study if they completed the Induction and Maintenance Period through Week 96.

Protocol waivers or exemptions were not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, were essential and required for study conduct.

Supplementary study conduct information not mandated to be present in the protocol was provided in the accompanying Study Procedures Manual (SPM). The SPM provided the site personnel with administrative and detailed technical information that does not impact subject safety.

Number of subjects: There were 309 subjects who enrolled into the study and a total of 288 subjects (93%) completed the Induction period with cabotegravir 30 mg + 2 Nucleoside reverse transcriptase inhibitor (NRTIs). Two hundred and eighty-six subjects qualified for and were included on Day 1 into the Maintenance Period. Of these, 258 subjects completed the Maintenance Period. At the time of this Week 160 analysis, 84% (240/286) of subjects remained in study.

Diagnosis and main criteria for inclusion:

Notable inclusion criteria:

- Male or female subjects at least 18 years old that were HIV-1 positive (HIV-1 RNA ≥1000 copies/millilitre [c/mL]).
- Women of childbearing potential were enrolled if they agreed to use adequate contraception for the life of the study and at least 52 weeks after withdrawal from an IM regimen.
- CD4+ cell count ≥200 cells/mm^3 (or higher as local guidelines dictate).
- Antiretroviral therapy (ART) naive (no more than 10 days of prior therapy with any antiretroviral agent following a diagnosis of HIV-1 infection. Any previous exposure to an HIV integrase inhibitor or non-nucleoside reverse transcriptase inhibitor [NNRTI] was exclusionary).

Notable exclusion criteria:

- Any evidence of primary resistance based on the presence of any major resistance-associated mutation in the Screening result or, if known, any historical resistance test result.
- Subjects with known moderate to severe hepatic impairment.
- History of ongoing or clinically relevant hepatitis within the previous 6 months, including chronic Hepatitis B Virus (HBV) infection (Hepatitis B Virus Surface Antigen [HBsAg] positive). Asymptomatic individuals with chronic Hepatitis C Virus (HCV) infection were not excluded, however Investigators carefully assessed if therapy specific for HCV infection was required; subjects who were anticipated to require such therapy were excluded.
- History of liver cirrhosis with or without hepatitis viral co-infection.
- Current or anticipated need for chronic anti-coagulation.
- Any verified Grade 4 laboratory abnormality.
- Any acute laboratory abnormality at Screening, which, in the opinion of the Investigator, precluded the subject's participation in the study of an investigational compound.
- Subject had estimated creatinine clearance <50 mL/min via Cockcroft-Gault method.
- Alanine aminotransferase (ALT) ≥5 times upper limit of normal (ULN). Subjects with ALT >2xULN but <5xULN participated in the study if, in the opinion of the Investigator and GlaxoSmithKline (GSK) medical monitor, the lab abnormality did not interfere with the study procedures or compromise subject safety.
- ALT ≥3xULN and bilirubin ≥1.5xULN (with >35% direct bilirubin).
- Subjects who were Human Leukocyte Antigen (HLA)-B*5701 positive and were unable to use an alternative nucleoside reverse transcriptase inhibitor (NRTI)

backbone (subjects who were HLA-B*5701 positive were enrolled if they use an alternative NRTI backbone that did not contain abacavir).

- Any clinically significant finding on screening or Baseline electrocardiograph (ECG).
- Tattoo or other dermatologic condition over gluteus region.
- Need for chronic anticoagulants.

Treatment administration:

In this study, IP referred to CAB, CAB LA, RPV and RPV LA. These were supplied by GSK and Janssen Pharmaceuticals, respectively. Epzicom / Kivexa was also considered IP from Day 1 of the Maintenance Period and were provided by GSK. Investigational products and the associated batch numbers have been verified by Supply Chain Management.

Other antiretrovirals administered in the study as dual background NRTIs (e.g. for subjects who are HLA-B*5701 positive or switched due to toxicity) were not considered IP. These were supplied regionally by GSK or reimbursement was provided.

Induction Period (Week -20 through Day 1)	
Week -20 to Week (-4) (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Week (-4) to Day 1 (3 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily Take 1 X RPV 25 mg tablet once daily • Take with a meal • Take Day 1 doses in the clinic
Maintenance Period (Day 1 to Week 96*)	
CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 4 – 2nd loading dose (1 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injections (No RPV LA)
Week 8 to Week 88 (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)	
Day 1 – loading dose (3 injections once)	Receive last dose of Induction regimen Receive CAB LA 800 mg given as 2 X 2 mL IM injections Receive RPV LA 600 mg given as 1 X 2 mL IM injection
Week 4 to Week 92 (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
CAB 30 mg + ABC/3TC once daily	
Day 1	Receive last dose of Induction regimen
Day 2 to Week 96 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
If eligible and continuing to Extension Period:	

Week 96 to Week 100 (2 tablets once daily)	Take 1 X ABC 600 mg / 3TC 300 mg tablet once daily Take 1 X CAB 30 mg tablet once daily
Extension Period (Week 96 plus+)	
CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks:	
Week 96 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
If switching from Oral Arm:	
Week 100 – 1st loading dose (2 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 – 2nd loading dose (1 injection once)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 112 plus+ (2 injections every 8 weeks)	Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks:	
Week 96 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection
If switching from Oral Arm:	
Week 100 – loading dose (2 injections once)	Receive last dose of Maintenance regimen Receive CAB LA 600 mg given as 1 X 3 mL IM injection Receive RPV LA 900 mg given as 1 X 3 mL IM injection
Week 104 plus+ (2 injections every 4 weeks)	Receive CAB LA 400 mg given as 1 X 2 mL IM injection Receive RPV LA 600 mg given as 1 X 2 mL IM injection

*Or through Week 100 if eligible to enter the Extension Period.
+until locally approved and commercially available, the subject no longer derives clinical benefit, the subject meets a protocol-defined reason for discontinuation or until development of CAB or RPV is terminated

Criteria for evaluation:

Primary endpoints

- The proportion of subjects with HIV-1 RNA <50 c/mL at Maintenance Week 32 based on intent to treat-maintenance exposed (ITT-ME) population using the Missing, Switch, or Discontinuation = Failure (MSDF) algorithm.
- Proportion of subjects with protocol defined virologic failures over time.
- Incidence and severity of AEs and laboratory abnormalities over time.

Secondary endpoints

- Proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL over time.
- Absolute values and change from Baseline in plasma HIV-1 RNA.
- Absolute values and changes from Baseline in CD4+ cell counts.
- Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome [AIDS] and death).

- Incidence and severity of AEs and laboratory abnormalities over time.
- Absolute values and changes in laboratory parameters over time.
- Proportion of subjects with protocol defined virologic failures over time.
- Incidence of disease progression (HIV associated conditions, AIDS and death).
- Plasma PK parameters for CAB LA and RPV LA (C_{trough} and concentrations post dose [~maximum plasma drug concentration (C_{max})]) during the Maintenance Period.
- Plasma CAB and RPV trough concentrations to determine when steady state was achieved for each CAB LA and RPV LA regimen.
- Relationship between plasma PK parameters and plasma HIV-1 RNA, CD4+ cell counts and/or occurrence of adverse events (AEs) through Week 48 of the Maintenance Period were explored.
- Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study ART.
- Summarize treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Status (HIVTSQ(s)) over time (through Week 96 of the Maintenance Period.).
- Measure change in treatment satisfaction using the HIV Treatment Satisfaction Questionnaire Change (HIVTSQ(c)) over time (through Week 32 of the Maintenance Period.).
- Summarize subject reported medication adherence using the HIV Medication Questionnaire (HIVMQ) over time.

Statistical methods: The study was designed to evaluate the efficacy and safety of CAB LA 400 mg IM plus RPV LA 600 mg IM every 4 weeks and CAB LA 600 mg IM plus RPV LA 900 mg IM every 8 weeks, relative to CAB 30 mg once daily plus ABC/3TC once daily, through Week 32 of the Maintenance Period.

To claim positive outcome, the following hypotheses were tested:

- H0: Response rate for CAB LA plus RPV LA two-drug regimen ≤ CAB plus ABC/3TC -10%
- H1: Response rate for CAB LA plus RPV LA two-drug regimen > CAB plus ABC/3TC -10%

The sample size of 45 subjects in the oral treatment arm and 90 subjects each in the IM treatment arms were chosen to ensure a high probability that a long-acting two drug treatment with truly poor response relative to CAB once daily plus ABC/3TC once daily will not be studied further, while allowing for formal considerations of other factors should efficacy be similar between the treatment arms. It was assumed that 85% subjects enrolled would be suppressed at Week (-16), approximately 265 subjects would be enrolled in order to have 225 subjects randomized at Day 1.

The study was designed to test the comparability of CAB LA plus RPV LA two-drug regimen to CAB 30 mg once daily plus ABC/3TC. The primary comparison of interest

was performed using a Bayesian probability model. If the posterior probability that the difference was greater than -10% was large (i.e., ≥90%), then sufficient statistical evidence had been provided for the positive outcome. A response rate of 82% in the CAB LA plus RPV LA two-drug regimen (compared with an CAB plus ABC/3TC response rate of 92%) would result in a rejection of the null hypothesis with a probability of approximately 0.064 (type I error). The given sample size was unlikely to select a random sample that would falsely conclude that CAB LA plus RPV LA two-drug regimen was comparable with CAB plus ABC/3TC if the response rates were truly 82% versus 92%, respectively. If the CAB LA plus RPV LA two-drug regimen yielded a response rate of greater than 92%, then there was a high probability of rejecting the null hypothesis and correctly concluding that CAB LA plus RPV LA two-drug regimen was at least as good as CAB plus ABC/3TC.

Incorporation of prior beliefs and information about population parameters was a required part of any Bayesian probability model. The assumptions made will help to provide a more reliable estimate when the prior beliefs were combined with the observed data than the data alone as long as the beliefs were reasonable. Therefore, the trial utilized a Beta (23, 2) distribution with the mean response rate being 92%, with 97.5th percentile of 99% and 2.5th percentile of 78%. Furthermore, a non- informative prior belief was assumed for the response rate for CAB LA plus RPV LA two-drug regimen. Therefore, the trial will conservatively utilize a Beta (1, 1) distribution.

The All Subjects Screened Population consisted of all subjects screened for inclusion in the study.

The ITT-E population consisted of all enrolled subjects who received at least one dose of IP during the induction period. The ITT-E population was used for efficacy analyses of induction period data (Week -20 to Day 1).

The ITT-ME population consisted of all randomized subjects who received at least one dose of IP during the Maintenance Period of the study. Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received. The ITT-ME population was the primary population for efficacy analyses.

The Randomized population consisted of all subjects who were randomized in the study and were used for select study population data listings.

The PP-ME population consisted of subjects in the ITT-ME population with the exception of major protocol violators (these were defined in the Reporting and Analysis Plan [RAP] of this study). The PP-ME population was a secondary population for efficacy purposes.

The PK Population included all subjects who received CAB and / or RPV and underwent PK sampling during the study and provided evaluable CAB and /or RPV plasma concentration data. Subjects in this population were included in the PK analysis.

The Safety Population consisted of all enrolled subjects who were exposed to investigational products with the exception of any subjects with documented evidence of not receiving any amount of Maintenance Period investigational product. Subjects were

analyzed according to the actual treatments received. The safety population was the primary population for safety analyses of induction period data.

The Safety Maintenance Population consisted of all subjects who entered the Maintenance period and received at least one dose of IP. Subjects were analyzed according to the actual treatments received. The safety maintenance population was the primary population for safety analyses of maintenance period data. The primary efficacy analysis data set were based on the ITT-ME population. The efficacy dataset included MSDF (also referred to as Snapshot), for the proportion of subjects with plasma HIV-1 RNA less than the pre-defined threshold (e.g., <200 c/mL and <50 The primary efficacy analysis was performed at Week 32 based on the proportion of subjects in the ITT-ME population with plasma HIV-1 RNA <50 c/mL using a MSDF approach identical to the current Food and Drug Administration (FDA) definition of the Snapshot algorithm. The primary comparison of interest compared the response rate of each IM dosing arm to the oral control arm using the Bayesian probability model described above. The probability of (Response rate for IM arm > Response rate for Oral arm -10%) was calculated.

The Safety Long-Term Follow-up Population consisted of all subjects receiving at least one dose of CAB LA and/or RPV LA who discontinued IP/withdrawn from maintenance period and had a least one Long-Term Follow-up period clinic visit. Subjects were analysed according to the actual treatments received during the maintenance period. This population was used to produce additional safety displays of long-term follow-up period data.

The PDVF Genotypic and Phenotypic populations consisted of all subjects in the ITT-E population with available On-treatment genotypic and phenotypic resistance data, respectively, at time of protocol defined virologic failure. These populations were used for analysis of On-treatment and treatment-emergent genotype and phenotype.

The Extension Switch population included all subjects randomized to the oral 30 mg + ABC/3TC arm who switched to and received at least one dose of the optimized IM dosing regimen of their choice (either Q8W or Q4W) in the Extension Period. The Extension Switch population was used to evaluate safety and efficacy of the optimized IM dosing regimens during the Extension Period.

The PDVF Genotypic and Phenotypic Extension Switch population consisted of all subjects in the Extension Switch population with available on-treatment genotypic and phenotypic resistance data, respectively, at time of protocol defined virologic failure during the Extension Period. This population was used for analysis of Extension Period on-treatment and treatment-emergent genotype and phenotype.

The Per Protocol Extension Switch Population (PP-ES) consisted of subjects in the Extension Switch population with protocol deviations on or after the first administration of IM loading dose (Week 100). This population was used for a supporting analysis of the Week 128 interim and the Week 160 endpoints. Such a supporting analysis will not be performed if the PP- ES Population comprises more than 95% of the Extension Switch Population.

Comparability between the Q8W and Q4W response rates was also assessed using a Bayesian Probability model. This analysis assumed a non-informative Beta (1,1) prior distribution for each IM regimen response rate. The posterior probability that the absolute treatment difference was less than 10% was calculated. A posterior probability >90% was pre-specified as the weight of statistical evidence necessary to conclude that the two IM dosing regimens are equivalent in terms of maintenance of virologic suppression.

An Independent Data Monitoring Committee (IDMC) reviewed interim analysis results at Day 1 (all subjects completing the induction period) and Week 24 (~50% of subjects completing Week 24 of the maintenance period). All available data was included in the interim analyses, including data beyond the designated time point except for the Day 1 analysis, which only included data from the Induction Period. The purpose of these planned analyses was to evaluate the efficacy, safety and tolerability at early time points in the study, with the possibility to discontinue a suboptimal regimen before all subjects transitioned to the Maintenance Period of the study. The sponsor was blinded to the Week 24 interim analysis. Continuous monitoring of protocol defined virologic failure was also performed.

This interim analysis schedule did not require an adjustment for multiplicity since there was no possibility of a false positive finding at any of the interim analyses conducted before Week 32, and since the Week 48 and 96 analyses were used to further characterise the long-term safety and efficacy profile of CAB. As no hypothesis was tested for rejection during the constant monitoring of virologic response, no adjustment for multiplicity was performed.

Summary:

Results presented represent the Week 160 analysis

Demographics: Subject disposition is provided below.

Table: Summary of Subject Accountability: Maintenance and Extension Period Conclusion Records (ITT-ME and Extension Switch Populations)

	Randomized			Optimized		
	Q8W IM[d] (N=115)	Q4W IM[e] (N=115)	IM Total (N=230)	Q8W IM[f] (N=34)	Q4W IM[g] (N=10)	IM Total (N=44)
Completion Status, n (%)						
Completed Maintenance Period[a]	110 (96)	101 (88)	211 (92)	-	-	-
Prematurely discontinued Maintenance Period	5 (4)	14 (12)	19 (8)	-	-	-
Prematurely discontinued Extension Period	3 (3)	7 (6)	10 (4)	1 (3)	1 (10)	2 (5)
Ongoing at time of analysis	104 (90)	94 (82)	198 (86)	33 (97)	9 (90)	42 (95)
Primary[b]/subreason[c] for withdrawal, n (%)						
Adverse Event	1 (<1)	12 (10)	13 (6)	0	1 (10)	1 (2)
Lack of efficacy	1 (<1)	0	1 (<1)	1 (3)	0	1 (2)
Protocol defined virologic failure	1 (<1)	0	1 (<1)	-	-	-
Insufficient viral load response	-	-	-	1 (3)	0	1 (2)
Protocol Specified Withdrawal Criterion Met		1 (<1)	1 (<1)	-	-	-
Subject met the GSK defined Liver chemistry stopping criteria		1 (<1)	1 (<1)	-	-	-
Protocol deviation	1 (<1)	3 (3)	4 (2)	-	-	-
Prohibited medication use	0	1 (<1)	1 (<1)	-	-	-
Non-compliance with protocol procedures	1 (<1)	1 (<1)	2 (<1)	-	-	-
Pregnancy	0	1 (<1)	1(<1)	-	-	-
Withdrawal by subject	4 (3)	4 (3)	8 (3)	-	-	-
Subject relocated	2 (2)	2 (2)	4 (2)	-	-	-
Intolerability of injections	1 (<1)	0	1 (<1)	-	-	-
Frequency of visits	1 (<1)	1 (<1)	2 (<1)	-	-	-
Burden of travel or lack of access to travel	1 (<1)	0	1 (<1)	-	-	-
She does not want to continue participating in the study due to pain in the injection site that makes walking difficult	0	1 (<1)	1 (<1)	-	-	-
Subject was incarcerated	1 (<1)	0	1 (<1)	-	-	-
Lost to follow-up	0	1 (<1)	1 (<1)	-	-	-
Physician decision	1 (<1)	0	1 (<1)	-	-	-
Patient decided to initiate medically assisted procreation. Thus, he should withdraw from protocol. Nonetheless, patient will go into the	1 (<1)	0	1 (<1)	-	-	-

	Randomized			Optimized		
	Q8W IM[d] (N=115)	Q4W IM[e] (N=115)	IM Total (N=230)	Q8W IM[f] (N=34)	Q4W IM[g] (N=10)	IM Total (N=44)
Long Term Followup Period.						

Note: All subjects received 20 weeks oral CAB in the Induction Period. At start of the Maintenance Period, eligible subjects were randomized to: Q8W IM, Q4W IM, or Oral CAB. Subjects randomized to Q8W/Q4W IM continued to receive their Maintenance Period IM dosing regimen in the Extension Period and are denoted as 'Randomized' in this table. Subjects who successfully completed 96 weeks of oral CAB in the Maintenance Period had the option of continuing study participation in the Extension Period by switching to an optimized IM dosing regimen of their choice and are denoted as 'Optimized' in this table. Data for subjects receiving oral comparator are not summarized.

a. 3 subjects from the randomized Q8W IM arm completed Maintenance and did not enter Extension
b. Subjects can have only one primary reason for withdrawal.
c. Subreasons may sum to more or less than 100%. Subjects may have more than one subreason underneath a single primary reason. Subjects are not required to indicate subreasons.
d. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)
e. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)
f. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during Extension
g. Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during Extension

Subject demographics characteristics for the Safety Population are provided below. In general, demographic characteristics were balanced across arms, with the exception of race/ethnicity. The majority of the subjects were white and male.

Table: Summary of Demographic Characteristics – Week 160 (ITT-ME Population)

	Randomized Treatment			Optimized Treatment	
Demographic Characteristic	Q8W IM[a] N=115	Q4W IM[b] N=115	Oral CAB[c] N=56	Q8W IM[d] N=34	Q4W IM[e] N=10
Age (yrs)					
Mean	36.4	36.8	35.6	35.9	39.4
Standard Deviation (SD)	10.95	9.70	10.18	9.47	11.66
Median	35.0	36.0	35.0	36.0	41.0
Min	20	19	19	19	21
Max	64	62	56	56	56
Sex, n (%)					
Female	8 (7)	6 (5)	10 (18)	6 (18)	2 (20)
Male	107 (93)	109 (95)	46 (82)	28 (82)	8 (80)
Weight (kg)					
Mean	75.6	75.6	74.8	76.7	73.0
Standard Deviation (SD)	12.33	12.62	16.90	18.57	14.06
Median	74.0	73.0	71.2	71.1	74.7
Min	52	51	48	56	54
Max	108	117	139	139	104
Body Mass Index (kg/m^2)					
n	115	114	56	34	10

Demographic Characteristic	Randomized Treatment			Optimized Treatment	
	Q8W IM[a] N=115	Q4W IM[b] N=115	Oral CAB[c] N=56	Q8W IM[d] N=34	Q4W IM[e] N=10
Mean	24.6	24.4	24.9	26.0	23.9
Standard Deviation (SD)	3.80	3.42	6.54	7.86	3.04
Median	23.8	24.1	23.3	23.5	24.3
Min	19	17	19	20	19
Max	35	37	62	62	30
Ethnicity, n (%)					
Hispanic / Latino	15 (13)	19 (17)	12 (21)	9 (26)	1 (10)
Not Hispanic / Latino	100 (87)	96 (83)	44 (79)	25 (74)	9 (90)
Race, n (%)					
Black or African American	17 (15)	12 (10)	15 (27)	10 (29)	3 (30)
American Indian or Alaskan Native	0	8 (7)	1 (2)	0	1 (10)
Asian-Central/South Asian Heritage	0	1 (<1)	0	0	0
Asian-Japanese Heritage	1 (<1)	0	0	0	0
Asian-South East Asian Heritage	1 (<1)	0	1 (2)	0	0
Native Hawaiian or Other Pacific Islander	1 (<1)	0	0	0	0
White-Arabic/North African Heritage	1 (<1)	4 (3)	1 (2)	1 (3)	0
White-White/Caucasian/European	92 (80)	90 (78)	38 (68)	23 (68)	6 (60)
Mixed Race	2 (2)	0	0	0	0

a. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks (Q8W)
b. Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks (Q4W)
c. Oral CAB: GSK744 30 mg + ABC/3TC once daily
d. Optimized Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 weeks during the Extension Period
e. Optimized Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 weeks during the Extension Period

Efficacy:

Primary Efficacy Analysis: At Week 160, 90% (Q8W IM arm) and 83% (Q4W IM) of subjects randomized to receive injectable dosing maintained virologic suppression (HIV-1 RNA <50 c/mL). At Week 160 (60 weeks of LA therapy), 97% (Optimized Q8W IM arm) and 100% (Optimized Q4W IM) of subjects who were randomized to receive oral CAB + 2 NRTIs and switched to an optimized injectable dosing regimen of their choice maintained virologic suppression (HIV-1 RNA <50 c/mL).

Across all arms, there were few virologic non-responders (HIV-1 RNA ≥50 c/mL) using the Snapshot (MSDF) algorithm through Week 160, with no virologic non-responders in the Q4W IM arm. The proportion of subjects with no virologic data in window was

higher in the Q4W IM arm (17%) compared to the Q8W IM arm (5%), driven by discontinuations due to AE/death or for other non-virologic reasons.

Table: Summary of Study Outcomes (<50 c/mL) at Week 160 – Snapshot (MSDF) Analysis (Randomized Q8W/Q4W)

Outcome	Q8W IM[a] N=115 n (%)	Q4W IM[b] N=115 n (%)	IM Total N=230 n (%)
HIV-1 RNA <50 c/mL, n (%)	**104 (90)**	**95 (83)**	**199 (87)**
HIV-1 RNA ≥50 c/mL, n (%)	**5 (4)**	**0**	**5 (2)**
Data in window not below threshold	1 (<1)	0	1 (<1)
Discontinued for lack of efficacy	1 (<1)	0	1 (<1)
Discontinued for other reason while not below threshold	3 (3)	0	3 (1)
No Virologic Data at Week 160 Window	**6 (5)**	**20 (17)**	**26 (11)**
Discontinued due to AE or Death	1 (<1)	12 (10)	13 (6)
Discontinued for Other Reasons	5 (4)	8 (7)	13 (6)

c. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Table: Summary of Study Outcomes (<50 c/mL) at Week 160 – Snapshot (MSDF) Analysis (Extension Switch Population)

Outcome	Optimized Q8W IM[a] N=34 n (%)	Optimized Q4W IM[b] N=10 n (%)	Total Optimized IM N=44 n (%)
HIV-1 RNA <50 c/mL, n (%)	33 (97)	10 (100)	43 (98)
HIV-1 RNA ≥50 c/mL, n (%)	1 (3)	0	1 (2)
Discontinued for lack of efficacy	1 (3)	0	1 (2)
No Virologic Data at Week 160 Window	0	0	0

a. Optimized Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 weeks during the Extension Period
b. Optimized Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 weeks during the Extension Period

Secondary Efficacy Analysis:

There were three subjects with PDVF, defined as confirmed viral load >200 c/mL, through 160 weeks of maintenance treatment (no additional PDVFs between the Week 48 and Week 160 analysis time points).

In evaluating the proportion of subjects with plasma HIV-1 RNA <50 c/mL by visit, a sustained antiviral response was observed across all arms through Week 160 of the Extension Period, with higher response rates noted for the Q8W IM arm compared to the Q4W IM arm at most time points assessed (90% Q8W and 83% Q4W). In the Extension

Period, the optimized IM arms demonstrated a strong antiviral response (97% optimized Q8W and 100% optimized Q4W).

The majority of subjects maintained HIV-1 RNA <200 c/mL through Week 160 of the study (Week 160: Q8W 91%, Q4W 83%, Optimized Q8W 97%, Optimized Q4W 100%). Two subjects (2%) in the Q8W arm had HIV-1 RNA ≥200 c/mL at Week 160, compared to no subjects in either the Q4W or the optimized IM arms.

At Week 160, the mean change from Baseline in plasma HIV-1 RNA was -2.76 $\log_{10}$ c/mL (SD: 0.617) and -2.89 $\log_{10}$ c/mL (SD: 0.726) in the Q8W and Q4W IM arms, respectively. There was minimal or no difference in this change from Baseline through 160 weeks of therapy. In the optimized IM arms there was little to no change from Extension Baseline.

An increase in CD4+ from Baseline was observed across all arms except the optimized Q8W arm which displayed minimal decrease. At Week 160, the mean change from Baseline in CD4+ was 308.6 cells/mm^3 (SD: 224.80) and 315.0 cells/mm^3 (SD: 250.56) in the Q8W and Q4W IM arms, respectively. In the optimized IM arms, the mean change from Extension Baseline in CD4+ was -17.2 cells/mm^3 (SD: 263.57) and 50.2 cells/mm^3 (SD: 193.24) in the optimized Q8W and optimized Q4W IM arms.

Disease progression was defined as HIV-associated conditions, AIDS, and death. Between randomized IM dosing arms, there were no real differences or trends in the number of subjects with newly diagnosed HIV-associated conditions in the Q8W arm in comparison to the Q4W arm. Since Week 96, one death (myocardial infarction) occurred in the Q4W. There were no newly diagnosed HIV-associated conditions in the optimized IM arms. Overall, the progression of HIV disease was low. Four subjects in Q8W IM arm progressed from class A to class C (Kaposi's sarcoma, Pneumonia, Herpes simplex [n=2]) and 2 subjects in Q4W IM arm progressed from a class A to Death. No subjects displayed a progression of HIV disease in the optimized IM arms.

Safety:

Adverse Events:

Overall, in the Maintenance and Extension Periods, injection site pain (97% of subjects) was the most commonly reported AE from Day 1 in the randomized IM dosing arms. Other commonly reported injection site reactions (ISRs) included injection site nodule (34% of subjects) and injection site swelling (31% of subjects). The most commonly reported non-ISR events included nasopharyngitis (38%), diarrhoea (22%), and headache (22%) across both randomized IM dosing arms. There were no clear differences in incidence of AEs suggesting a regimen-specific trend. During the Extension Period, injection site pain (84% of subjects) was the most commonly reported AE through 60 weeks of LA therapy in the optimized IM arms. Other commonly reported ISRs included injection site nodule (27% of subjects) and injection site swelling (16% of subjects). The most commonly reported non-injection site AEs included nasopharyngitis (14%), back pain (11%), and influenza (11%) across both optimized IM dosing arms. The sample size was insufficient to make a meaningful comparison of the relative frequency or severity of AEs in the Extension Switch Population.

Table: Summary of All Common Maintenance and Extension Period On-treatment Adverse Events by Overall Frequency – Randomized Q8W/Q4W (Safety Maintenance Population)

Preferred Term	Q8W IM[a] (N=115) n (%)	Q4W IM[b] (N=115) n (%)	IM Total (N=230) n (%)
Any event	115 (100)	115 (100)	230 (100)
Injection site pain	110 (96)	113 (98)	223 (97)
Nasopharyngitis	41 (36)	46 (40)	87 (38)
Injection site nodule	34 (30)	44 (38)	78 (34)
Injection site swelling	36 (31)	36 (31)	72 (31)
Injection site pruritus	29 (25)	36 (31)	65 (28)
Injection site induration	29 (25)	29 (25)	58 (25)
Injection site warmth	28 (24)	26 (23)	54 (23)
Diarrhoea	25 (22)	25 (22)	50 (22)
Headache	27 (23)	23 (20)	50 (22)
Upper respiratory tract infection	27 (23)	21 (18)	48 (21)
Syphilis	25 (22)	17 (15)	42 (18)
Gastroenteritis	19 (17)	18 (16)	37 (16)
Injection site bruising	22 (19)	15 (13)	37 (16)
Influenza	15 (13)	21 (18)	36 (16)
Injection site erythema	15 (13)	21 (18)	36 (16)
Back pain	14 (12)	18 (16)	32 (14)
Pyrexia	16 (14)	16 (14)	32 (14)
Bronchitis	14 (12)	15 (13)	29 (13)
Pharyngitis	13 (11)	15 (13)	28 (12)
Arthralgia	15 (13)	11 (10)	26 (11)
Cough	10 (9)	15 (13)	25 (11)
Anogenital warts	8 (7)	13 (11)	21 (9)
Insomnia	12 (10)	9 (8)	21 (9)
Fatigue	8 (7)	12 (10)	20 (9)
Rhinitis	8 (7)	12 (10)	20 (9)
Gonorrhoea	13 (11)	6 (5)	19 (8)
Abdominal pain	8 (7)	10 (9)	18 (8)
Anxiety	10 (9)	8 (7)	18 (8)
Myalgia	9 (8)	9 (8)	18 (8)
Influenza like illness	5 (4)	12 (10)	17 (7)
Sinusitis	8 (7)	9 (8)	17 (7)
Nausea	7 (6)	9 (8)	16 (7)
Oral herpes	5 (4)	11 (10)	16 (7)
Oropharyngeal pain	7 (6)	9 (8)	16 (7)
Respiratory tract infection	6 (5)	10 (9)	16 (7)
Conjunctivitis	9 (8)	6 (5)	15 (7)
Depression	7 (6)	8 (7)	15 (7)
Pain in extremity	6 (5)	9 (8)	15 (7)

2.7.6 Synopses of Individual Studies

Preferred Term	Q8W IM[a] (N=115) n (%)	Q4W IM[b] (N=115) n (%)	IM Total (N=230) n (%)
Toothache	7 (6)	7 (6)	14 (6)
Vomiting	7 (6)	7 (6)	14 (6)
Asthenia	4 (3)	9 (8)	13 (6)
Constipation	4 (3)	9 (8)	13 (6)
Haemorrhoids	5 (4)	8 (7)	13 (6)
Hypertension	8 (7)	5 (4)	13 (6)
Proctitis	7 (6)	6 (5)	13 (6)
Pruritus	5 (4)	8 (7)	13 (6)
Rash	5 (4)	8 (7)	13 (6)
Seasonal allergy	9 (8)	4 (3)	13 (6)
Dizziness	4 (3)	8 (7)	12 (5)
Herpes zoster	5 (4)	7 (6)	12 (5)
Rhinitis allergic	8 (7)	4 (3)	12 (5)
Tonsillitis	6 (5)	6 (5)	12 (5)
Urethritis	3 (3)	9 (8)	12 (5)
Urinary tract infection	7 (6)	5 (4)	12 (5)
Abdominal pain upper	7 (6)	4 (3)	11 (5)
Chlamydial infection	8 (7)	3 (3)	11 (5)
Injection site discolouration	5 (4)	6 (5)	11 (5)
Contusion	4 (3)	6 (5)	10 (4)
Gastrooesophageal reflux disease	3 (3)	7 (6)	10 (4)
Subcutaneous abscess	4 (3)	6 (5)	10 (4)
Hypercholesterolaemia	3 (3)	6 (5)	9 (4)
Injection site haematoma	3 (3)	6 (5)	9 (4)
Oropharyngeal gonococcal infection	8 (7)	1 (<1)	9 (4)
Vitamin D deficiency	7 (6)	1 (<1)	8 (3)
Chest pain	1 (<1)	6 (5)	7 (3)
Musculoskeletal pain	1 (<1)	6 (5)	7 (3)
Odynophagia	2 (2)	5 (4)	7 (3)
Tooth infection	0	6 (5)	6 (3)

Note: AEs reported in this table are those with ≥5% overall incidence in any arm. Included all Maintenance and Extension period adverse events.

d. Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks
Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks

Table: Summary of All Extension Period On-treatment Adverse Events by Overall Frequency (Extension Switch Population)

Preferred Term	Optimized Q8W IM[a] (N=34) n (%)	Optimized Q4W IM[b] (N=10) n (%)	Optimized IM Total (N=44) n (%)
Any event	**34 (100)**	**9 (90)**	**43 (98)**
Injection site pain	29 (85)	8 (80)	37 (84)
Injection site nodule	9 (26)	3 (30)	12 (27)
Injection site swelling	5 (15)	2 (20)	7 (16)
Nasopharyngitis	2 (6)	4 (40)	6 (14)
Back pain	3 (9)	2 (20)	5 (11)
Influenza	3 (9)	2 (20)	5 (11)
Injection site induration	3 (9)	1 (10)	4 (9)
Upper respiratory tract infection	3 (9)	1 (10)	4 (9)
Diarrhoea	2 (6)	1 (10)	3 (7)
Gastroenteritis	3 (9)	0	3 (7)
Gastroenteritis viral	2 (6)	1 (10)	3 (7)
Pain in extremity	3 (9)	0	3 (7)
Pharyngitis	3 (9)	0	3 (7)
Syphilis	2 (6)	1 (10)	3 (7)
Toothache	3 (9)	0	3 (7)
Arthralgia	1 (3)	1 (10)	2 (5)
Chlamydial infection	1 (3)	1 (10)	2 (5)
Cough	0	2 (20)	2 (5)
Dizziness	1 (3)	1 (10)	2 (5)
Fungal infection	1 (3)	1 (10)	2 (5)
Injection site erythema	2 (6)	0	2 (5)
Injection site pruritus	2 (6)	0	2 (5)
Injection site warmth	2 (6)	0	2 (5)
Insomnia	2 (6)	0	2 (5)
Paraesthesia	1 (3)	1 (10)	2 (5)
Pneumonia	1 (3)	1 (10)	2 (5)
Sciatica	2 (6)	0	2 (5)
Tinea versicolour	2 (6)	0	2 (5)
Urethritis gonococcal	2 (6)	0	2 (5)
Viral infection	2 (6)	0	2 (5)
Anxiety	0	1 (10)	1 (2)
Asthenia	0	1 (10)	1 (2)
Candida infection	0	1 (10)	1 (2)
Contusion	0	1 (10)	1 (2)
Dermal cyst	0	1 (10)	1 (2)
Eczema nummular	0	1 (10)	1 (2)
Epididymitis	0	1 (10)	1 (2)
Eye contusion	0	1 (10)	1 (2)

Preferred Term	Optimized Q8W IM[a] (N=34) n (%)	Optimized Q4W IM[b] (N=10) n (%)	Optimized IM Total (N=44) n (%)
Eye pain	0	1 (10)	1 (2)
Gastrooesophageal reflux disease	0	1 (10)	1 (2)
Hypoaesthesia	0	1 (10)	1 (2)
Ligament injury	0	1 (10)	1 (2)
Lipase increased	0	1 (10)	1 (2)
Migraine	0	1 (10)	1 (2)
Night sweats	0	1 (10)	1 (2)
Palpitations	0	1 (10)	1 (2)
Plantar fasciitis	0	1 (10)	1 (2)
Pulpitis dental	0	1 (10)	1 (2)
Respiratory tract infection	0	1 (10)	1 (2)
Rhabdomyolysis	0	1 (10)	1 (2)
Skin hyperpigmentation	0	1 (10)	1 (2)
Somnolence	0	1 (10)	1 (2)
Testicular pain	0	1 (10)	1 (2)
Viral upper respiratory tract infection	0	1 (10)	1 (2)

e. Optimized Q8W IM: GSK744 LA 600 mg + TMC278 LA 900 mg IM every 8 Weeks during the Extension Period
Optimized Q4W IM: GSK744 LA 400 mg + TMC278 LA 600 mg IM every 4 Weeks during the Extension Period

During the Maintenance and Extension Periods, the majority of events reported were considered Grade 2 or Grade 3 in maximum intensity in the randomized IM arms. The number of Grade 3 events was driven by General disorders and administration site conditions (18/50 Grade 3 events, 36%), Infections and infestations (9/50 Grade 3 events, 18%) and Psychiatric disorders (9/50 Grade 3 events, 18%). In the optimized IM arms, the majority of events reported were considered Grade 1 or Grade 2 in maximum intensity and were driven primarily by ISRs. There was only 1 maximum Grade 4 AE (optimized Q4W, lipase increase).

In the randomized IM arms, the most commonly reported non-ISR drug-related (per investigator) AEs included pyrexia (5%), headache (3%), fatigue (3%) and influenza like illness (3%) across both IM dosing arms. There were no clear differences in incidence of drug-related AEs suggesting a regimen-specific trend. The most commonly reported drug-related (per investigator) AEs, excluding ISRs, in the optimized IM arms included asthenia, fatigue, musculoskeletal stiffness and palpitations, each occurring as isolated events only. The sample size and numbers of events was insufficient to allow any comparison of the relative frequency of drug-related AEs in the Extension Switch Population.

Through Week 160, 17 (15%) and 21 (18%) subjects reported an SAE in the randomized Q8W and Q4W IM arms, respectively. Most events occurred as single events in either arm (with the exception of suicidal attempt, intravertebral disc protrusion and overdose) with no demonstrated trends per study arm. In the optimized IM arms, 2 (5%) subjects reported a SAE.

Through 160 weeks of treatment there was only one drug-related serious adverse event (SAE) reported in a subject in the randomised Q4 arm (Myocardial Infarction). There were no drug-related SAEs reported in the optimized IM arms during the Extension Period.

Two deaths, both in the randomized Q4W arm, were reported in this study in the Maintenance and Extension periods through the Week 160 data cutoff. One subject, a 4[redacted]-year-old male found deceased at home due to a suspected myocardial infarction (Long-term Follow-up [LTFU] Day 18, 1117 days after first dose of study drug). The investigator considered that a causal relationship to study drugs could not be excluded, despite 3 years of drug exposure, although underlying disease provided a possible explanation. Another subject, a 3[redacted]-year-old male died due to refractory epilepsy. Forty-eight weeks following initial CAB administration and 32 weeks following initial RPV administration, the subject developed acute onset status epilepticus lasting for approximately six hours while alone in his apartment, leading to anoxic brain injury and death. While an association with IP cannot be fully excluded in this case, the time to onset, lack of any prodromal symptoms, and acute presentation around the time of known or suspected recreational drug use, led to a conclusion that it is not reasonably likely that IP was causally linked with the seizure in this subject.

The proportion of AEs leading to withdrawal during the Maintenance and Extension periods was low across all randomized IM arms (Q8W IM: n=3, 3%; Q4W IM: n=12, 10%). With the exception of injection site pain, all other individually reported AE preferred terms resulting in withdrawal had an incidence of one subject in any arm. In the optimized IM arms, injection site pain (optimized Q4W) was the only adverse event that led to withdrawal or permanent discontinuation of the investigational product in this population subset in the Extension Period.

A total of 6361 ISR events were reported during the Maintenance and Extension Periods, of which nearly all were classified as either mild (Grade 1: 85%) or moderate (Grade 2: 14%), with <1% of reactions classified as severe, with a similar distribution in each IM arm. Eight subjects (Q8W) had ISRs leading to withdrawal while no subjects withdrew due to ISRs in the Q4W IM arm. There were no other major differences between the randomized IM arms. The median duration of overall ISR events was 3 days in each dosing arm, with duration for specific ISR events ranging from 1 day to 713 days across both arms. A total of 401 ISR events were reported during the Extension Period for the optimized IM arms, of which nearly all were classified as either mild (Grade 1: 81%) or moderate (Grade 2: 17%), with 2% of reactions classified as severe, with a similar distribution in each IM arm. Two subjects (optimized Q4W) had ISRs leading to withdrawal. The median duration of overall ISR events was 3 days in each dosing arm, with duration for specific ISR events ranging from 1 day to 102 days across both arms.

During the Maintenance and Extension Periods, overall rates of any treatment emergent graded lab abnormalities from Day 1 reported by maximum toxicity were similar between the randomized IM arms, 94% (Q8W) vs. 97% (Q4W). When analyzed by grade, Q8W had a higher rate of Grade 2 (Q8W: 49 [43%]; Q4W: 41 [36%]) laboratory abnormalities, and Q4W had higher rates of Grade 3 (Q8W: 15 [13%]; Q4W: 28 [24%]) abnormalities. Grades 1 and 4 abnormalities were similar between the randomized arms. During the Extension Period, the overall rate of any treatment emergent graded lab abnormalities from Week 100 reported by maximum toxicity was 77% in the optimized IM arms. Most laboratory abnormalities were Grade 1, 30%, and Grade 2, 39% with few Grade 3/4 abnormalities between the two optimized IM arms.

Since Week 96, 2 subjects (both randomized Q8W arm) met liver stopping criteria. One subject, male, within the age range of 20-30 years, was withdrawn from the study. This subject had a Grade 1 AE of Hepatitis C, not related to study drug. The other subject, a 50 to 60-year-old male, who met liver stopping criteria had a Grade 4 AE of ischemic hepatitis. The AE was considered serious, and not related to study drug. The ischaemic hepatitis was secondary to urological sepsis. The subject's dose was not changed due to this AE. The summary of subjects meeting liver stopping criteria throughout the study (from Baseline/Week -20 to the Week 160 analysis) can be found in the table below.

Table: Summary of Subjects Meeting Liver Stopping Criteria Since Induction Baseline

Subj	ALT ULN	AST ULN	Bili ULN	Comment	Study Withdrawal? Reason
CAB: not randomized but received oral CAB during Induction Period					
[redacted]	7xULN	11xULN	2xULN	Week 4 onset, Patient with Chronic active hepatitis C and Grade 3 or 4 fibrosis Probable DILI	Y, Liver Stopping Criteria
[redacted]	10xULN	8xULN	WNL	Acute HCV Unlikely DILI	Y, Liver Stopping Criteria
[redacted]	18xULN	11xULN	1xULN	Second acute HCV infection Unlikely DILI	Y, Liver Stopping Criteria
CAB: oral during Maintenance Period					
[redacted]	8xULN	5xULN	WNL	Acute HCV Unlikely DILI	Y Liver Stopping Criteria
[redacted]	9xULN	6.4xULN	WNL	Probable DILI	Y, not possible to exclude CAB as a possible contributing factor. Underlying hepatic steatosis is a possible risk factor.
CAB: Q4W IM					
[redacted]	7.8xULN	3xULN	WNL	Hepatitis / syphilis Unlikely DILI	N

Subj	ALT ULN	AST ULN	Bili ULN	Comment	Study Withdrawal? Reason
[redacted]	11xULN	6xULN	0.6xULN	Acute HCV Unlikely DILI	Subject discontinued IM regimen and is being followed on study in the long-term follow up period.
[redacted]	9.4xULN	9.9xULN	1.8xULN	Acute HCV Unlikely DILI	N, transaminases stabilized. VSLC decision to continue treatment and monitor closely.
[redacted]	10xULN	5.9xULN	WNL	Acute HCV Unlikely DILI	Y, Liver Stopping Criteria
[redacted]	13.2 xULN	8.9 xULN	0.8 xULN	Acute HCV, Unlikely DILI	N, being monitored on study
CAB: Q8W IM					
[redacted]	25.3 xULN	13.5 xULN	0.7 xULN	Acute HCV, Syphilis Reinfection Unlikely DILI	N, being monitored on study
[redacted]	13.4x ULN	11.5xULN	1.2 x ULN	Acute HCV Unlikely DILI	N, being monitored on study
[redacted]	8.3xULN	2.7xULN	WNL	Acute HCV Unlikely DILI	N, being monitored on study
[redacted]	5.5xULN	3.1xULN	WNL	Hepatitis C Unlikely DILI	Y, Liver Stopping Criteria
[redacted]	WNL	-	WNL	Ischemic Hepatitis Unlikely DILI	N, being monitored on study

WNL=within normal limits
DILI=Drug induced liver injury
VSLC=ViiV Safety and Labelling Committee

Change from Baseline in ECG parameters at Week 160 were similar between the randomized IM arms and the optimized IM arms. None of the changes over time including mean heart rate, QRS duration, QTc, QTcB, QTcF, PR or RR interval were clinically significant.

Pharmacokinetics:

Subjects randomized on Day 1 to CAB LA + RPV LA continued their Q8W or Q4W regimens through Week 96. Based on the Week 48 assessments in this study, steady state was established for CAB and RPV by Week 40 or earlier for both LA regimens. In the ATLAS study (201585), with monthly CAB LA + RPV LA dosing, steady state was confirmed for CAB by Week 44 but was not confirmed for RPV by Week 48 primary endpoint. Visual inspection of the concentration data collected between Week 56 and Week 96 in this study suggested some ongoing accumulation in the second year of LA treatment. Although steady state was not reassessed, trough concentrations appeared to have plateaued by Week 96.

Twenty-four subjects who withdrew from the study for any reason entered into the long-term follow up phase. PK data were available in 14 subjects (13 male, 1 female) who entered LTFU, and 12 subjects completed the 12-month follow-up period at the time of the data cut for this report. Four (33%) of 12 subjects (3/11 or 27% of males) completing the 12-month follow-up period had measurable CAB concentrations (all below the PA-IC_{90}) and 48 to 60 weeks following the final injection. This is consistent with observations following discontinuation of CAB LA 800 mg IM Q12W x 3 doses or 600 mg IM Q8W x 5 doses in healthy males, 40% of whom had measurable CAB concentrations 48-weeks following the final injection and 23% of whom had measurable CAB concentrations 60-weeks following the final injection. In that same study, CAB concentrations were measurable in 76% of females 48-weeks following the final injection and in 63% of females 60-weeks following the final injection. The only female with LTFU PK data in this study had measurable CAB at the 12-month follow-up visit which occurred 60-weeks following the final injection. In another study, 17% of healthy male subjects receiving CAB LA 800 mg IM Q12W x 3 doses had measurable CAB 52-weeks following the final injection visit.

Twelve of 12 subjects completing the 12-month follow-up period in this study had measurable RPV concentrations, 6 of which were greater than the in vitro PA-IC_{90}.

These HIV infected subjects were switched to appropriate oral ART regimens upon discontinuation of LA treatment. The impact of potential CYP3A and/or UGT1A1 inhibitors included in ART regimens on the PK profiles observed during the follow-up phase is unknown.

Of note, the female who entered into the LTFU period was exposed to therapeutic CAB and RPV concentrations throughout her pregnancy. She delivered a healthy baby during the follow-up phase of the study.

Pharmacogenetics:

UGT1A1 reduced-function polymorphisms were significantly associated with CAB PK parameters in HIV-infected patients who received CAB by LA IM administration ($p<0.05$). The UGT1A1 polymorphisms, UGT1A1*28 and *6, have been reported to result in decreased enzymatic activity by approximately 70%. There was 1.2-fold vs. 1.38-fold difference in mean steady-state CAB PK parameter values between subjects with low versus normal predicted UGT1A1 activity following CAB LA Q4W/Q8W and oral CAB administration in 200056, respectively, which was similar to the overall impact of 1.3- to 1,5-fold observed following oral CAB in healthy and HIV infected subjects combined. In addition, the impact of UGT1A1 genotypes on CAB LA PK parameters was smaller than that observed for oral CAB dosing, which may indicate that LA sustained drug delivery can blunt the impact from UGT1A1 genetic variation.

Conclusions:

Efficacy:

- Both IM dosing regimens of CAB LA + RPV LA continued to demonstrate strong antiviral activity through 160 weeks of treatment in virologically suppressed patients.
- At Week 160, subjects randomized to receive injectable dosing at Day 1, maintained virologic suppression (HIV-1 RNA <50 c/mL). Subjects receiving injectable dosing at Week 100, after 96 weeks of oral therapy with CAB and NRTIs, maintained virologic suppression (HIV-1 RNA <50 c/mL).
- There were no snapshot virologic failures in the Q4W treatment arm. The proportion of subjects with no virologic data in window was higher in the Q4W IM arm (17%) compared to the Q8W IM arm (5%) driven by discontinuations due to AE/death or for other non-virologic reasons.
- Regarding increases in mean CD4+ cell count from Baseline, a good response continued to be observed across all arms with no significant differences between arms.

Safety:

- Over 160 weeks, the safety data from this randomized, open-label Phase IIb study is favorable and consistent with other Phase II and ongoing III trials. No new AEs of clinical concern were observed.
- CAB LA + RPV LA continues to be well tolerated through Week 160 for both the Q8W and Q4W dosing regimens, as demonstrated by a low number of discontinuations due to AEs (5 since Week 96), including ISR related AEs in either dosing arm, with no significant trends in safety parameters.
- Few subjects reported an SAE in the study during the Maintenance and Extension Periods. Most events occurred as single events (with the exception of suicidal attempt, intravertebral disc protrusion and overdose) with no demonstrated trends per study arm.
- After 160 weeks of treatment in the study, there has been a single drug-related SAE reported (myocardial infarction, fatal outcome). The investigator considered that a causal relationship to study drugs could not be excluded, despite 3 years of drug exposure, although underlying disease provided a possible explanation. An autopsy was performed but results have not been made available to the study
- The proportion of AEs leading to withdrawal during the Maintenance and Extension periods was low across all IM arms. Except for injection site pain, all other individually reported AEs resulting in withdrawal had an incidence of one subject in any arm.

- Two additional subjects met liver stopping criteria since the Week 96 analysis (acute hepatitis C and ischemic hepatitis), with one of these subjects withdrawing from the study (acute hepatitis C). Neither subject was considered to have had DILI.

- The majority of ISRs were mild or moderate in severity and resolved within a median of 3 days. There have been no additional withdrawals due to ISRs since Week 32 in the randomized IM arms. One subject in the optimized IM arms withdrew due to ISRs (injection site pain).

- During the Maintenance and Extension Periods, two deaths was reported (epilepsy (not considered study drug related) and myocardial infarction (as noted above).

Virology:

- No additional PDVFs have been identified since the Week 48 analysis.

Pharmacokinetics:

- Steady state conditions appeared to have been reached for both CAB and RPV by 96-weeks of CAB LA + RPV LA administration.

- Of the 12 subjects who completed the long-term follow-up phase, 4 had measurable plasma CAB concentrations and 12 had measurable plasma RPV concentrations one year after discontinuing LA injections.

Pharmacogenetics:

- *UGT1A1* reduced function polymorphisms modestly increased CAB PK parameters in HIV-infected patients who received CAB by oral or IM injection administration. There was approximate 1.2-fold difference in mean CAB LA PK parameter values between patients with low versus normal predicted UGT1A1 activity, which is lower than that observed with oral CAB.

- Based on the accumulated safety profile of CAB, individuals with UGT1A1 reduced function polymorphisms do not require dose adjustment for either oral or LA CAB administration.

Effective Date: [redacted]

Synopsis for Study 200056 CSF Substudy

Name of company: GlaxoSmithKline Research & Development Limited

Name of finished product: Not available/Not known at the time of this report

Name of active substance: GSK1265744 (Cabotegravir) and GSK13229758 or TMC278 (Rilpivirine)

Study Number: 200056

Title: An assessment of the Pharmacokinetics (PK) of Cabotegravir (CAB) and Rilpivirine (RPV) in the Plasma and Cerebrospinal Fluid (CSF) following LA Intramuscular Administration in Subjects Currently Enrolled into the LATTE-2 Phase 2b Study

A Country Specific Amendment to LATTE-2 (200056): A Phase IIb Study Evaluating a Long-Acting Intramuscular Regimen of GSK1265744 plus TMC278 for the Maintenance of Virologic Suppression Following an Induction of Virologic Suppression on an Oral regimen of GSK1265744 plus Abacavir/Lamivudine in HIV-1 Infected, Antiretroviral Therapy-Naive Adult Subjects

Investigator(s):

This was a multicenter study; 6 investigators screened and enrolled subjects to 200056 CSF sub-study.

Study center(s):

This sub-study was conducted at 6 centers in the United States.

Publication(s):

Margolis DA, Gonzalez-Garcia J, Stellbrink HJ, Eron JJ, Yazdanpanah Y, Podzamczer D, Lutz T, Angel JB, Richmond GJ, Clotet B, Gutierrez F. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. The Lancet. 2017; 390(10101):1499-1510

Study Period: 31 Oct 2017 - 21 Feb 2018

Phase of Development: IIb

Objectives:

1. To determine plasma (total and unbound) and cerebrospinal fluid [CSF (total)] cabotegravir (CAB) concentrations and evaluate the relationship between CAB concentrations in plasma and CSF following long-acting (LA) administration.

2. To determine plasma (total) and CSF (total) rilpivirine (RPV) concentrations and evaluate the relationship between RPV concentrations in plasma and CSF following LA administration.

3. To assess human immunodeficiency virus type 1 (HIV-1) RNA suppression in plasma and CSF.

4. To assess the relationship between the concentration of CAB and RPV in the CSF with HIV-1 RNA levels in the central nervous system (CNS), if applicable.

5. To assess the safety and adverse event (AE)-related events associated with this sub-study.

Methodology:

Study 200056 is a Phase IIb, randomized, multicenter, parallel group, open-label, three-part study (induction, maintenance and extension) conducted in HIV-1-infected, antiretroviral (ARV) treatment (ART)-naive adults. This study consists of a Screening Period, Induction Period, Maintenance Period, Extension Period, and a Long-term Follow-up Period (withdrawn intramuscular [IM] dosing regimen subjects only).

The CSF pharmacokinetic (PK) sub-study was conducted concurrently with the Extension Period of LATTE-2 with some additional visits for this sub-study. Sub-study visits were aligned with a scheduled injection visit during the Extension Period (which commenced after 96 weeks since the start of antiretroviral treatment) and one or two extra visits.

For subjects in every 8 weeks (Q8W) group of LATTE-2, an extra visit was required to obtain the screening information within 30 days prior to the next LATTE-2 injection visit. For subjects in every 4 weeks (Q4W) group of LATTE-2, the scheduled LATTE-2 visit was used as a screening visit for the CSF sub-study. The screening period was 30 days during which HIV-1 RNA levels, cluster of differentiation 4 (CD4) absolute cell count, complete blood count (CBC), differential count, and platelet count were obtained. If the CD4 assessment was conducted within 30 days of screening, the CD4 assessment was not repeated at the screening visit.

Subjects continued on their designated Extension Period IM dosing regimen (Q8W or Q4W dosing) during the CSF PK sub-study. After an injection visit as per LATTE-2 visit schedule, two time-matched PK samples (one from plasma and the other from CSF) were collected 7 days (±3 days) after an injection visit as per the schedule of events for the CSF PK sub-study to assess peak concentrations of CAB and RPV (CSF PK sub-study visit). The PK samples were simultaneously collected from plasma and CSF (via lumbar puncture [LP]) to assess total and unbound CAB and total RPV concentrations in plasma (2 mL of blood for CAB and 3 mL of blood for RPV), and total CAB (2 mL) and total RPV (2 mL) in CSF 7 days (±3 days) after an injection visit. Plasma PK samples were collected, processed, and stored at −80°C within 1 hour of CSF PK sample collection. The CSF PK analyses were performed after the last subject enrolled in the sub-study completed the CSF collection procedures.

Plasma HIV-1 RNA levels were assessed prior to the injection on Day 1. In addition, two samples were collected from plasma and in CSF (via LP) for the assessment of HIV-1 RNA levels using SuperLow assay 7 days (±3) after the injection visit. An Abbott Real-time HIV-1 RNA assay (LLOD=40 copies/mL[c/mL]) was done using the plasma sample. A validated single-copy analysis (SCA) with an HIV-1 SuperLow assay (by bioMONTR) was also used to measure HIV-1 RNA levels with a lower limit of detection (LLOD) of 2 c/mL.

Protocol waivers or exemptions were not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements were considered essential and were required for study conduct.

Eligible subjects at participating sites, where there were appropriate expertise and adequate facilities to perform LP, participated in the CSF PK sub-study. Subjects were considered to have completed the sub-study when they provided CSF and plasma samples at the time point detailed above and had a final follow up visit 2 weeks after the LP. A follow up phone call was conducted 2 weeks following the LP procedure to assess signs or symptoms suggesting complications related to the LP procedure. If during the phone call, the subject described any signs or symptoms that occurred within the preceding 2 weeks and that were not showing improvement, the subject was asked to return to clinic for a medical evaluation. A symptom directed physical examination and safety assessment were performed.

Number of subjects:

A maximum of 39 potential subjects enrolled at 6 Unites States (US) sites participating in LATTE-2 were eligible to participate in the sub-study. Out of 39 potential subjects, a total of approximately 20 sets of CSF-plasma samples (1 set of paired plasma and CSF samples per subject) were targeted to be obtained from the LP Visit for this CSF PK sub-study. If fewer than 8 subjects were enrolled in the Q4W group, additional eligible subjects could be enrolled from the Q8W group in order to have a total of 20 evaluable subjects across both dosing regimens.

Main criteria for inclusion:

Inclusion Criteria for CSF PK Sub-study

In addition to the inclusion criteria for Study 200056, subjects screened for the CSF PK sub-study must:

Have documented HIV-1 RNA levels <50 copies/mL prior to screening

Be willing to undergo LP as outlined in study evaluations

Exclusion Criteria for CSF PK Sub-study

In addition to the exclusion criteria for Study 200056, subjects meeting any of the following criteria were **not** enrolled in the CSF PK sub-study:

Relative or absolute contraindication to LP, such as current coagulopathy, thrombocytopenia (platelets <50,000/µL), hemophilia, or use of anticoagulant medication

Uncontrolled hypertension with systolic blood pressure (BP) >180 mmHg and diastolic BP >120 mmHg

Treatment administration:

Investigational Product	Strength and Packaging	Batch Numbers
CAB LA	200 mg/mL injectable suspension; 2 mL per vial	[redacted]; ; ;
RPV LA	300 mg/mL injectable suspension; 2 mL per vial	[redacted]; ;

Criteria for evaluation:

Endpoints for objective 1:

- Total CSF CAB concentration obtained 7 days (±3 days) after an injection visit
- Total and unbound plasma CAB concentration obtained at the same time point as the total CSF CAB concentration as detailed above
- Relationship between Total CAB concentration in plasma and Total CAB concentration in CSF obtained 7 days (±3 days) after an injection visit

Endpoints for objective 2:

- Total CSF RPV concentration obtained 7 days (±3 days) after an injection visit
- Total plasma RPV concentration obtained at the same time point as the total CSF RPV concentration as detailed above
- Relationship between Total RPV concentration in plasma and Total RPV concentration in CSF obtained 7 days (±3 days) after an injection visit

Endpoints for objective 3:

- Percent of CSF HIV-1 RNA levels <50 c/mL or <2 c/mL, or actual measurement (if available) from the LP visit
- Percent of Plasma HIV-1 RNA levels <50 c/mL or <2 c/mL, or actual measurement (if available) from the LP visit
- Relationship between plasma HIV-1 RNA and CSF HIV-1 RNA levels

Endpoint for objective 4:

- Relationship between maximum plasma concentration (C_{max}) of CAB and RPV and HIV-1 RNA levels in CSF using a SuperLow assay obtained 7 days (±3 days) after the injection visit

Endpoint for objective 5:

- Incidence and severity of AEs and laboratory abnormalities

Statistical methods:

Hypotheses

No formal hypothesis was tested. This study was designed to estimate CAB and RPV concentrations in plasma and CSF following LA intramuscular administration and determine the relationship between the concentrations in plasma and CSF.

Sample Size Considerations

This CSF PK sub-study was designed to assess the potential of CAB and RPV to enter the CSF compartment; no formal hypothesis was being tested and no formal calculation of power or sample size was done for this study. An estimation approach was used to describe the sub-study data.

Analysis Populations

Population	Definition / Criteria	Analyses Evaluated
CSF Screened	• All participants who signed the informed consent form to participate in this sub-study and were screened for eligibility	• Study Population
CSF Safety	• All screened participants who received Day 1 injection. • This population was based on the treatment the subject was already receiving.	• Safety
CSF Plasma Efficacy	• All participants in the CSF safety population who provided evaluable plasma efficacy results	• Efficacy in plasma
CSF Efficacy	• All participants in the CSF safety population who provided evaluable efficacy results in CSF	• Efficacy in CSF
CSF Plasma PK Concentrations	• All participants in the CSF Safety population who had at least 1 plasma PK assessment (Non-quantifiable [NQ] values were considered as non-missing values).	• PK Listing
CSF Plasma PK Parameters	• All participants in the CSF Safety population who had evaluable plasma PK parameters.	• PK parameter summary, figure
CSF LP Procedure	• All participants in the CSF Safety population who underwent lumbar puncture	• CSF LP listing
CSF	• All participants in the CSF Safety population who had at	• CSF PK and

Population	Definition / Criteria	Analyses Evaluated
Concentration	least 1 CSF sample collection	HIV-1 RNA listing
CSF Parameter	• All participants in the CSF Safety population who had at least 1 CSF sample with either evaluable PK or HIV-1 RNA assessment (Non-quantifiable [NQ] values were considered as non-missing values and were included in this population).	• CSF PK and HIV-1 RNA Summary
CSF PKPD Population	• All participants in the CSF parameters population with measurable PK parameter or HIV-1 RNA values	• PKPD correlation if needed.

Final Analysis

Efficacy Analyses

The number and proportion of subjects <50 c/mL, <2 c/mL and /or actual measured HIV-1 RNA levels in plasma or in CSF or HIV-1 RNA levels at screening, on Day 1 and at LP visit were summarized by treatment group.

The relationship between plasma HIV-1 RNA levels and CSF HIV-1 RNA levels at LP visit was evaluated with the CSF:plasma HIV -1 RNA <50 c/mL or <2 c/mL paired data. Percentages of subjects in each category were plotted by treatment and with the number of subjects as plasma HIV-1 RNA levels <50 c/mL or not (or <2 c/mL or not) vs number of the subjects who had CSF HIV-1 RNA levels <50 c/mL or not.

If both CSF and plasma HIV-1 RNA levels had actual measurable data, SAS PROC Corr was used to evaluate the correlation.

Safety Analyses

Adverse events analyses including the analysis of adverse events (AEs) collected from Day 1 to follow-up, serious adverse events (SAEs) collected from screening to follow-up were summarized by treatment and listed for each subject based on GlaxoSmithKline (GSK) Core Data Standards.

Laboratory evaluations including CBC and differential count, CD4 absolute cell count, CSF sample and total cell count, white blood cells (WBC) and red blood cells (RBC) count, and total protein in CSF were summarized by treatment for each visit.

The analyses of non-laboratory safety test results including ECGs and vital signs were based on GSK Core Data Standards, unless otherwise specified.

Pharmacokinetic Analyses

Plasma CAB (Total and unbound) and RPV (Total) Cmax, CSF CAB and RPV Total Cmax were listed and summarized by treatment. Total and unbound CAB and total RPV PK concentrations in plasma and Total CAB and Total RPV concentrations in CSF were obtained 7 days (±3) after an injection visit and were assayed by Covance for CAB samples and by PRA for RPV samples.

Plasma and CSF PK concentrations and their collection times were listed with injection times of CAB and RPV and summarized by Q8W and Q4W regimens and visit.

CAB and RPV PK concentrations in plasma that were collected 7 days (±3) post injection without any major protocol violation were considered Cmax values.

Pharmacokinetic and Pharmacokinetic/Pharmacodynamics Analyses

Correlations between Total plasma CAB and Total CSF CAB, between Total plasma RPV and Total CSF RPV and between Total plasma CAB and unbound plasma CAB was evaluated using SAS PROC Corr. The relationship between plasma PK and CSF samples (PK and HIV-RNA) was assessed by using plots or Pearson correlation coefficient with examples of the following:

CAB and RPV plasma PK concentration (C_{max}) [Total and unbound for CAB; total for RPV) vs. CSF (Total)] at 1 week post injection visit.

CAB and RPV CSF PK concentration and HIV-1 RNA levels in CSF utilizing a SuperLow HIV-1 RNA assay at 1 week post injection visit.

Summary:

Study Population Results

Subject Disposition (Safety Population)			
Number of Subjects	**Q8W IM (N=15)**	**Q4W IM (N=3)**	**Total (N=18)**
Number of subjects screened [N]	15	3	18
Number of subjects enrolled [N]	15	3	18
Number of subjects completed [n (%)]	15 (100)	3 (100)	18 (100)
Number of subjects prematurely discontinued [n (%)]			
Adverse event	0	0	0
Protocol deviation	0	0	0
Subject reached protocol defined stopping criteria	0	0	0
Study closed/terminated	0	0	0
Lost to follow-up	0	0	0
Medical monitor decision or PI discretion	0	0	0
Withdrew consent	0	0	0

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

Summary of Demographic Characteristics (Safety Population)			
Demographics	**Q8W IM (N=15)**	**Q4W IM (N=3)**	**Total (N=18)**
Age in years [Mean (SD)]	37.2 (11.12)	44.0 (13.08)	38.3 (11.35)
Sex [n (%)]			
Female	3 (20)	0	3 (17)
Male:	12 (80)	3 (100)	15 (83)
BMI (kg/m^2) [Mean (SD)]	26.7 (5.28)	26.0 (1.51)	26.5 (4.83)
Height (cm) [Mean (SD)]	175.7 (7.85)	182.0 (15.00)	176.8 (9.11)
Weight (kg) [Mean (SD)]	82.2 (15.27)	87.0 (18.81)	83.0 (15.40)
Ethnicity [n (%)]			
Hispanic or Latino:	4 (27)	0	4 (22)
Not Hispanic or Latino:	11 (73)	3 (100)	14 (78)
Race [n (%)]			
American Indian or Alaska Native	0	0	0
Asian	1 (7)	1 (33)	2 (11)
Black or African American	5 (33)	0	5 (28)
White	9 (60)	2 (67)	11 (61)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

Pharmacokinetic Results:

Plasma and CSF concentrations of Cabotegravir

Median CAB total plasma concentrations were in the range of 3.02-3.92 µg/mL for the two LA treatments. Median CAB total CSF concentrations were in the range of 0.30 – 0.34% of their paired total plasma concentrations for the two LA regimens.

Summary of Cabotegravir Concentrations in Plasma and CSF (PK Concentrations Population)		
	Q8W IM (n=15)	**Q4W IM (n=3)**
	Median (min, max)	Median (min, max)
Plasma total (µg/mL)	3.92 (1.30, 6.41)	3.02 (2.37, 5.10)
Plasma Unbound (µg/mL)	0.0047 (0.0007, 0.0220)	0.0019 (0.0014, 0.0698)
Unbound fraction in Plasma (%)	0.103 (0.056, 0.912)	0.075 (0.062, 1.45)
CSF total (µg/mL)	0.0106 (0.0053, 0.0245)[1]	0.0127 (0.0082, 0.0159)
Ratio CSF:Plasma (%)	0.304 (0.218, 0.449)[1]	0.344 (0.312, 0.421)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
[1]n=13; two subjects had failed attempts at CSF collection during LP

Plasma and CSF concentrations of Rilpivirine

The median total plasma RPV concentrations were in the range of 134-192 ng/mL for the two LA treatment groups. Median RPV total CSF concentrations were in the range of 1.07 – 1.32% of their paired total plasma concentrations for the two LA treatments.

Summary of Rilpivirine Concentrations in Plasma and CSF (PK Concentrations Population)

	Q8W (n=15)	Q4W (n=3)
	Median (min, max)	Median (min, max)
Plasma total (ng/mL)	192 (91.7, 378)	134 (83.0, 187)
CSF total (ng/mL)	1.84 (NQ, 2.90)[1,2]	1.67 (1.40, 2.47)
Ratio CSF:Plasma (%)	1.07 (0.0, 1.52)[1]	1.32 (1.25, 1.69)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
[1]n=13; two subjects had failed attempts at CSF collection during LP
[2]One subject's RPV concentration was non-quantifiable (NQ), which was imputed to 0 for the calculation.

Efficacy Results:

CSF HIV-1 RNA levels for SuperLow Assay

At scheduled Day 8 LP visit, all subjects in the Q8W IM and Q4W IM group had CSF HIV-1 RNA levels <50 c/mL.

Summary of percentage of subjects with CSF SuperLow Assay HIV-1 RNA levels<50 c/mL (CSF Efficacy Population)

Visit	Q8W IM (N=13) n/N (%)	Q4W IM (N=3) n/N (%)
Sub-study Day 8	13/13 (100)	3/ (100)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
SuperLow Assay Lower limit of detection is 2 c/mL

At Day 8, 12 subjects (92%) in the Q8W IM group and 3 subjects (100%) in the Q4W IM group had CSF HIV-1 RNA levels <2 c/mL.

Summary of percentage of subjects with CSF HIV-1 RNA levels<2 c/mL (CSF Efficacy Population

Visit	Q8W IM (N=13) n/N (%)	Q4W IM (N=3) n/N (%)
Sub-study Day 8	12/13 (92)	3/3 (100)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)
SuperLow Assay Lower limit of detection is 2 c/mL

Plasma HIV-1 RNA levels for Abbott Real-time Assay

At scheduled Day 8 LP visit, all subjects in the Q8W IM and all subjects in the Q4W IM group had plasma HIV-1 RNA levels <50 c/mL.

Summary of percentage of subjects with Plasma HIV-1 RNA levels<50 c/mL (Plasma Efficacy Population)

Visit	Q8W IM (N=15) n/N (%)	Q4W IM (N=3) n/N (%)
Sub-study Screening	15/15 (100)	3/3 (100)
Sub-study Day 1	10/11 (91)	2/2 (100)
Sub-study Day 8	15/15 (100)	3/3 (100)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

At Day 1, 8 subjects (53%) and at Day 8, 9 subjects (60%) had plasma HIV-1 RNA levels <2 c/mL in the Q8W IM group. At Day 1 and at Day 8, all subjects in the Q4W IM group had plasma HIV-1 RNA levels <2 c/mL.

Summary of percentage of subjects with Plasma HIV-1 RNA levels <2 c/mL (Plasma Efficacy Population)

Visit	Q8W IM (N=15) n/N (%)	Q4W IM (N=3) n/N (%)
Sub-study Day 1	8/15 (53)	3/3 (100)
Sub-study Day 8	9/15 (60)	3/3 (100)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

Relationship between Plasma and CSF HIV-1 RNA Response with SuperLow Assay

At Day 8, there was 100% agreement between plasma HIV-1 RNA and CSF HIV-1 RNA with criteria of <50 c/mL in both groups.

Summary of HIV-1 RNA <50 c/mL CSF:Plasma Paired Data Categories (CSF PKPD Population)			
CSF HIV-1 RNA	Plasma HIV-1 RNA		
	<50 c/mL n (%)	≥50 c/mL n (%)	Total n (%)
Q8W IM			
<50 c/mL	13 (100)	0	13 (100)
≥50 c/mL	0	0	0
Total	13 (100)	0	13 (100)
Q4W IM			
<50 c/mL	3 (100)	0	3 (100)
≥50 c/mL	0	0	0
Total	3 (100)	0	3 (100)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

Six subjects (46%) in the Q8W IM group and 3 subjects (100%) in the Q4W IM group had an agreement between plasma SuperLow HIV-1 RNA and CSF SuperLow HIV-1 RNA with <2 c/mL criteria.

Summary of SuperLow HIV-1 RNA <2 c/mL CSF:Plasma Paired Data Categories (CSF PKPD Population)			
CSF HIV-1 RNA	Plasma HIV-1 RNA		
	<2 c/mL n (%)	≥2 c/mL n (%)	Total n (%)
Q8W IM			
<2 c/mL	6 (46)	6 (46)	12 (92)
≥2 c/mL	1 (8)	0	1 (8)
Total	7 (54)	6 (46)	13 (100)
Q4W IM			
<2 c/mL	3 (100)	0	3 (100)
≥2 c/mL	0	0	0
Total	3 (100)	0	3 (100)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

PK and PKPD Correlation Results:

Relationship between CSF and Plasma Concentrations of CAB and RPV

In the Q8W dose group, there was a statistically significant correlation between total CSF and total plasma CAB concentrations (Pearson correlation coefficient [P-value] = 0.899 [<0.001]. There was no significant correlation between total plasma and unbound plasma CAB concentrations (Pearson correlation coefficient [P-value] = 0.229 [0.451].

Similarly, there was no significant correlation between total CSF and unbound plasma CAB concentrations (Pearson correlation coefficient [P-value] = 0.156 [0.612].

In the Q8W dose group, there was no statistically significant correlation found between total CSF and total plasma RPV concentrations.

Relationship between CSF or Plasma Concentrations of CAB and RPV and CSF HIV-1 RNA Levels (SuperLow HIV-1 RNA)

There was no significant correlation between total CAB plasma or CAB concentrations and CSF HIV-1 RNA levels (for CAB total plasma Pearson correlation coefficient [P-value] = 0.322 [0.283]; for CAB total CSF Pearson correlation coefficient [P-value] = 0.325 [0.278]).

No correlation between total plasma RPV concentrations and CSF HIV-1 RNA levels (Pearson correlation coefficient [P-value] = -0.012 [0.968]) was found. Correlation was not evaluated between total CSF RPV concentrations and CSF HIV-1 RNA levels.

Summary of Pearson Correlation Coefficients (P-value) Between PK Concentrations and Between PK and CSF SuperLow HIV-1 RNA Assay (CSF PKPD Population)

Correlation	Coefficients (P-values) for CAB	Coefficients (p-value) for RPV
Total Plasma vs total CSF concentration	0.899 (<0.001)	0.432 (0.140)
Total Plasma vs unbound plasma concentration	0.229 (0.451)	NA
Total CSF and unbound plasma	0.156 (0.612)	NA
Plasma total vs CSF HIV-1 RNA	0.322 (0.283)	-0.012 (0.968)
Total CSF vs CSF HIV-1 RNA	0.325 (0.278)	NE

NA: not applicable, NE: not evaluated

Safety Results:

Overall Adverse Events

A total of 20 AEs occurrence (1 AE occurred during screening and 19 AEs occurred during treatment) were reported in 8 subjects during the sub-study. The majority of AEs (13 out of 20 AE occurrences) were classified as Grade 1 in intensity. There were 6 AEs of Grade 2 intensity and 1 AE of Grade 3 intensity. Adverse events reported in this sub-study were consistent with types and rates of AEs reported in the parent study; few AEs were related to sub-study participation.

Summary of All Adverse Events by treatment (Safety Population)			
Preferred Term n (%)	**Q8W IM (N=15)**	**Q4W IM (N=3)**	**Total (N=18)**
Number of subjects with any AEs	6 (40)	2 (67)	8 (44)
Injection site pain	2 (13)	1 (33)	3 (17)
Injection site nodule	0	1 (33)	1 (6)
Injection site pruritus	1 (7)	0	1 (6)
Injection site swelling	1 (7)	0	1 (6)
Headache	2 (13)	1 (33)	3 (17)
Sinus headache	1 (7)	0	1 (6)
Back pain	2 (13)	1 (33)	3 (17)
Post lumbar puncture syndrome	2 (13)	0	2 (11)
Eye pain	0	1 (33)	1 (6)
Sinus congestion	1 (7)	0	1 (6)
Dermatitis contact	0	1 (33)	1 (6)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

A total of 4 subjects (2 subjects in the Q8W IM group and 2 subjects in the Q4W IM group) reported injection site reactions (ISR from both CAB and RPV injections). In the Q8W group, the maximum duration for ISR events, ISR pruritus and ISR pain from the RPV injection, lasted 14 days for both events in Q8W IM group. The max duration for the ISR event of ISR nodule from the RPV injection lasted for 57 days in Q4W IM group.

Drug-Related Adverse Events

All drug-related adverse events were injection site adverse events and were Grade 1 to Grade 2 in intensity. Injection site pain (17%) was the most commonly reported drug-related adverse event.

Summary of Drug-Related Adverse Events (Safety Population)			
Preferred Term n (%)	**Q8W IM (N=15)**	**Q4W IM (N=3)**	**Total (N=18)**

Summary of Drug-Related Adverse Events (Safety Population)			
Preferred Term n (%)	**Q8W IM (N=15)**	**Q4W IM (N=3)**	**Total (N=18)**
Injection site pain	2 (13)	1 (33)	3 (17)
Injection site nodule	0	1 (33)	1 (6)
Injection site pruritus	1 (7)	0	1 (6)
Injection site swelling	1 (7)	0	1 (6)

Q8W IM: CAB LA 600 mg + RPV LA 900 mg IM every 8 Weeks (Q8W)
Q4W IM: CAB LA 400 mg + RPV LA 600 mg IM every 4 Weeks (Q4W)

Deaths

No deaths were reported during the sub-study.

Other Serious Adverse Events

No non-fatal SAEs were reported during the sub-study.

Other Significant Adverse Events

Two subjects reported an adverse event of post lumbar puncture syndrome (Grade 2 and Grade 3 intensity).

No AEs that led to permanent discontinuation of the study treatment or withdrawal from the study were reported during the sub-study.

Conclusions:

CAB and RPV concentrations were detectable in CSF at steady-state for Q8W and Q4W IM groups and exceeded their respective *in vitro* IC_{50} values for the majority of subjects suggesting a dual regimen of CAB and RPV can achieve therapeutic concentrations in the CSF.

CAB concentrations in the CSF (evaluated 1 week after injection) were higher than unbound CAB concentration in plasma.

CAB concentrations in CSF were statistically significantly correlated with CAB total plasma concentrations.

All subjects maintained Plasma and CSF HIV-1 RNA levels <50 c/mL during the study with a dual CAB LA + RPV LA IM regimen.

The dual CAB LA + RPV LA IM regimen administered as Q8W or Q4W penetrated into the CSF compartment with 92-100% of subjects achieving CSF HIV-1 RNA levels <2 c/mL.

The dual CAB LA + RPV LA IM regimen administered in Q8W or Q4W maintained virologic suppression with plasma HIV-1 RNA levels <2 c/mL in 100% subjects (n=3) at Day 1 and Day 8 in the Q4W IM group and 53% and 60% subjects at Day 1 and Day 8, respectively (n=13) in the Q8W IM group.

CAB LA + RPV LA was well tolerated in both the Q8W IM and Q4W IM dosing regimens. No discontinuation due to AEs, including injection site reaction (ISR) related AEs occurred during the sub-study.

Effective Date: [redacted]

Synopsis for Study 201584

Synopsis for Study 201584 Week 48

Name of company: ViiV Healthcare

Name of finished product:
Not available at the time of this report

Name of active substance:
GSK1265744(Cabotegravir) and GSK1329758 (Rilpivirine)

Study Number: 201584

Title: A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naive Adult Participants: Week 48 - Primary Endpoint

Investigator(s): Multicenter study

Study center(s): 108 centers in 11 countries: Canada (6 centers), France (8 centers), Germany (11 centers), Italy (5 centers), Japan (3 centers), Netherlands (4 centers), Russia (13 centers), South Africa (8 centers), Spain (18 centers), United Kingdom (7 centers) and the USA (25 centers).

Publication(s): None at the time of this report

Study Period: The first subject was screened on 27 October 2016. The last subject visit for the primary endpoint analysis at Week 48 was 30 August 2018.

Phase of Development: III

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To demonstrate the non-inferior antiviral activity of switching to intramuscular (IM) Cabotegravir (CAB) + Rilpivirine (RPV) every 4 weeks (monthly) compared to continuation of continued/current antiretroviral regimen (CAR) over 48 weeks in human immunodeficiency virus-1 (HIV-1) antiretroviral naïve subjects.	• Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Missing, Switch, or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] Population).
Secondary	
To demonstrate the antiviral and immunologic activity of switching to IM	• Proportion of subjects with plasma HIV-1 ribonucleic acid (RNA) <50 copies/mL (c/mL) at

Objectives	Endpoints
CAB + RPV every 4 weeks (monthly) compared to continuation of CAR.	Week 48 using the FDA Snapshot algorithm (ITT-E Population). • Proportion of subjects with plasma HIV-1 RNA <200 c/mL at Week 48 using the FDA Snapshot algorithm (ITT-E Population). • Proportion of subjects with confirmed virologic failure (CVF) at Week 48 • Absolute values and change from Baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Week 48 • Absolute values and changes from Baseline in CD4+ cell counts over time including Week 48 • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome (AIDS) and death).
To evaluate the safety and tolerability of switching to CAB + RPV every 4 weeks (monthly) compared to continuation of CAR over time.	• Incidence and severity of adverse events (AEs) and laboratory abnormalities over time including Week 48 • Proportion of subjects who discontinue treatment due to AEs over time including Week 48 • Absolute values and changes in laboratory parameters over time including Week 48
To evaluate the effects of CAB + RPV every 4 weeks on fasting lipids over time compared to continuation of CAR over time.	• Change from Baseline in fasting lipids over time including Week 48
To assess the development of viral resistance in subjects experiencing protocol-defined virologic failure.	• Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study antiretroviral therapy (ART) at Week 48
To characterize CAB and RPV concentrations and population pharmacokinetics (PK) and identify important determinants of variability.	• Plasma PK parameters for CAB and RPV (when evaluable, Ctrough, concentrations post dose [~Cmax] and AUC). • Demographic parameters including, but not limited to, age, sex, race, body weight, body mass index (BMI), and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-subject variability for PK parameters.

Objectives	Endpoints
To assess the acceptance of pain and injection site reactions (ISRs) following injections.	• Change from Week 5 in Dimension scores (e.g., "Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of INjection (PIN) questionnaire. • Proportion of subjects considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the PIN questionnaire.
To assess treatment satisfaction of CAB + RPV compared to continuation of CAR.	• Change from Baseline in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Questionnaire (status version) (HIVTSQs) at Week 4b, Week 24 and Week 44 (or Withdrawal). • Change in treatment satisfaction over time (using the HIV Treatment Satisfaction Questionnaire (change version) (HIVTSQc) at Week 48 (or Withdrawal).
To assess degree of Health-related Quality of Life (HR QoL).	• Change from Baseline in HR QoL using the HAT-QoL short format Week 24 and Week 48 (or Withdrawal).
To assess health status.	• Change from Baseline in health status at Week 24 and Week 48 (or Withdrawal) using the 12-item Short Form Survey (SF-12).
To assess treatment acceptance.	• Change from Baseline in treatment acceptance at Week 8, Week 24 and Week 48 (or Withdrawal) using the "General Acceptance" dimension of the Chronic Treatment Acceptance Questionnaire (ACCEPT).
To assess tolerability of injections.	• Change from Week 4b in tolerability of injections at Week 5, Week 40 and Week 41 using the Numeric Rating Scale (NRS) within the CAB + RPV arm.

Methodology: This was a 120-week Phase III, multi-phase, randomized, open label, active-controlled, multicenter, parallel-group, non-inferiority study in HIV-1, ART-naïve adult subjects.

All subjects completed the Screening Phase of up to 35 days prior to Induction Baseline (Week -20). Eligible subjects were enrolled into the Induction Phase of the study and received ABC/DTG/3TC for 20 weeks (Week -20 to Day 1). For subjects who were HLA-b*5701 positive, DTG was taken with a non-abacavir nucleoside reverse transcriptase inhibitor (NRTI) backbone, chosen per investigator.

Subjects who had an HIV 1 RNA <50 c/mL at the Week -4 Visit were eligible to enter the Maintenance Phase. Eligible subjects were randomized (1:1) to receive either oral CAR (ABC/DTG/3TC or the alternative non-abacavir backbone) or oral CAB◦30◦mg +◦RPV 25 mg once daily for a minimum of 4 weeks (Oral Lead-in [OLI]) followed by IM CAB + RPV every 4 weeks thereafter. Randomization was stratified by subject's Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥ 100,000◦c/mL) and sex at birth.

Subjects randomized to CAR during the Maintenance Phase will continue CAR for at least an additional 100 weeks. Subjects who successfully complete Week 100 (without meeting study defined withdrawal criteria and who remained virologically suppressed at Week 96: HIV-1 RNA <50 c/mL) will be given the option to switch to the IM CAB + RPV arm in the Extension Phase or be withdrawn from the study. The transition from CAR to CAB + RPV within the Extension Phase can be completed with or without an OLI prior to commencement of injectable treatment. The OLI decision will be made by the subject in consultation with the investigator and must be appropriately documented.

All subjects randomized to CAB + RPV during the Maintenance Phase will continue IM CAB + RPV for at least an additional 96 weeks and will continue to have access to IM CAB + RPV in the Extension Phase. Any subject who received at least a single dose of IM CAB and/or RPV and discontinued the CAB + RPV regimen for any reason entered a 52-week Long-Term Follow-Up Phase. Subjects were to be put on oral highly active antiretroviral therapy (HAART) as soon as possible after discontinuing CAB + RPV and were to remain on HAART for at least 52 weeks after the last dose of IM CAB and/or RPV.

Number of subjects: A total of 809 subjects were screened; of these 180 subjects were classed as screen failures. A total of 631 subjects entered the Induction Phase of which 629 subjects received study drug (ABC/DTG/3TC or DTG with a non-abacavir NRTI backbone for subjects who were HLA-B*5701 positive). Of the subjects that completed the Induction Phase, 566 eligible subjects were randomized 1:1 into the Maintenance Phase (CAB + RPV 283 subjects; CAR 283 subjects).

Diagnosis and main criteria for inclusion: This study recruited HIV-1 infected (Screening plasma HIV-1 RNA ≥1000 c/mL), ART-naïve (≤ 10 days of prior therapy with any ART following a diagnosis of HIV-1 infection), male and female (non-pregnant, non-lactating and practicing adequate contraception) subjects, aged ≥18.

Treatment administration: All subjects received abacavir/dolutegravir/lamivudine, (TRIUMEQ™; ABC/DTG/3TC) during the Induction Phase (unless the subject was HLA-b*5701 positive at Screening in which case a non-abacavir containing DTG

regimen was chosen). At the end of the Induction Phase, eligible subjects were randomized 1:1 into the Maintenance Phase to receive either:

- Oral CAB 30 mg + RPV 25 mg once daily for a minimum of 4 weeks followed by IM injections of CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4b, IM CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter. Subjects were to receive IM injections of CAB + RPV for at least 96 Weeks, or;

- Oral CAR (ABC/DTG/3TC or DTG + the alternative non-abacavir backbone) for at least 100 Weeks.

Batch numbers are summarized below.

Investigational Product	Formulation and Route of Administration	Batch Numbers
ABC/DTG/3TC	600 mg of abacavir, 50 mg dolutegravir, and 300 mg of lamivudine tablet Oral	[redacted]
DTG	50 mg tablet Oral	[redacted]
CAB	30 mg tablet Oral	[redacted]
CAB LA	200 mg/mL IM	[redacted]
RPV	25 mg tablet Oral	
RPV LA	300 mg/mL IM	[redacted]

Criteria for evaluation: Primary and secondary endpoints are tabulated above under objectives.

Statistical methods:

Sample Size Estimation:

This study planned to randomize approximately 285 subjects per arm. Assuming the true virologic failure rate is 3% for the CAB + RPV injectable regimen and 2% for the continuation of CAR arm, a non-inferiority margin of 6%, and a 2.5% one-sided significance level, this would provide approximately 97% power to show non-inferiority for the proportion of subjects with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48.

The sample size of 285 subjects per arm also provides at least 90% power to show non-inferiority in the proportion of subjects with plasma HIV-1 RNA <50 c/mL (per FDA's Snapshot algorithm) at Week 48 over a range of true response rates, based on a -10% non-inferiority margin and 2.5% one-sided significance level. Assuming true

response rates for the CAB + RPV arm and CAR arm were both 87%, the power is at least 94% to show non-inferiority for this key secondary endpoint.

Key Analysis Populations:

Population	Definition / Criteria
All Subjects Screened	• Comprised of all subjects screened for inclusion in the study. • Subjects could be re-screened once, for which they received a new subject number. • Only the latest re-screening data is included in the screening population summaries/analyses.
All Participants Enrolled	• All enrolled subjects who received at least one dose of study drug during the Induction Phase.
All Participants Randomized	• All randomized subjects
ITT-E Population	• All randomized subjects who received at least one dose of study drug during the Maintenance Phase of the study (on or after Day 1 visit). • Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received.
Per Protocol (PP) Population	• Comprised of all subjects in the ITT-E Population with the exception of major protocol violators.
Safety	• All randomized subjects who received at least one dose of study drug during the Maintenance Phase of the study (on or after Day 1 visit). • Subjects were assessed according to actual treatment received.
Pharmacokinetic (PK) Population	• All subjects who received CAB and / or RPV and had PK sampling during the study and provided evaluable CAB and / or RPV plasma concentration data (i.e., at least 1 non-missing PK assessment
CVF Population	• Comprised of all subjects in the ITT-E Population who met CVF

Statistical Methods

Primary Efficacy Analysis:

The primary analysis was based on the ITT-E Population using the Snapshot algorithm. The primary comparison was evaluated at a one-sided 2.5% level of significance. Treatment with CAB + RPV was declared non-inferior to CAR if the upper end of a two-sided 95% CI for the difference between the two groups ([CAB + RPV] – CAR) in virologic failure rates at Week 48 was below 6%.

For the primary comparison, the treatment difference and associated 2-sided 95% CI were calculated based on stratum-adjusted proportions using Cochran-Mantel-Haenszel (CMH) weights, with stratification by Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL) and sex at birth. The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 groups.

Homogeneity of the treatment difference was examined individually across each stratification factor using weighted least squares chi-squared statistics and a one-sided 10% level of significance.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

The proportion of subjects with Snapshot HIV-1 RNA≥50 c/mL at Week 48 for each treatment group and the difference between the 2 groups at Week 48 were also summarized within demographic and Baseline characteristic subgroups. The 95% confidence intervals (CIs) for the treatment differences within subgroups were calculated using an unconditional exact method based on 2 inverted 1-sided tests.

Secondary Efficacy Analyses

Key Secondary Efficacy Analysis: A key secondary analysis was to evaluate the proportion of responders (HIV-1 RNA <50 c/mL per Snapshot) at Week 48 based on the ITT-E Population using the same analysis method and stratification factors as specified for the primary endpoint. A non-inferiority margin of -10% was used for this secondary comparison, where if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than -10%, non-inferiority would be demonstrated.

The analysis described above was also performed using the PP Population and the results were compared for consistency with the results from the ITT-E Population.

Similar subgroup analyses (as described above for the primary efficacy endpoint) were also performed for the key secondary efficacy endpoint.

Additional Secondary Efficacy Analysis: Proportion of subjects in each treatment group with plasma HIV-1 RNA <200 c/mL and <50 c/mL, and HIV-1 RNA ≥200 c/mL and ≥50 c/mL, respectively, over time during the Maintenance Phase was summarized using the Snapshot algorithm. The proportion of subjects with confirmed virologic failure during the Maintenance Phase was also be summarized over time.

Absolute values and change from Maintenance (Day 1) Baseline for CD4+ lymphocyte count, and absolute values for plasma HIV-1 RNA, were summarized over time using descriptive statistics (mean, median, interquartile range, min and max). The incidence of HIV-1 disease progression (AIDS and death) during the Maintenance Phase was presented. Data from low level of HIV-1 RNA quantification were summarized at Maintenance (Day 1) Baseline and Week 48.

Time-to-event analyses of failure were performed to estimate the proportion of subjects in each treatment group without efficacy-related (confirmed virologic failure or discontinuation due to lack of efficacy) or treatment-related failure (confirmed virologic failure, discontinuation due to lack of efficacy, drug-related AE, intolerability of injection, or protocol defined safety stopping criteria), respectively, using the Kaplan-Meier nonparametric method. Subjects without any of these events were censored. The

estimated proportion of subjects without any of these events at Week 48 for each treatment group, and the treatment difference with 95% CI were presented.

Safety Analysis:

Safety data (AEs, serious adverse events [SAEs], ISRs, withdrawals) were listed and summarized by treatment group.

The extent of exposure was summarized for each treatment group. Adherence to the CAB + RPV dosing schedule in relation to the projected date was assessed.

Changes from Maintenance Baseline (Day 1) in laboratory (including fasting lipids), vital signs and electrocardiograms (ECG) data were summarized. In addition, the number and percentage of subjects with maximum graded laboratory toxicities (of increased severity relative to last value collected up to including the start of maintenance phase study drug, based on Division of Acquired Immunodeficiency Syndrome [DAIDS] categories) were summarized by treatment group.

Exploratory Safety Analyses: Changes from Baseline in renal and bone biomarkers were summarized by treatment and visit. Treatment differences with respect to log-transformed bone biomarker parameters at Week 48 were assessed using an analysis of covariance (ANCOVA) model, including treatment, Log-transformed bone marker value at Maintenance Baseline (Day 1) and other prespecified Baseline and demographic characteristic factors as fixed effects. Model adjusted treatment differences and associated 95% CIs, expressed as the geometric treatment ratio (CAB + RPV over CAR), and p-values were presented.

Pharmacokinetic Analyses:

Plasma CAB and RPV concentrations over time were summarized by visit for the subjects switching to CAB + RPV.

The statistical analysis of plasma steady state concentration was performed for CAB and RPV separately.

Pharmacokinetic/Pharmacodynamic Analyses:

The relationship between the plasma CAB and RPV concentrations and Snapshot HIV-1 RNA ≥50 c/mL at Week 48, and predictors of efficacy failure, were explored using univariable and multivariable logistic regression analysis (using backwards covariate selection of predictors that were significant in the univariable analysis with $p < 0.15$). Fisher's Exact test was also used as post-hoc analyses when the univariate logistic model could not converge. In addition, the relationship between plasma CAB and RPV concentrations and the following measures during Maintenance Phase were assessed graphically:

- Change from Maintenance Baseline (Day 1) in 2hr post-dose QTc at Week 4b and Week 48
- Maximum change from Maintenance Baseline (Day 1) in ALT/total bilirubin

Viral Genotyping Analyses:

The incidence of treatment emergent genotypic and phenotypic resistance was summarized by treatment arm for subjects meeting confirmed virologic failure criteria.

Health Outcomes Analyses:

The following endpoints were summarized for the Observed Case values by visit during the Maintenance Phase. In addition, these endpoints were also summarized by visit with missing values imputed by LOCF.

Change from Week 5 in Dimension Scores and proportion of subjects considering pain and local reactions following injection using PIN (Perception of Injection Questionnaire) (CAB + RPV group only);

Change from Maintenance Baseline (Day 1) in HATQoL (Life satisfaction, HIV medications, disclosure worries) at Week 24 and 48

Change from Maintenance Baseline (Day 1) in SF-12: Total Score, Physical Component Summary (PCS) and Mental Component Summary (MCS) at Week 24 and 48

Change from Maintenance Baseline (Day 1) in ACCEPT general acceptance score at Week 8, 24 and 48

Change from Week 4b in tolerability of injections using NRS at Week 5, 40 and 41 (CAB +RPV arm only)

Change from Baseline (Day 1) in HIVTSQs total treatment satisfaction score and individual item scores at Week 4b, 24 and 44;

Treatment Satisfaction Score (HIVTSQs change version) and individual item scores at Week 48

Patients' treatment preference at Week 48 (CAB + RPV group only)

A statistical comparison between treatment groups was performed at each visit for HATQoL, HIVTSQs, HIVTSQc, ACCEPT, and SF-12 using an ANCOVA model with treatment, age, Induction Baseline (Week -20) viral load, sex at birth, race and Baseline score value (except for HIVTSQc) as fixed effects and last observation carried forward (LOCF) imputation for missing data.

Changes from Week 5 in PIN acceptance score to Week 41 and Week 48, respectively, based on LOCF imputation for missing data were evaluated using a Wilcoxon Signed-Rank Test.

Summary:

Results presented represent the primary 48 Week analysis.

Demographics: Subject disposition is provided below:

Table: Summary of Subject Accountability: Maintenance Phase Conclusion Record (ITT-E Population)

	CAB + RPV (N=283)	CAR (N=283)
Subject Status		
Randomized	283	283
Ongoing, n (%)	258 (91)	261 (92)
Completed, n (%)	0	0
Withdrawn, n (%)	25 (9)	22 (8)
Primary[a]/Subreason[b] for Study Withdrawal, n (%)		
AE	9 (3)	4 (1)
Lack of efficacy	5 (2)	3 (1)
CVF	5 (2)[e]	3 (1)
Protocol deviation	0	1 (<1)
Prohibited medication use	0	1 (<1)
Lost to follow-up	2 (<1)	2 (<1)
Physician Decision	2 (<1)	5 (2)
Pregnancy	0	1 (<1)
Other[c]	2 (<1)	4 (1)
Withdrawal by Subject	7 (2)	7 (2)
Frequency of visits	1 (<1)	4 (1)
Burden of travel or lack of access to travel	1 (<1)	0
Subject relocated	1 (<1)	1 (<1)
Intolerability of injections	2 (<1)	0
Subject was incarcerated	1 (<1)	0
Other, specify[d]	1 (<1)	2 (<1)
Outcome of AEs Resulting in Study Withdrawal		
Fatal	0	0
Non-fatal	9 (3)	4 (1)

a. Subjects may have only 1 primary reason for withdrawal.
b. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than 1 subreason underneath a single primary reason. Subjects are not required to indicate subreasons.
c. CAB + RPV: 1 Subject needed at least 6 months anti-coagulation for thrombosis; 1 Subject was unreliable with appointments and frequently rescheduled (Investigator feared prolonged dosing interval with subsequent virologic failure). CAR: 2 Subjects noncompliance with study treatment and protocol procedures; 1 Subject ViiV Safety and Labelling Committee decision (subject had acute hepatitis E infection followed by continued cocaine use); 1 Subject did not show up or was late for visits.
d. CAB + RPV: pregnancy thoughts in near future; CAR: Relocation; Subject decision to stop CAR
e. One subject did not meet CVF (Subject had low level viremia at Week 48: 128 c/mL, retest 149 c/mL; Week 52: 229 c/mL; Long term follow-up Month 1 – prior to initiation of new ART: 109 c/mL)

Subject demographics characteristics for the Safety Population are provided below. Demographic characteristics were generally similar between treatment groups. Although the majority of subjects were male, the study exceeded the goal to enroll at least 20% female subjects. Most subjects were aged 18 to <50 years of age (88%) with a median (range) of 34 (18 to 68) years. The predominant race was White-White/Caucasian/European heritage.

Table: Summary of Demographic Characteristics (ITT-E Population)

Demographic Characteristic	CAB + RPV (N=283)	CAR (N=283)
Age (y), n		
Mean	35.9	36.0
SD	10.17	9.82
Median	34.0	34.0
Min.	19	18
Max.	68	68
Age Group (y), n (%)		
<35	143 (51)	145 (51)
35 to <50	107 (38)	109 (39)
≥50	33 (12)	29 (10)
Sex, n (%)		
Female	63 (22)	64 (23)
Male	220 (78)	219 (77)
Race, n (%)		
White	216 (76)	201 (71)
Non-White	67 (24)	80 (28)
American Indian or Alaska Native	3 (1)	6 (2)
Asian-Central/South Asian Heritage	2 (<1)	1 (<1)
Asian-East Asian Heritage	1 (<1)	2 (<1)
Asian-Japanese Heritage	8 (3)	12 (4)
Asian-South East Asian Heritage	1 (<1)	0
Black or African American	47 (17)	56 (20)
Native Hawaiian or Other Pacific Islander	1 (<1)	0
White-Arabic/North African Heritage	5 (2)	3 (1)
White-White/Caucasian/European Heritage	211 (75)	198 (70)
Multiple	4 (1)	3 (1)
Missing	0	2 (<1)
Ethnicity, n (%)		
Hispanic or Latino	28 (10)	40 (14)
Not Hispanic or Latino	255 (90)	243 (86)
BMI (kg/m^2) at Induction Baseline (Week -20)		
Mean	25.109	24.934
SD	4.4190	4.8797
Median	24.100	24.000
Min.	17.30	12.60
Max.	44.90	47.40

Baseline characteristics were generally similar between treatment groups, except for viral hepatitis status at Induction Baseline (Week -20). At Induction Baseline (Week -20), 18 (6%) subjects in the CAB + RPV group and 9 (3%) subjects in the CAR group tested positive for hepatitis C (HCV) only. No subjects tested positive for hepatitis B (HBV) only. One subject in the CAB + RPV group tested positive for HBV (HbsAg NR; anti-Hbcore positive; Hbs antibody negative) and HCV. The HBV virus positive subject had a local hepatitis B virus DNA obtained that was <12 IU/mL, therefore the subject was not considered to have violated the exclusion criteria and was enrolled in the study.

Efficacy:

Primary Analysis: The primary efficacy analysis demonstrated that once-monthly CAB + RPV was non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects at Week 48, with the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot Algorithm in the ITT-E and PP Populations meeting the predefined non-inferiority margin of 6%.

Table: Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Maintenance Phase) Snapshot Analysis (ITT-E and PP Populations)

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	283	6/283 (2.1)	-0.4 (-2.8, 2.1)	-0.4 (-2.8, 2.1)
CAR	283	7/283 (2.5)		
PP Population				
CAB + RPV	278	6/278 (2.2)	-0.3 (-2.8, 2.2)	-0.3 (-2.8, 2.2)
CAR	282	7/282 (2.5)		

a. Difference: Proportion on CAB + RPV - Proportion on CAR
b. Based on CMH stratified analysis adjusting for the following Baseline stratification factors: sex at birth (male, female) and Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL)

Treatment differences for the primary endpoint for each randomization stratification factor (Induction Baseline [Week -20] HIV-1 RNA [<100,000, ≥100,000 c/mL] and sex at birth) support the non-inferiority of CAB + RPV vs. CAR.

Study outcomes based on HIV-1 RNA ≥50 c/mL at Week 48 Snapshot analysis were similar for both treatment groups. The majority of subjects remained suppressed with HIV-1 RNA <50 c/mL at Week 48 Snapshot analysis. A small number of subjects had HIV-1 RNA ≥50 c/mL at Week 48 or had no virologic data. Within the Week 48 Snapshot analysis under the category of no virologic data, there were more AEs leading to withdrawal in the CAB + RPV group compared to the CAR group and more discontinuations for other reasons in the CAR group compared to the CAB + RPV group

Table: Summary of Study Outcomes (Plasma HIV-1 RNA of 50 c/mL cut off) at Week 48 (Maintenance Phase) Snapshot Analysis (ITT-E Population)

Outcome	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)
HIV-1 RNA <50 c/mL	265 (93.6)	264 (93.3)
HIV-1 RNA ≥50 c/mL	6 (2.1)	7 (2.5)
Data in window not below threshold	2 (0.7)	2 (0.7)
Discontinued for lack of efficacy	4 (1.4)	3 (1.1)
Discontinued for other reason while not below threshold	0	2 (0.7)[a]
Change in background therapy	0	0
No virologic data	12 (4.2)	12 (4.2)
Discontinued study due to AE or death	8 (2.8)	2 (0.7)
Discontinued study for other reasons	4 (1.4)[b]	10 (3.5)[c]
On study but missing data in window	0	0

1 relocation, 1 lost to follow-up.
1 tolerability of injections, 1 incarceration, 2 lost to follow-up.
4 frequency of visits (subject decision), 2 noncompliance with study treatment and protocol procedures, 1 relocation, 1 subject decision to stop treatment, 1 late to attend visits, 1 lost to follow-up.

Key Secondary Efficacy Analyses: Results showed that CAB + RPV is non-inferior to CAR for the proportion of subjects with <50 c/mL plasma HIV-1 RNA at Week 48 per the Snapshot Algorithm in the ITT-E and PP Populations, meeting the predefined non-inferiority margin of -10%.

Table: Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (Maintenance Phase) – Snapshot Analysis – (ITT-E and PP Populations)

Treatment	N	Number of HIV-1 RNA <50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	283	265 / 283 (94)	0.4 (-3.7, 4.4)	0.4 (-3.7, 4.5)
CAR	283	264 / 283 (93)		
PP Population				
CAB + RPV	278	260 / 278 (94)	0.3 (-3.9, 4.4)	0.3 (-3.8, 4.4)
CAR	282	263 / 282 (93)		

f. Difference: Proportion on CAB + RPV - proportion on CAR
Based on CMH stratified analysis adjusting for the following Baseline stratification factors: sex at birth (male, female) and Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL)

Non-inferiority in the key secondary endpoint was also supported across randomization factors (Induction Baseline [Week -20] HIV-1 RNA [<100,000, ≥100,000 c/mL] and sex at birth).

The proportion of subjects for the Maintenance Phase with plasma HIV-1 RNA <50 c/mL by visit was similar for both treatment groups (plasma HIV-1 RNA <50 c/mL: CAB + RPV: 94%; CAR: 93%).

Additional Secondary Efficacy Analyses

The proportion of subjects with plasma HIV-1 RNA ≥200 c/mL by visit for the Maintenance Phase was low and similar in both treatment groups. The proportion of subjects with plasma HIV-1 RNA <200 c/mL by visit for the Maintenance Phase was high and similar in both treatment groups. At Week 48, 94% (95% CI: 91%, 97%) of CAB + RPV subjects and 94% (95% CI: 91%, 97%) of CAR subjects had plasma HIV-1 RNA <200 c/mL.

The endpoint for the treatment related discontinuation = failure analysis was a composite of the following efficacy and safety/intolerability events (based on the primary reason for discontinuation from the Maintenance Phase by Study Day 350): CVF (CAB + RPV 4 vs CAR 3), lack of efficacy (CAB + RPV 1 vs CAR 0), drug-related adverse events (CAB + RPV 2 vs CAR 2), protocol defined safety stopping criteria (CAB + RPV 0 vs CAR 0) and intolerance to injections (CAB + RPV 2 vs CAR 0). The endpoint for the efficacy related discontinuation = failure analysis pertained to efficacy related discontinuation only: CVF (CAB + RPV 4 vs CAR 3), lack of efficacy (CAB + RPV 1 vs CAR 0). Results of these analyses were consistent with the non-inferiority findings for the key secondary endpoint plasma HIV-1 RNA <50 c/mL.

No clinically relevant differences in absolute values and changes from Maintenance Baseline (Day 1) in CD4+, CD8+ counts CD4+/CD8+ ratio through Week 48 were observed between the treatment groups.

Disease progression was defined as HIV-associated conditions, AIDS, and death. There were no deaths during the Maintenance Phase. Rates of disease progression to Center for Disease Control (CDC) Stage 3 were similar in both treatment groups. Nine (3%) subjects in the CAB + RPV group and 11 (4%) subjects in the CAR group had post-Maintenance Baseline (Day 1) HIV-1 disease progression to CDC Stage 3 disease during the Maintenance Phase.

Safety:

Adverse Events

Table: Overall Summary of Adverse Events - Maintenance Phase (Safety Population)

	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)
Any AE	267 (94)	225 (80)
Any AE, excluding ISRs	246 (87)	225 (80)
ISR AE	239 (86)	NA
Any Grade 3 to 4 AEs	31 (11)	11 (4)
Grade 3 to 4 AEs, excluding ISRs	22(8)	11 (4)
AEs leading to withdrawal	9 (3)	4 (1)
Drug-related AEs leading to withdrawal	2 (<1)	3 (1)
Any SAE	18 (6)	12 (4)
Fatal SAEs	0	0
Drug-related AEs	236 (83)	28 (10)
Drug-related AE, excluding ISRs	79 (28)	28 (10)
Drug-related Grade 3 to 4 AE	14 (5)	0
Drug related Grade 3 to 4 AE, excluding ISR	4 (1)	0
Drug-related SAEs	1 (<1)[a]	0
Drug-related fatal SAEs	0	0

a. Drug-related SAE in the CAB + RPV group was right knee monoarthritis
Note: Only on-treatment events are considered.

The percentage of subjects reporting any AE was higher in the CAB + RPV group (94%) compared to the CAR group (80%). This was at least in part attributable to the frequency of ISRs in the CAB + RPV group. The frequency of common AEs (≥5%) was comparable in the 2 treatment groups, with the exception of ISR events (pain, nodule, induration, swelling, pruritus) which were specific to the CAB + RPV group, and headache (14% vs 7%), pyrexia (8% vs.1%), hemorrhoids (6% vs. 1%) and dizziness (5% vs 1%) which were reported more frequently in the CAB + RPV group.

Non-ISR AEs consisted primarily of Grade 1-2 events. Non-ISR Grade 3 AEs occurred in 14 (5%) subjects in the CAB + RPV group and 10 (4%) subjects in the CAR group. Non-ISR Grade 4 AEs occurred in 8 (3%) subjects in the CAB + RPV group and 1 (<1%) subjects in the CAR group.

Non-ISR drug-related AEs consisted primarily of Grade 1-2 events and were reported more frequently for CAB + RPV (79 [28%] subjects compared to CAR 28 [10%] subjects).

During the Maintenance Phase 9 (3%) subjects in the CAB + RPV group and 4 (1%) subjects in the CAR group had AEs leading to withdrawal/permanent discontinuation of

study drug. Three of the subjects in the CAB + RPV group withdrew during OLI and never received IM CAB + RPV injections.

During the Maintenance Phase 18 (6%) subjects in the CAB + RPV group and 12 (4%) subjects in the CAR group had non-fatal SAEs. There were no discernible patterns of SAEs by preferred term, with only one SAE (hepatitis A in the CAB + RPV group) being reported by more than a single subject in either treatment group. There was one SAE assessed by the investigator as related to CAB + RPV (right knee mono-arthritis).

Overall, injections with CAB + RPV were well tolerated. ISRs were reported frequently and most commonly comprised of mild (Grade 1 or 2), short-lived and self-resolving pain events. There were no Grade 4 ISRs and no ISRs were SAEs. Few ISRs (5%) lasted more than 14 days (median duration 3 days). Injections seldom led to withdrawal (2 subjects withdrew citing ISR pain, and 2 additional subjects withdrew consent stating general 'intolerability of injections'), and overall health outcomes data demonstrated consistent and high levels of acceptability of injections. A majority of subjects had ISRs at the initial 3 mL loading injections; however, the incidence of ISRs decreased over time through Week 48. In addition, all ISRs reported after Week 8 were mild/moderate (Grades 1 or 2).

Hepatotoxicity was categorized as an AE of special interest for the current study. There were no liver findings that raised a concern for the CAB + RPV regimen and there were no cases considered to represent DILI. Six of the 7 subjects in the study who met liver stopping criteria on the CAB + RPV group had an acute hepatitis infection (3 subjects acute hepatitis A; 2 subjects acute hepatitis B; 1 subject acute hepatitis C) and 1 subject had transaminitis related to illicit drug use and inorganic solvent abuse.

Clinical Laboratory Evaluations

No clinically relevant differences were observed in clinical laboratory abnormalities, for either chemistry or hematology, between the CAB + RPV and CAR groups. No clinically significant differences were observed for graded abnormalities for any of the following parameters: alanine aminotransferase (ALT), aspartate amino transferase (AST), bilirubin, or lipase.

There were no reported events of rhabdomyolysis associated with any of the transient Grade 1 to 4 elevations of creatine phosphokinase (CPK).

Fasting lipid National Cholesterol Education Program (NCEP) categories at Week 48 versus Baseline were similar in the 2 treatment groups. No clinically relevant patterns of change in NCEP fasting lipids from Baseline to maximum post Baseline category were observed in either treatment group.

Suicidal Ideation or Behavior

Fifteen (5%) subjects in the CAB + RPV group and 16 (6%) subjects in the CAR group reported suicidal ideation or behavior during Maintenance Phase. Possible suicidality-related AEs (PSRAE) data showed 4 (1%) subjects in the CAB + RPV group and 5 (2%) subjects in the CAR group with positive alerts. Depression and suicidal AEs based on a

subject's prior history of depression, anxiety, or suicidal ideation were similar between the 2 treatment groups. These types of AEs were reported in subjects regardless of whether they had or did not have a history of depression, anxiety, or suicidal ideation. However, subjects who had a prior history appeared to be at increased risk of reporting these events.

Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

Following completion of the 4-week OLI, Week 4b CAB concentrations were consistent with oral dosing of CAB 30 mg once daily. Similarly, Week 4b RPV concentrations were consistent with historical data on oral dosing of RPV 25 mg once daily.

Following the initial CAB LA injection at Week 4b, geometric mean (95% CI) Week 8 CAB concentration was 1.56 (1.45, 1.68) μ g/mL, similar to that of 1.23 [1.13, 1.33] μ g/mL observed in subjects (n=252) receiving an initial dose of 600 mg IM in the Q4W regimen of the Study 201585 as well as to that of 1.18 [0.395, 3.50] μ g/mL observed in oral switch subjects (n=7) receiving an initial dose of 600 mg IM in the Q4W regimen of the Study 200056 Extension Phase. Geometric mean [95% CI] Week 48 CAB trough concentration was 3.13 μg/mL (2.95, 3.33), more than double the value observed following the initial injection and similar to that of 2.84 μg/mL and 2.58 μg/mL observed at Week 48 in studies 201585 and 200056, respectively. Geometric mean [95% CI] Week 41 CAB concentration obtained 3 to 10 days following the Week 40 injection was 4.03 (3.85, 4.23) μ g/mL, similar to that of 3.39 (3.18, 3.61) μ g/mL and of 3.5 (3.3, 3.8) μ g/mL observed in studies 201585 and 200056, respectively. Using evaluable trough concentrations collected within 26 to 30 days of the prior injection, steady state was confirmed by Week 44; this is similar to Study 200056 where steady state was confirmed by Week 40 for the Q4W regimen.

Following the initial RPV LA injection at Week 4b, geometric mean (95% CI) Week 8 RPV concentration was 41.2 (38.7, 43.9) ng/mL, similar to that of 38.6 [36.0, 41.4] ng/mL observed in subjects (n=251) receiving an initial dose of 900 mg IM in the Q4W regimen of Study 201585 as well as to that of 40.3 [28.4, 57.2] ng/mL observed in the oral switch subjects (n=7) receiving an initial dose of 900 mg IM in the Q4W regimen of the Study 200056 Extension Phase. Geometric mean (95% CI) Week 48 RPV trough concentration was 82.4 ng/mL (77.8, 87.2), more than double the value observed following the initial injection and similar to that achieved following oral RPV 25 mg once daily at the end of the OLI (79.1 [74.1, 84.3]). Geometric mean Week 41 RPV concentration obtained 3 to 10 days following the Week 40 injection was 106 ng/mL (101, 111), approaching the geometric mean observed Cmax of 110 (103, 118) and 127 (118, 136) ng/mL observed for the Q4W regimen in studies 201585 and 200056, respectively. RPV steady state was not yet confirmed by Week 48.

In a univariate analysis, HIV-1 subtype (A1 vs. others; post hoc grouping of subtype categories), Induction Baseline BMI (>30 kg/m^2), RPV Week 8 trough concentration, CAB Week 8 trough concentration, and last RPV trough concentration were identified as statistically significant predictors ($p < 0.05$) of having HIV RNA ≥50 c/mL at Week 48 (based on the Snapshot algorithm).

In the multivariable analysis, only HIV-1 subtype A1 vs. others (odds ratio [95% CI; p-value] 114 [9.143, >999.999; p<0.001]) and the RPV Week 8 trough concentration (19.5 [1.33, 285, p=0.030]; per doubling of concentration) were retained as statistically significant predictors of Week 48 HIV RNA ≥50 c/mL.

Given the few subjects who were identified as cases of CVF on CAB + RPV, and the fact that there was a high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it was difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. In addition, multiple factors including CAB and RPV plasma concentrations may be associated with the occurrence of virologic failure. It should be noted that the low number of failures limits the reliability of the multivariable logistic modelling and backwards selection procedure. Furthermore, the dichotomization of subtype into A1 vs. others was made post hoc, which may have introduced selection bias, and not all relevant factors could be measured and included in the multivariable analysis, such as Baseline phenotypic susceptibility. For these reasons, the predictors identified from these analyses should be interpreted with caution and considered as exploratory findings

No relationships between CAB or RPV concentrations and safety parameters of interest (Maximum change from Baseline in ALT/total bilirubin and change from Baseline in QTcF at Week 4b 2 hours post dose) were identified.

Biomarkers:

Renal Biomarkers: There was a slight median increase from Maintenance Baseline (Day 1) to Week 48 in urine retinol binding protein for the CAR group (0.5969 nmol/L) and no median change in the CAB + RPV group. Serum retinol binding protein showed a slight decrease for both groups (CAB + RPV group -0.35 nmol/L; CAR group -0.20 nmol/L).

Urine protein/creatinine showed a small median decrease from Maintenance Baseline (Day 1) to Week 48 in the CAB + RPV group (-0.15 g/mol) compared to a small increase in the CAR group (0.20 g/mol). There was a slight median decrease from Maintenance Baseline (Day 1) to Week◦48 in serum creatinine for the CAB + RPV group (8.80 μmol/L), and no median change for the CAR group. There were no median changes from Maintenance Baseline (Day 1) in urine albumin/creatinine ratio or urine phosphate.

Bone Biomarkers: Median values for bone specific alkaline phosphatase, osteocalcin, type I collagen C-telopeptides, procollagen 1 N-terminal propeptide and vitamin D were similar in both treatment groups at Maintenance Baseline (Day 1).

Median values for bone specific alkaline phosphatase decreased from Maintenance Baseline (Day 1) to Week 48 in both groups. The model adjusted geometric mean for treatment ratio (95% CI) was 0.988 (0.955, 1.021). The result was not statistically significant (p=0.462).

Median values for vitamin D decreased from Maintenance Baseline (Day 1) to Week 48 in both groups. The model adjusted geometric mean for treatment ratio (95% CI) was 1.132 (1.064, 1.203). The decrease observed in vitamin D ($p<0.001$) was greater in the CAR group compared to the CAB◦+◦RPV group.

The median osteocalcin value decreased from Maintenance Baseline (Day 1) to Week 48 in the CAR group with no change observed in the CAB + RPV group. The model adjusted geometric mean for treatment ratio (95% CI) was 1.096 (1.023, 1.173). The decrease observed in osteocalcin ($p=0.009$) was greater in the CAR group compared to the CAB◦+◦RPV group.

Median values for procollagen 1 N-terminal propeptide remained relatively unchanged from Maintenance Baseline (Day 1) to Week 48 in both groups. However, based on the model adjusted geometric mean for treatment ratio (95% CI) geometric mean ratio (1.064 [1.001, 1.131]), a greater decrease in the CAR group compared to the CAB + RPV group was observed ($p=0.0462$).

Median values for type I collagen C-telopeptides increased from Maintenance Baseline (Day 1) to Week 48 in both groups. The model adjusted geometric mean for treatment ratio (95% CI) was 0.936 (0.861, 1.018). The result was not statistically significant ($p=0.123$).

Viral Genotyping

CVF through Week 48 was low in the study and was similar between the 2 treatment groups, with 7 subjects meeting CVF: 4 subjects in the CAB + RPV group and 3 subjects in the CAR group. In the CAB + RPV group, 1 subject had CVF without receiving an injection and therefore virology data were not generated. The remaining 3 CVF subjects in the CAB + RPV group had treatment-emergent non-nucleoside reverse transcriptase inhibitor (RPV) and integrase resistance-associated mutation (IN RAMs) at SVF. All 3 of these subjects had BMIs >30 kg/m^2, were from Russia, and had Subtype A1 virus. None of the three CVF subjects on CAR had treatment emergent resistance mutations at the time of suspected virologic failure (SVF). While 1 subject was from Russia with Subtype A1, the other 2 subjects were from Spain and the USA and had Subtype B virus.

Health Outcomes

At Week 48, subjects in the CAB + RPV arm reported a statistically significant improvement in treatment satisfaction from induction phase compared with subjects in the CAR group according to the HIVTSQc. According to the HIVTSQs, overall treatment satisfaction in the CAB + RPV arm was high and remained high for the whole study duration.

For most subjects receiving CAB + RPV, acceptance of ISRs following their first injection was high and significantly improved over time across measured visits, according to the PIN.

Overall treatment acceptance in the CAB + RPV arm was high and remained high for the study duration according to the ACCEPT.

"Life Satisfaction" and general health status were high at Baseline and remained high for both treatment groups.

Out of the responders in the CAB + RPV arm, 99.2% (257/259) selected monthly injections of CAB + RPV LA over daily oral as their preferred HIV treatment at Week 48.

The NRS analog scale showed the maximum level of pain associated with CAB + RPV injections on the day of injection remained relatively stable across measured visits. The maximum level of pain experienced within one week following CAB+RPV injections decreased over time from Week 5 to Week 41. Notably the frequency of ISRs decreased over time.

Conclusions:

- The switch to a novel 2-drug injectable regimen of CAB + RPV demonstrated high efficacy and was non-inferior to the continuation of CAR in virologically suppressed HIV-1-infected adults. This 2-drug regimen administered monthly was able to maintain HIV-1 suppression through the 48 Week primary endpoint as effectively as oral CAR taken once daily. The safety profiles of the injectable regimen demonstrated that the monthly regimen was well tolerated.
- CAB + RPV offers the option to switch subjects to a well-tolerated dual ART regimen, which effectively maintains viral suppression.

Efficacy

The primary efficacy analysis demonstrated that CAB+ RPV is non-inferior to CAR and provided good clinical efficacy based on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot analysis) (CAB + RPV 6 [2.1%] subjects; CAR 7 [2.5%] subjects) for the ITT-E Population. The adjusted treatment difference (95% CI) between CAB + RPV and CAR (-0.4 [-2.8, 2.1]) met the non-inferiority criterion, set below 6%.

The key secondary analysis (HIV-1 RNA <50 c/mL) also demonstrated that CAB + RPV is non-inferior to CAR at Week 48 (Snapshot analysis) for the ITT-E, and PP populations. The adjusted treatment difference between CAB + RPV (94% responders) and CAR (93% responders) met the non-inferiority criterion, set above -10%.

Treatment differences for the primary endpoint for each randomization stratification factor (Induction Baseline [Week -20] HIV-1 RNA [<100,000, ≥100,000 c/mL] and sex at birth) support the non-inferiority of CAB + RPV vs. CAR.

Pre-planned subgroup analyses support the consistency of the primary and key secondary efficacy endpoint conclusions among different subpopulations defined by demographic and baseline characteristics, with consideration for lack of precision in estimation for subgroups with smaller sample sizes.

The 2-drug once monthly injectable regimen effectively maintained virologic suppression, with few CVF. Rates of CVF were 1.4% in the CAB + RPV group and 1.1% in the CAR group through Week 48.

- Taken together, these results indicate that the CAB + RPV regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure.

Safety

- Over 48 weeks, the safety data from this randomized, open-label Phase III study of subjects switching to CAB + RPV is favorable and consistent with prior Phase II trials. No new AEs of clinical concern were observed.
- Greater proportions of subjects in CAB + RPV group compared with those in the CAR group had AEs. Differences between the groups were primarily driven by ISRs in the CAB + RPV group, as would be expected.
- The higher incidence of AEs leading to withdrawal in the CAB+RPV group was primarily due to the higher incidence of hepatitis (mainly acute viral hepatitis which were considered unrelated to study treatment) and ISRs in the CAB+RPV group.
- Overall, injections with CAB + RPV were well tolerated, ISRs being generally mild and of short duration. Injection site pain was the most frequently reported ISR (80% subjects) however ISRs resulted in few withdrawals (<1%).

For AEs of special interest there was a lack evidence of study treatment on QT prolongation, hypersensitivity reactions, seizures, rhabdomyolysis, pancreatitis and impact on creatinine.

There was increased incidence of anxiety and drug- related adverse events (anxiety, depression and abnormal dreams) in CAB+RPV compared to CAR. There was some evidence of increased weight gain in the CAB+RPV group compared to the CAR group.

- No clinically relevant differences were observed in clinical laboratory abnormalities, for either chemistry or hematology, between the CAB + RPV and CAR groups. No clinically significant differences were observed for graded abnormalities for any of the following parameters: ALT, AST, bilirubin, or lipase.
- No clinically relevant patterns in changes in NCEP fasting lipids from Baseline category to maximum post Baseline category for the Maintenance Phase were observed in either treatment group for triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, or total cholesterol/HDL ratio.
- The OLI for CAB + RPV was well tolerated with no patterns observed for clinical AEs or laboratory abnormalities, and few subject withdrawals.

Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

- Geometric mean CAB and RPV concentrations were consistent with those observed in Phase II and III studies. CAB LA steady state was confirmed by Week 44.
- Given the few subjects who experienced CVF on CAB + RPV, and the fact that there was a high proportion of subjects with virologic success while having

similar CAB and RPV concentrations as those observed in subjects with CVF, it was difficult to establish a robust relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. In addition, multiple factors including CAB and RPV plasma concentrations may be associated with the occurrence of virologic failure.

- No associations between CAB or RPV concentrations and safety findings of interest were identified.

Biomarkers

- Bone specific alkaline phosphatase and vitamin D decreased from Maintenance Baseline (Day 1) to Week 48 in both groups. The decrease observed in vitamin D ($p<0.001$) was greater in the CAR group compared to the CAB + RPV group. No change from Maintenance Baseline (Day 1) to Week 48 was observed in osteocalcin or procollagen 1 N-terminal propeptide. Median values for type I collagen C-telopeptides increased from Maintenance Baseline (Day 1) to Week 48 in both groups. The results suggest that the switch from CAR to a 2-drug NRTI sparing regimen is not associated with an increased reduction in bone turnover.

Viral Genotyping and Phenotyping

- CVF was rare in this study; 4 subjects in the CAB + RPV group and 3 subjects in the CAR group.
- Three CVFs in the CAB+ RPV group had treatment emergent RPV and INI resistant mutations. All 3 had CAB resistance in vitro; 2 of the 3 had RPV resistance in vitro. The fourth CVF never received an injection and virology data were not generated.
- None of the 3 CVFs on CAR had treatment-emergent resistance mutations.

Health Outcomes

- At Week 48, subjects in the CAB + RPV arm reported a statistically significant improvement in treatment satisfaction from induction phase compared with subjects in the CAR group according to the HIVTSQc.
- According to the HIVTSQs, overall treatment satisfaction in the CAB + RPV arm was high and remained high for the whole study duration.
- For most subjects receiving CAB + RPV, acceptance of ISRs following their first injection was high and significantly improved over time across measured visits, according to the PIN.
- Overall treatment acceptance in the CAB + RPV arm was high and remained high for the study duration according to the ACCEPT.
- “Life Satisfaction” and general health status were high at Baseline and remained high for both treatment groups.

- Out of the responders, 99.2% selected CAB + RPV over daily oral as their preferred HIV treatment at Week 48.

Effective Date: [redacted]

Synopsis for Study 201584 Week 96

Title: A Phase III, Randomized, Multicenter, Parallel-group, Open-Label Study Evaluating the Efficacy, Safety, and Tolerability of Long-Acting Intramuscular Cabotegravir and Rilpivirine for Maintenance of Virologic Suppression Following Switch from an Integrase Inhibitor Single Tablet Regimen in HIV-1 Infected Antiretroviral Therapy Naive Adult Participants: Week 96/100 Results – Secondary Endpoint

Investigator(s): Multicenter study

Study center(s): 108 centers in 11 countries: Canada (6 centers), France (8 centers), Germany (11 centers), Italy (5 centers), Japan (3 centers), Netherlands (4 centers), Russia (13 centers), South Africa (8 centers), Spain (18 centers), United Kingdom (7 centers) and the USA (25 centers).

Publication(s): Orkin C, Arasteh K, Hernandez-Mora, G, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. NEJM, Mar. 2020. doi: 10.1056/NEJMoa1909512. Accessed March 10, 2020.

Study Period: The first subject was screened on 27 October 2016. The last subject visit for the secondary endpoint analysis at Week 96 was 12 September 2019.

Phase of Development: III

Objectives:

Objectives	Endpoints
Primary	
To demonstrate the non-inferior antiviral activity of switching to intramuscular (IM) Cabotegravir (CAB) + Rilpivirine (RPV) every 4 weeks (monthly) compared with continuation of continued/current antiretroviral regimen (CAR) over 48 weeks in human immunodeficiency virus-1 (HIV-1) antiretroviral naïve subjects.	• Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Missing, Switch, or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] Population).
Secondary	
To demonstrate the antiviral and immunologic activity of switching to IM CAB + RPV every 4 weeks (monthly) compared with continuation of CAR.	• Proportion of subjects with plasma HIV-1 RNA <200 c/mL and HIV-1 RNA <50 c/mL at Week 96 using the FDA Snapshot algorithm (ITT-E population). • Proportion of subjects with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 96. • Proportion of subjects with confirmed virologic

Objectives	Endpoints
	failure (CVF) at Week 96. • Absolute values and change from Baseline in plasma HIV-1 RNA (log_{10} copies/mL) at Week 96. • Absolute values and changes from Baseline in CD4+ cell counts over time including Week 96. • Incidence of disease progression (HIV-associated conditions, acquired immunodeficiency syndrome (AIDS) and death).
To evaluate the safety and tolerability of switching to CAB + RPV every 4 weeks (monthly) compared with continuation of CAR over time.	• Incidence and severity of adverse events (AEs) and laboratory abnormalities over time including Week 96. • Proportion of subjects who discontinue treatment due to AEs over time including Week 96. • Absolute values and changes in laboratory parameters over time including Week 96.
To evaluate the effects of CAB + RPV every 4 weeks on fasting lipids over time compared with continuation of CAR over time.	• Change from Baseline in fasting lipids over time including Week 96.
To assess the development of viral resistance in subjects experiencing protocol-defined virologic failure.	• Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV, and other on-study antiretroviral therapy (ART) at Week 96.
To summarize CAB and RPV plasma concentrations collected at specific time points between Week 48 and Week 96.	• Plasma PK concentrations for CAB and RPV (when evaluable, Ctrough, concentrations post dose [~Cmax]).
To assess the acceptance of pain and injection site reactions (ISRs) following injections.	• Change from Week 5 in Dimension scores (e.g., “Bother of ISRs”, “Leg movement”, “Sleep”, and “Injection Acceptance”) and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of INjection (PIN) questionnaire. • Proportion of subjects considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the PIN questionnaire.
To assess degree of Health-related Quality of Life (HR QoL).	• Change from Baseline in HR QoL using the HAT-QoL short form at Week 24, Week 48, Week

Objectives	Endpoints
	96 (or Withdrawal).
To assess treatment satisfaction of CAB + RPV compared with continuation of CAR.	• Change from Baseline in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Questionnaire (status version) (HIVTSQs) at Week 4b, Week 24 and Week 44, Week 96 (or Withdrawal).
To assess health status.	• Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12).
To assess treatment acceptance.	• Change from Baseline in treatment acceptance at Week 8, Week 24, Week 48, Week 96 (or Withdrawal) using the "General Acceptance" dimension of the Chronic Treatment Acceptance Questionnaire (ACCEPT).

Objectives	Endpoints
To assess tolerability of injections.	• Change from Week 4b in tolerability of injections at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating Scale (NRS) within the CAB + RPV arm.
Other	
To examine plasma concentrations of CAB and RPV in Japanese subjects compared to the overall study population	• Oral CAB and RPV PK parameters on Day 1 and CAB and RPV plasma PK concentrations collected at specific time points between Week 4b and Week 96 in Japanese subjects, following IM CAB LA + RPV LA every 4 weeks.

Methodology:

This was a 120-week Phase III, multi-phase, randomized, open label, active-controlled, multicenter, parallel-group, non-inferiority study in HIV-1, ART-naïve adult subjects.

All subjects completed the Screening Phase of up to 35 days prior to Induction Baseline (Week -20). Eligible subjects were enrolled into the Induction Phase of the study and received ABC/DTG/3TC for 20 weeks (Week -20 to Day 1). For subjects who were HLA-b*5701 positive, DTG was taken with a non-abacavir nucleoside reverse transcriptase inhibitor (NRTI) backbone, chosen per investigator.

Subjects who had an HIV 1 RNA <50 c/mL at the Week -4 Visit were eligible to enter the Maintenance Phase. Eligible subjects were randomized (1:1) to receive either oral CAR (ABC/DTG/3TC or the alternative non-abacavir backbone) or oral CAB 30 mg + RPV 25 mg once daily for a minimum of 4 weeks (Oral Lead-in [OLI]) followed by IM CAB + RPV every 4 weeks thereafter. Randomization was stratified by subject's Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥ 100,000◦c/mL) and sex at birth.

Subjects randomized to CAR during the Maintenance Phase continued CAR for at least an additional 100 weeks. Subjects who successfully completed Week 100 (without meeting study defined withdrawal criteria and who remained virologically suppressed at Week 96: HIV-1 RNA <50 c/mL) were given the option to switch to the IM CAB + RPV arm in the Extension Phase or be withdrawn from the study. The transition from CAR to CAB + RPV within the Extension Phase could be completed with or without an OLI prior to commencement of injectable treatment. The OLI decision was made by the subject in consultation with the investigator and had to be appropriately documented.

All subjects randomized to CAB + RPV during the Maintenance Phase continued IM CAB + RPV for at least an additional 96 weeks and continued to have access to IM CAB + RPV in the Extension Phase.

Any subject who received at least a single dose of IM CAB and/or RPV and discontinued the CAB + RPV regimen for any reason entered a 52-week Long-Term Follow-Up Phase. Subjects were to be put on oral highly active antiretroviral therapy (HAART) as soon as

possible after discontinuing CAB + RPV and were to remain on HAART for at least 52 weeks after the last dose of IM CAB and/or RPV.

Number of subjects: A total of 809 subjects were screened, of these, 180 were classified as screen failures. A total of 631 subjects entered the Induction Phase of which 629 subjects received study drug (ABC/DTG/3TC or DTG with a non-abacavir NRTI backbone for subjects who were HLA-B*5701 positive). Of the subjects that completed the Induction Phase, 566 eligible subjects were randomized 1:1 into the Maintenance Phase (CAB + RPV 283 subjects; CAR 283 subjects).

Diagnosis and main criteria for inclusion: This study recruited HIV-1 infected (Screening plasma HIV-1 RNA ≥1000 c/mL), ART-naïve (≤ 10 days of prior therapy with any ART following a diagnosis of HIV-1 infection), male and female (non-pregnant, non-lactating and practicing adequate contraception) subjects, aged ≥18.

Treatment administration: All subjects received abacavir/dolutegravir/lamivudine, (TRIUMEQ™; ABC/DTG/3TC) during the Induction Phase (unless the subject was HLA-b*5701 positive at Screening in which case a non-abacavir containing DTG regimen was chosen). At the end of the Induction Phase, eligible subjects were randomized 1:1 into the Maintenance Phase to receive either:

- Oral CAB 30 mg + RPV 25 mg once daily for a minimum of 4 weeks followed by IM injections of CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4b, IM CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter). Subjects were to receive IM injections of CAB + RPV for at least 96 Weeks, or;

- Oral CAR (ABC/DTG/3TC or DTG + the alternative non-abacavir backbone) for at least 100 Weeks.

Batch numbers are summarized below.

Investigational Product	Formulation and Route of Administration	Batch Numbers
ABC/DTG/3TC	600 mg of abacavir, 50 mg dolutegravir, and 300 mg of lamivudine tablet Oral	[redacted]
DTG	50 mg tablet Oral	
CAB	30 mg tablet Oral	
CAB LA	200 mg/mL IM	
RPV	25 mg tablet Oral	
RPV LA	300 mg/mL IM	

Criteria for evaluation: Primary and secondary endpoints are tabulated above under objectives.

Statistical methods:

Sample Size Estimation:

This study planned to randomize approximately 285 subjects per arm. Assuming the true virologic failure rate is 3% for the CAB + RPV injectable regimen and 2% for the continuation of CAR arm, a non-inferiority margin of 6%, and a 2.5% one-sided significance level, this would provide approximately 97% power to show non-inferiority for the proportion of subjects with virologic failure (per FDA's snapshot algorithm for assessing HIV-1 RNA ≥ 50 c/mL) at Week 48.

The sample size of 285 subjects per arm also provides at least 90% power to show non-inferiority in the proportion of subjects with plasma HIV-1 RNA <50 c/mL (per

FDA's Snapshot algorithm) at Week 48 over a range of true response rates, based on a -10% non-inferiority margin and 2.5% one-sided significance level. Assuming true response rates for the CAB + RPV arm and CAR arm were both 87%, the power is at least 94% to show non-inferiority for this key secondary endpoint at Week 48.

Key Analysis Populations:

Population	Definition / Criteria
All Subjects Screened	• Comprised of all subjects screened for inclusion in the study. • Subjects could be re-screened once, for which they received a new subject number. • Only the latest re-screening data is included in the screening population summaries/analyses.
All Subjects Enrolled	• All enrolled subjects who received at least one dose of study drug during the Induction Phase.
Randomized	• All randomized subjects
ITT-E	• All randomized subjects who received at least one dose of study drug during the Maintenance Phase of the study (on or after Day 1 visit). • Subjects were analyzed according to the randomized treatment regardless of what treatment was actually received.
PP	• Comprised of all subjects in the ITT-E Population with the exception of major protocol violators.
Safety	• All randomized subjects who received at least one dose of study drug during the Maintenance Phase of the study (on or after Day 1 visit). • Subjects were assessed according to actual treatment received.
PK	• All subjects who received CAB and / or RPV and had PK sampling during the study and provided evaluable CAB and /or RPV plasma concentration data (i.e., at least 1 non-missing PK assessment (NQ values will be considered as non-missing values).
CVF	• Comprised of all subjects in the ITT-E Population who met CVF *CVF during the Maintenance and Extension Phases is defined as: rebound as indicated by two consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL
Extension Switch (ES)	• All randomized subjects from ABC/DTC/3TC arm who received at least one dose of CAB and/or RPV during the Extension Phase of the study. • Subjects were assessed according to actual treatment received during the Extension Phase.
Long-Term Follow-Up (LTFU)	• All subjects receiving at least one dose of CAB LA and/or RPV

Population	Definition / Criteria
	LA who have discontinued the CAB LA+ RPV LA regimen and have a least one Long-Term Follow-up Phase clinic visit.
Japan PK	• All Japanese heritage subjects (living in Japan) who received CAB and / or RPV and underwent PK sampling and provided evaluable CAB and /or RPV plasma concentration data (i.e. at least 1 non-missing PK assessment (Non-quantifiable [NQ] values were considered as non-missing values)). PK assay results from samples collected from a subject with emesis occurring within 4 hours of the dose were to be considered as evaluable.

Statistical Methods

Primary Efficacy Analyses:

The primary analysis was based on the ITT-E Population using the Snapshot algorithm. The primary comparison was evaluated at a one-sided 2.5% level of significance. Treatment with CAB + RPV was declared non-inferior to CAR if the upper end of a two-sided 95% CI for the difference between the two groups ([CAB + RPV] – CAR) in virologic failure rates at Week 48 was below 6%.

For the primary comparison, the treatment difference and associated 2-sided 95% CI were calculated based on stratum-adjusted proportions using Cochran-Mantel-Haenszel (CMH) weights, with stratification by Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL) and sex at birth. The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 groups.

Homogeneity of the treatment difference was examined individually across each stratification factor using weighted least squares chi-squared statistics and a one-sided 10% level of significance.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

The proportion of subjects with Snapshot HIV-1 RNA≥50 c/mL at Week 48 for each treatment group and the difference between the 2 groups at Week 48 were also summarized within demographic and Baseline characteristic subgroups. The 95% confidence intervals (CIs) for the treatment differences within subgroups were calculated using an unconditional exact method based on 2 inverted 1-sided tests.

Secondary Efficacy Analyses

Key Secondary Efficacy Analysis: A key secondary analysis was to evaluate the proportion of responders (HIV-1 RNA <50 c/mL per Snapshot) at Week 48 based on the ITT-E Population using the same analysis method and stratification factors as specified

for the primary endpoint. A non-inferiority margin of -10% was used for this secondary comparison at Week 48, where if the lower limit of the 95% CI of the difference in responder rate between the two treatment groups was greater than -10%, non-inferiority would be demonstrated.

The analysis described above was also performed using the PP Population and the results were compared for consistency with the results from the ITT-E Population.

Similar subgroup analyses (as described above for the primary efficacy endpoint) were also performed for the key secondary efficacy endpoint.

Additional Secondary Efficacy Analyses: Proportion of subjects in each treatment group with plasma HIV-1 RNA <200 c/mL and <50 c/mL, and HIV-1 RNA ≥200 c/mL and ≥50 c/mL, respectively, over time during the Maintenance Phase was summarized using the Snapshot algorithm. The proportion of subjects with confirmed virologic failure during the Maintenance Phase was also summarized over time.

Absolute values and change from Maintenance (Day 1) Baseline for CD4+ lymphocyte count, and absolute values for plasma HIV-1 RNA, were summarized over time using descriptive statistics (mean, median, interquartile range, min and max). The incidence of HIV-1 disease progression (AIDS and death) during the Maintenance Phase was presented. Data from low level of HIV-1 RNA quantification were summarized at Maintenance (Day 1) Baseline and Week 48.

Time-to-event analyses of failure were performed to estimate the proportion of subjects in each treatment group without efficacy-related (confirmed virologic failure or discontinuation due to lack of efficacy) or treatment-related failure (confirmed virologic failure, discontinuation due to lack of efficacy, drug-related AE, intolerability of injection, or protocol defined safety stopping criteria), respectively, using the Kaplan-Meier nonparametric method. Subjects without any of these events were censored. The estimated proportion of subjects without any of these events at Week 48 for each treatment group, and the treatment difference with 95% CI were presented.

Safety Analyses:

Safety data (AEs, serious adverse events [SAEs], ISRs, withdrawals) were listed and summarized by treatment group.

The extent of exposure was summarized for each treatment group. Adherence to the CAB + RPV dosing schedule in relation to the projected date was assessed.

Changes from Maintenance Baseline (Day 1) in laboratory (including fasting lipids), vital signs and electrocardiograms (ECG) data were summarized. In addition, the number and percentage of subjects with maximum graded laboratory toxicities (of increased severity relative to last value collected up to and including the start of maintenance phase study drug, based on Division of Acquired Immunodeficiency Syndrome [DAIDS] categories) were summarized by treatment group.

Pharmacokinetic Analyses:

Plasma CAB and RPV concentrations over time were summarized by visit for the subjects switching to CAB + RPV. The statistical analysis of plasma steady state concentration through Week 48 was performed for CAB and RPV separately.

Plasma CAB and RPV concentrations following Day 1 oral dosing in Japanese subjects were summarized. Plasma CAB and RPV trough concentrations from Week 4b through Week 96, in Japanese subjects, were summarized and compared to the overall study population.

Pharmacokinetic/Pharmacodynamic Analyses:

The relationship between the plasma CAB and RPV concentrations and Snapshot HIV-1 RNA ≥50 c/mL at Week 48, and predictors of efficacy failure, was explored using univariable and multivariable logistic regression analysis (using backwards covariate selection of predictors that were significant in the univariable analysis with $p < 0.15$). Fisher's Exact test was also used as post-hoc analyses when the univariate logistic model could not converge. In addition, the relationship between plasma CAB and RPV concentrations and the following measures during Maintenance Phase was assessed graphically:

- Change from Maintenance Baseline (Day 1) in 2hr post-dose QTc at Week 4b and Week 48
- Maximum change from Maintenance Baseline (Day 1) in ALT/total bilirubin
- Relationship between the plasma CAB and RPV concentrations and Snapshot HIV-1 RNA ≥ 50 c/mL during Maintenance Phase at Week 96

Viral Genotyping Analyses:

The incidence of treatment emergent genotypic and phenotypic resistance was summarized by treatment arm for subjects meeting confirmed virologic failure criteria.

Health Outcomes Analyses:

The following endpoints were summarized for the Observed Case values by visit during the Maintenance Phase. In addition, these endpoints were also summarized by visit with missing values imputed by LOCF.

- Change from Week 5 in Dimension Scores and proportion of subjects considering pain and local reactions following injection using PIN (Perception of Injection Questionnaire) (CAB + RPV group only)
- Change from Maintenance Baseline (Day 1) in HATQoL (Life satisfaction, HIV medications, disclosure worries) at Week 24, 48, 96 (or withdrawal)
- Change from Maintenance Baseline (Day 1) in SF-12: Total Score, Physical Component Summary (PCS) and Mental Component Summary (MCS) at Week 24, 48, 96 (or withdrawal)

Change from Maintenance Baseline (Day 1) in ACCEPT general acceptance score at Week 8, 24,48, 96 (or withdrawal)

Change from Week 4b in tolerability of injections using NRS at Week 5, 40, 41, and 96 (CAB +RPV arm only)

Change from Baseline (Day 1) in HIVTSQs total treatment satisfaction score and individual item scores at Week 4b, 24, 44, 96 (or withdrawal)

Treatment Satisfaction Score (HIVTSQs change version) and individual item scores at Week 96

A statistical comparison between treatment groups was performed at each visit for HATQoL, HIVTSQs, HIVTSQc, ACCEPT, and SF-12 using an ANCOVA model with treatment, age, Induction Baseline (Week -20) viral load, sex at birth, race and Baseline score value (except for HIVTSQc) as fixed effects and last observation carried forward (LOCF) imputation for missing data.

Changes from Week 5 in PIN acceptance score to Week 41 and Week 48, respectively, based on LOCF imputation for missing data were evaluated using a Wilcoxon Signed-Rank Test.

Summary:

Results presented represent the 96 Week analysis:

Demographics: Subject disposition is provided below:

Table: Summary of Subject Accountability at Week 96/100 Analysis: Maintenance Phase Conclusion Record (ITT-E Population)

	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)
Subject Status at Week 96/100 Analysis		
Randomized	283 (100)	283 (100)
Ongoing, n (%)	0	0
Completed, n (%)	244 (86)	253 (89)
Withdrawn, n (%)	39 (14)	30 (11)
Primary[a]/subreason[b] for study withdrawal, n (%)		
AE	14 (5)	4 (1)
Lack of efficacy	6 (2)	5 (2)
Insufficient viral load response	2 (<1)	1 (<1)
CVF	4 (1)	4 (1)
Protocol deviation	0	2 (<1)
Non-compliance with protocol procedures	0	1 (<1)
Non-compliance with study treatment	0	1 (<1)
Prohibited medication use	0	1 (<1)
Withdrawal by subject	14 (5)	10 (4)
Burden of travel or lack of access to travel	1 (<1)	0
Frequency of injections	1 (<1)	0
Frequency of visits	3 (1)	5 (2)
Intolerability of injections	3 (1)	0
Subject relocated	4 (1)	1 (<1)
Subject was incarcerated	1 (<1)	0
Other, specify[c]	3 (1)	4 (1)
Lost to follow-up	2 (<1)	3 (1)
Physician decision	3 (1)	6 (2)
Pregnancy	1 (<1)	1 (<1)
Other[d]	2 (<1)	5 (2)
Outcome of AEs resulting in study withdrawal		
Fatal	0	0
Non-fatal	14 (5)	4 (1)

a. Subjects may have only 1 primary reason for withdrawal.
b. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than 1 subreason underneath a single primary reason. Subjects are not required to indicate subreasons.
c. CAB + RPV: 2 subjects wanted to get pregnant, 1 subject changed jobs and couldn't make study visits; CAR: 1 relocation; 1 subject decision to stop CAR, 1 unspecified reason, 1 subject [redacted] from country.
d. CAB + RPV: 1 subject needed at least 6 months anti-coagulation for thrombosis; 1 subject was unreliable with appointments and frequently rescheduled (Investigator feared prolonged dosing interval with subsequent virologic failure). CAR: 2 subjects had noncompliance with study treatment and protocol procedures; 1 subject ViiV Safety and Labelling Committee decision (subject had acute Hepatitis E infection followed by continued [redacted] use); 1 subject did not show up or was late for visits, 1 subject had substance abuse.

Demographic characteristics were generally similar between treatment groups. Although the majority were male, the study exceeded the goal to enroll at least 20% female subjects. Most subjects were aged 18 to <50 years of age (89%) with a median (range) of 34 (18 to 68) years. The predominant race was White-White/Caucasian/European heritage.

Demographic characteristics of the study population were similar between the Week 48 and Week 96 analyses; any small numerical updates to baseline demographic values between the two analyses are a result of query resolution and database updates. Outlying baseline weight values were queried for some subjects and missing race information for 2 subjects in the Week 48 analysis was updated for the Week 96 analysis.

Table: Summary of Demographic Characteristics (ITT-E Population)

Demographic Characteristic	CAB + RPV (N=283)	CAR (N=283)
Age (y), n		
Mean	35.9	36.0
SD	10.17	9.82
Median	34.0	34.0
Min.	19	18
Max.	68	68
Age group (y), n (%)		
<35	143 (51)	145 (51)
35 to <50	107 (38)	109 (39)
≥50	33 (12)	29 (10)
Sex at birth, n (%)[a]		
Female	63 (22)	64 (23)
Male	220 (78)	219 (77)
Race, n (%)		
White	216 (76)	203 (72)
Non-White	67 (24)	80 (28)
American Indian or Alaska Native	3 (1)	6 (2)
Asian-Central/South Asian Heritage	2 (<1)	1 (<1)
Asian-East Asian Heritage	1 (<1)	2 (<1)
Asian-Japanese Heritage	8 (3)	12 (4)
Asian-South East Asian Heritage	1 (<1)	0
Black or African American	47 (17)	56 (20)
Native Hawaiian or Other Pacific Islander	1 (<1)	0
White-Arabic/North African Heritage	5 (2)	3 (1)
White-White/Caucasian/European Heritage	211 (75)	200 (71)
Multiple	4 (1)	3 (1)
Ethnicity, n (%)		
Hispanic or Latino	28 (10)	40 (14)
Not Hispanic or Latino	255 (90)	243 (86)
BMI (kg/m^2) at Induction Baseline (Week -20)		
Mean	25.126	24.986
SD	4.4500	4.8182
Median	24.100	24.000
Min.	17.30	16.20
Max.	44.90	47.40

a. Reported gender was also collected. Two individuals who were male at birth identified themselves as female at study enrolment.

Baseline characteristics were generally similar between treatment groups, except for viral hepatitis status at Induction Baseline (Week -20). At Induction Baseline (Week -20), 18 (6%) subjects in the CAB + RPV group and 9 (3%) subjects in the CAR group tested positive for hepatitis C (HCV) only. No subjects tested positive for hepatitis B (HBV) only. One subject in the CAB + RPV group tested positive for HBV (HbsAg NR; antiHbcore positive; Hbs antibody negative) and HCV. The HBV virus positive subject had a local hepatitis B virus DNA obtained that was <12 IU/mL, therefore the subject was not considered to have violated the exclusion criteria and was enrolled in the study.

Efficacy Results for the Week 96 Analysis:

Primary Analysis: Previously reported in the Week 48 CSR.

Secondary Efficacy Analyses: Results demonstrated that once-monthly CAB + RPV continued to maintain virologic suppression and was non-inferior to CAR, with few subjects having plasma HIV-1 RNA ≥50 c/mL at Week 96 per the Snapshot Algorithm in either group for the ITT-E and PP Populations. The upper bound of 95% CI for the adjusted treatment difference between CAB + RPV and CAR was less than the pre-defined non-inferiority margin of 6%.

Table: Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 96 (Maintenance Phase) Snapshot Analysis (ITT-E and PP Population)

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	283	9 / 283 (3.2)	0.0 (-2.9, 2.9)	0.0 (-2.9, 2.9)
CAR	283	9 / 283 (3.2)		
PP Population				
CAB + RPV	278	9 / 278 (3.2)	0.0 (-2.9, 3.0)	0.0 (-2.9, 2.9)
CAR	281	9 / 281 (3.2)		

a. Difference: proportion on CAB + RPV - proportion on CAR
b. Based on CMH stratified analysis adjusting for the following Baseline stratification factors: sex at birth (male, female) and Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL)

Treatment differences for the secondary endpoint for each randomization stratification factor (Induction Baseline [Week -20] HIV-1 RNA [<100,000 c/mL] and sex at birth) support the non-inferiority of CAB + RPV compared with CAR.

Study outcomes based on HIV-1 RNA ≥50 c/mL at Week 96 Snapshot analysis were similar for both treatment groups. The majority of subjects remained suppressed with HIV-1 RNA <50 c/mL at Week 96 Snapshot analysis. A small number of subjects had HIV-1 RNA ≥50 c/mL at Week 96 (CAB + RPV 9 [3.2%] subjects; CAR 9 [3.2%] subjects; or had no virologic data (CAB + RPV 29 [10.2%] subjects; CAR 21 [7.4%] subjects). Within the Week 96 Snapshot analysis under the category of no virologic data,

there were more AEs leading to withdrawal in the CAB + RPV group compared with the CAR group.

Table: Summary of Study Outcomes (Plasma HIV-1 RNA of 50 c/mL cut off) at Week 96 (Maintenance Phase) Snapshot Analysis (ITT-E Population)

Outcome	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)
HIV-1 RNA <50 c/mL	245 (86.6)	253 (89.4)
HIV-1 RNA ≥50 c/mL	9 (3.2)	9 (3.2)
Data in window not below threshold	3 (1.1)	2 (0.7)
Discontinued for lack of efficacy	6 (2.1)	5 (1.8)
Discontinued for other reason while not below threshold	0	2 (0.7)
Change in background therapy	0	0
No virologic data	29 (10.2)	21 (7.4)
Discontinued study due to AE	12 (4.2)[a]	4 (1.4)[b]
Discontinued study for other reasons	16 (5.7)[c]	17 (6.0)[d]
On study but missing data in window	1 (0.4)	0

a. 3 injection site pain, 2 Hepatitis C, 1 Hepatitis A, 1 Hepatitis B, 1 transaminases, 1 syphilis,1 depression, 1 adenocarcinoma, 1 nasopharyngitis.
b. 1 tremor, 1 disturbance in attention and dysarthria, 1 renal insufficiency, 1 dizziness, fatigue, nausea.
c. 3 subject relocation, 2 intolerability of injections, 2 lost to follow-up, 2 pregnancy plans, 1 burden of travel, 1 job change, 1 subject unreliable, 1 need for anticoagulation, 1 incarceration, 1 pregnancy, 1 frequency of visits.
d. 4 frequency of visits (subject decision), 3 noncompliance with study treatment and protocol procedures, 2 relocation, 1 subject decision to stop treatment, 1 late to attend visits, 1 lost to follow-up, 1 pregnancy, 1 substance abuse, 1 burden of travel, 1 ViiV Safety and Labelling Committee decision, 1 unspecified.

Results showed that CAB + RPV is non-inferior to CAR for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 96 per the Snapshot Algorithm in the ITT-E and PP Populations.

Table: Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 96 (Maintenance Phase) – Snapshot Analysis (ITT-E and PP Population)

Treatment	N	Number of HIV-1 RNA <50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	283	245 / 283 (87)	-2.8 (-8.2, 2.5)	-2.8 (-8.2, 2.5)
CAR	283	253 / 283 (89)		
PP Population				
CAB + RPV	278	241 / 278 (87)	-3.0 (-8.3, 2.4)	-3.0 (-8.3, 2.4)
CAR	281	252 / 281 (90)		

a. Difference: Proportion on CAB + RPV - Proportion on CAR
b. Based on CMH stratified analysis adjusting for the following Baseline stratification factors: sex at birth (male, female) and Induction Baseline (Week -20) HIV-1 RNA (<100,000, ≥100,000 c/mL)

The proportion of subjects with plasma HIV-1 RNA ≥50 c/mL by visit was generally similar for both treatment groups. Note that, per protocol, viral loads were only obtained every 8 weeks starting at Week 48 for the CAR group and at Week 64 for the CAB + RPV group.

The proportion of subjects with CVF (2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) during the Maintenance Phase was low. The proportion of subjects with CVF in the CAB + RPV group was 1.4% (4 subjects) and in the CAR group was 1.4% (4 subjects) with no new CVFs in the CAB + RPV group since the Week 48 analysis. The proportion of subjects with plasma HIV-1 RNA <200 c/mL by visit for the Maintenance Phase was high and similar in both treatment groups. At Week 96, 88% (95% CI: 84%, 91%) of CAB + RPV subjects and 90% (95% CI: 87%, 94%) of CAR subjects had plasma HIV-1 RNA <200 c/mL.

The endpoint for the treatment related discontinuation = failure analysis was a composite of the following efficacy and safety/intolerability events (based on the primary reason for discontinuation from the Maintenance Phase by Study Day 686): CVF (CAB + RPV 4 vs CAR 4), lack of efficacy (CAB + RPV 2 vs CAR 1), drug-related adverse events (CAB + RPV 5 vs CAR 3), protocol defined safety stopping criteria (CAB + RPV 0 vs CAR 0) and intolerance to injections (CAB + RPV 3 vs CAR 0). The endpoint for the efficacy related discontinuation = failure analysis pertained to efficacy related discontinuation only: CVF (CAB + RPV 4 vs CAR 4), lack of efficacy (CAB + RPV 2 vs CAR 1). Results of these analyses were consistent with the findings for the secondary endpoint plasma HIV-1 RNA <50 c/mL.

No clinically relevant differences in absolute values and changes from Maintenance Baseline (Day 1) in CD4+, CD8+ counts and CD4+/CD8+ ratio through Week 96 were observed between the treatment groups.

Disease progression was defined as HIV-associated conditions, AIDS, and death. There were no deaths during the Maintenance Phase. Rates of disease progression to Center for Disease Control (CDC) Stage 3 were similar in both treatment groups. Ten (4%) subjects in the CAB + RPV group and 15 (5%) subjects in the CAR group had disease progression to CDC Stage 3 disease during the Maintenance Phase.

Safety:

Adverse Events

Table: Overall Summary of Adverse Events – Maintenance Phase through 100 Weeks (Safety Population)

	CAB + RPV (N=283) n (%)	CAR (N=283) n (%)
Any AE	274 (97)	242 (86)
Any AE, excluding ISRs	264 (93)	242 (86)
ISR AE	245 (88)	NA
Any Grade 3 to 4 AEs	40 (14)	16 (6)
Grade 3 to 4 AEs, excluding ISRs	29 (10)	16 (6)
AEs leading to withdrawal	14 (5)	4 (1)
Drug-related AEs leading to withdrawal	5 (2)	3 (1)
Drug-related AEs	246 (87)	33 (12)
Drug-related AE, excluding ISRs	95 (34)	33 (12)
Drug-related Grade 3 to 4 AE	16 (6)	0
Drug related Grade 3 to 4 AE, excluding ISR	4 (1)	0
Any SAE	24 (8)	22 (8)
Drug-related SAEs	1 (<1)[a]	0
Fatal SAEs	0	0
Drug-related fatal SAEs	0	0

a. Drug-related SAE in the CAB + RPV group was right knee monoarthritis
Note: Only on-treatment events are considered.

The percentage of subjects reporting any AE was higher in the CAB + RPV group (97%) compared to the CAR group (86%). This was at least in part attributable to the frequency of ISRs in the CAB + RPV group. The frequency of individual common AEs (≥5%) was comparable in the 2 treatment groups, with the exception of ISR events (pain, nodule, induration, swelling, pruritus, and erythema) which were specific to the CAB + RPV group, and pyrexia (11% vs 2%), hemorrhoids (7% vs 2%), myalgia (6% vs 2%),

oropharyngeal pain (6% vs 2%), oral herpes (6% vs 2%), dizziness (6% vs 1%), vomiting (6% vs 2%), dyspepsia (6% vs 1%), and asthenia (6% vs <1%) which were reported more frequently in the CAB + RPV group.

Non-ISR AEs consisted primarily of Grade 1-2 events. Non-ISR Grade 3 AEs occurred in 21 (7%) subjects in the CAB + RPV group and 10 (4%) subjects in the CAR group. Non-ISR Grade 4 AEs occurred in 8 (3%) subjects in the CAB + RPV group and 6 (2%) subjects in the CAR group.

Non-ISR drug-related AEs consisted primarily of Grade 1-2 events and were reported more frequently for CAB + RPV (95 [34%] subjects) compared with CAR (33 [12%] subjects).

During the Maintenance Phase, 14 (5%) subjects in the CAB + RPV group and 4 (1%) subjects in the CAR group had AEs leading to withdrawal/permanent discontinuation of study drug.

During the Maintenance Phase, 24 (8%) subjects in the CAB + RPV group and 22 (8%) subjects in the CAR group had non-fatal SAEs. There were no discernible patterns of SAEs by preferred term, with only Hepatitis A, anogenital warts, and anal abscess being reported by more than one subject. There was one SAE assessed by the investigator as related to CAB + RPV (right knee monoarthritis).

Overall, injections with CAB + RPV were well tolerated. ISRs were reported frequently and most commonly comprised of mild (Grade 1 or 2), short-lived and self-resolving pain events. There were no Grade 4 ISRs and no ISRs were SAEs. Few ISRs (5%) lasted more than 14 days(median duration 3 days). Injections seldom led to withdrawal (3 subjects withdrew citing ISR pain and 3 additional subjects withdrew consent stating general ‘intolerability of injections’), and overall health outcomes data demonstrated consistent and high levels of acceptability of injections. A majority of subjects had ISRs at the initial 3 mL loading injections; however, the incidence of ISRs decreased over time through Week 96.

Hepatotoxicity was categorized as an AE of special interest for the current study. There were no liver findings that raised a concern for the CAB + RPV regimen and there were no cases considered to represent DILI. Eight of the 9 subjects in the study who met liver stopping criteria on the CAB + RPV group had an acute hepatitis infection (4 subjects acute hepatitis A; 2 subjects acute hepatitis B; 2 subjects acute hepatitis C) and 1 subject had transaminitis related to illicit drug use and inorganic solvent abuse.

Clinical Laboratory Evaluations

No clinically relevant differences were observed in clinical laboratory abnormalities, for either chemistry or hematology, between the CAB + RPV and CAR groups. No clinically significant differences were observed for graded abnormalities for any of the following parameters: alanine aminotransferase (ALT), aspartate aminotransferase (AST), bilirubin, or lipase.

There were no reported events of rhabdomyolysis associated with any of the transient Grade 1 to 4 elevations of creatine phosphokinase (CPK).

Fasting lipid National Cholesterol Education Program (NCEP) categories at Week 96 versus Baseline were similar in the 2 treatment groups. No clinically relevant patterns of change in NCEP fasting lipids from Baseline to maximum post Baseline category were observed in either treatment group.

Suicidal Ideation or Behavior

Sixteen (6%) subjects in the CAB + RPV group and 18 (6%) subjects in the CAR group reported suicidal ideation or behavior during Maintenance Phase. Five (2%) subjects in the CAB + RPV group and 5 (2%) subjects in the CAR group had positive suicidal ideation or behavior alerts, of which 1 and 3 alerts were confirmed by investigator clinical assessment for the CAB + RPV and CAB groups, respectively. Depression and suicidal AEs based on a subject's prior history of depression, anxiety, or suicidal ideation were similar between the 2 treatment groups. These types of AEs were reported in subjects regardless of whether they had or did not have a history of depression, anxiety, or suicidal ideation. However, subjects who had a prior history appeared to be at increased risk of reporting these events.

Pharmacokinetic and Pharmacodynamic Analyses

Primary Analysis: Pharmacokinetics and the Pharmacokinetic /Pharmacodynamic analyses through Week 48 was reported in the Week 48 report.

CAB steady state was confirmed at Week 44. Week 96 geometric mean (95% CI) CAB predose concentration of 2.80 µg/mL (2.64, 2.97) was similar to the Week 48 CAB predose concentration of 3.13 µg/mL (2.95, 3.33). Steady-state CAB concentrations at Week 96 were similar to the geometric mean (95% CI) of 3.13 µg/mL (2.61, 3.76) following CAB LA + RPV LA Q4W IM for 96 weeks in another Phase III Study.

Week 96 geometric mean (95%) RPV predose concentration of 112 ng/mL (106, 118) was 36% higher than Week 48 RPV predose concentration of 82.4 ng/mL (77.8, 87.2), consistent with an estimated terminal half-life of 28 weeks. RPV concentrations were starting to plateau showing that they were close to achieving steady-state. Week 96 RPV concentrations were similar to the geometric mean (95% CI) of 111 ng/mL (94.4, 130) following CAB LA + RPV LA Q4W IM for 96 weeks in another Phase III Study.

Similar to the overall population, CAB concentrations in Japanese subjects appear to achieve steady-state by Week 48. CAB trough and Cmax concentrations from Week 48 to Week 96 were 14 to 46% higher in Japanese subjects, though they did not exceed the long-term safety threshold (13.1 µg/mL). The trend to higher CAB exposure in the subjects in Japan is not considered to be of clinical concern and likely reflects differences in population average anthropometric measures (such as body weight and BMI). RPV predose concentrations were 32% higher in Japanese subjects at Week 48 compared to the overall population. From Week 52 to Week 96, RPV predose concentrations were similar to the overall population. Accumulation of RPV to Week 96 in Japanese subjects was comparable to the overall population. None of the 8 Japanese subjects had

HIV-1 RNA ≥50 c/mL at both the Week 48 and Week 96 Visit, consistent with the low rate of HIV-1 RNA ≥50 c/mL observed in the overall study population at these timepoints.

Given the few subjects who were identified as CVFs on CAB + RPV, together with no additional CVF between Week 48 and Week 96 and the fact that there was a high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it was difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure.

Viral Genotyping

CVF through Week 100 was low in the study with 4 (1.4%) subjects meeting CVF in the CAB + RPV group and 4 (1.4%) subjects in the CAR group. Since the Week 48 analysis, there was one additional CVF during the Maintenance Phase in the CAR group at Week 64. The CVF in the CAR group had no treatment emergent INSTI mutations at Week 64. This subject was from Russia and had Subtype A virus by Q2 and Complex Subtype by Monogram. INSTI polymorphism L74I was present at Baseline and at Week 64. There were no treatment emergent INSTI mutations at Week 64. During the Extension Phase, there was a CVF in the CAB + RPV group at Week 108. The subject's baseline RT had no NNRTI mutations with full susceptibility to all NNRTIs. Baseline INSTI had L74I with susceptibility to CAB, DTG, RAL, and EVG. At Week 108, the subject had NNRTI resistance mutations V106V/A, V108V/I, E138G, and M230L and INSTI resistance mutations N155H and R263K. The subject was from Russia and had Subtype A1.

Health Outcomes:

According to the HIVTSQs, high overall treatment satisfaction was observed at Baseline for both groups. Statistically significant improvement from Baseline was observed for the CAB + RPV LA group compared with the CAR group at Weeks 24 and 96.

For most subjects receiving CAB + RPV, acceptance of ISRs following their first injection was high and significantly improved over time across measured visits, according to the PIN.

Overall treatment acceptance in the CAB + RPV arm was high and remained high for the study duration according to the ACCEPT.

"Life Satisfaction" and general health status were high at Baseline and remained high for both treatment groups.

Conclusions:

Efficacy

Monthly CAB + RPV was shown to be non-inferior to continued oral CAR with respect to the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL and <50 c/mL (respectively) at Week 96 (Snapshot Analysis).

Pre-planned subgroup analyses support the consistency of the Snapshot efficacy endpoint conclusions among different subpopulations defined by demographic and Baseline characteristics, with consideration for lack of precision in estimation for subgroups with smaller sample sizes.

The 2-drug once monthly injectable regimen effectively maintained virologic suppression, with few CVFs. There were no additional CVFs in the CAB + RPV group between Week 48 and Week 96.

The overall proportion of subjects with CVF in this Week 96 analysis, including subjects with dosing beyond Week 96, in the CAB + RPV group was 1.8% (5 subjects, 1 of 5 occurring after Week 96) and in the CAR group was 1.4% (4 subjects).

- Taken together, these results indicate that the CAB + RPV regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure.

Safety

- Over 96 weeks, the safety data from this randomized, open-label Phase III study of subjects switching to CAB + RPV is favorable and consistent with prior Phase II trials. No new AEs of clinical concern were observed.
- Greater proportions of subjects in CAB + RPV group compared with those in the CAR group had AEs. Differences between the groups were primarily driven by ISRs in the CAB + RPV group, as would be expected.
- The higher incidence of AEs leading to withdrawal in the CAB+RPV group was primarily due to the higher incidence of hepatitis (mainly acute viral hepatitis which were considered unrelated to study treatment) and ISRs in the CAB+RPV group.
- Overall, injections with CAB + RPV were well tolerated, ISRs being generally mild and of short duration. Injection site pain was the most frequently reported ISR (82% subjects) however ISRs resulted in few withdrawals (<1%).
- For AEs of special interest, there was a lack evidence of an effect of study treatment on QT prolongation, hypersensitivity reactions, seizures, rhabdomyolysis, pancreatitis and impact on creatinine.
- There was increased incidence of anxiety and drug- related adverse events (anxiety, depression and abnormal dreams) in CAB+RPV compared to CAR. There was some evidence of increased weight gain in the CAB+RPV group compared to the CAR group.
- No clinically relevant differences were observed in clinical laboratory abnormalities, for either chemistry or hematology, between the CAB + RPV and CAR groups. No

clinically significant differences were observed for graded abnormalities for any of the following parameters: ALT, AST, bilirubin, or lipase.

- No clinically relevant patterns in changes in NCEP fasting lipids from Baseline category to maximum post Baseline category for the Maintenance Phase were observed in either treatment group for triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, or total cholesterol/HDL ratio.
- Weight gain was observed over 96 weeks.

Pharmacokinetics:

Week 96 CAB and RPV concentrations were similar for CAB + RPV Q4W IM treated subjects in other Phase III studies

Week 96 CAB concentrations were similar to Week 48 CAB concentrations, consistent with the achievement of steady-state after 44 weeks.

In line with the RPV LA half-life, there was some further accumulation of RPV between Week 48 and Week 96, but RPV predose concentrations appeared to plateau between Week 60 and Week 96.

At the 12-month LTFU visit, following discontinuation of CAB LA + RPV LA injections, CAB was detectable in 5/11 (45%) subjects and RPV was detectable in 10/10 (100%) subjects (not receiving oral RPV).

High 2-hour CAB and RPV concentrations due to suspected dosing errors were infrequent and did not result in virologic failure or AEs leading to withdrawal.

CAB and RPV concentrations in subjects who were Hepatitis C antibody positive at Baseline were similar to subjects who were not Hepatitis C antibody positive and none of these subjects met CVF criteria at Week 48 or Week 96.

In the Japanese subjects, mean trough and Cmax values for CAB and RPV concentrations tended to be higher than observed in the overall study population but were within the clinically appropriate ranges as determined by the overall population results. Therefore, the higher exposures are not considered to be of clinical concern.

Viral Genotyping and Phenotyping

- CVF was rare in this study and comparable between treatment groups, with a total of 4 CVFs observed for each treatment arm through Week 96 of the Maintenance phase. During the Maintenance phase, no CVFs occurred after Week 48 in the CAB + RPV group and 1 subject in the CAR group had CVF. One additional subject in the CAB + RPV group had CVF during the Extension Phase.
- The Subject in the CAR group had no treatment emergent resistance mutations.
- The subject in the CAB + RPV group with CVF at Week 108 had NNRTI resistance mutations V106V/A, V108V/I, E138G, and M230L with 27-FC to RPV and IN resistance mutations N155H and R263K with 9 FC to CAB, 3.78 FC to DTG (below the clinical cut-off of 4).

Health Outcomes

- According to the HIVTSQs, high overall treatment satisfaction was observed at Baseline for both groups. Statistically significant improvement from Baseline was

observed for the CAB + RPV LA group compared with the CAR group at Weeks 24 and 96.

- For most subjects receiving CAB + RPV, acceptance of ISRs following their first injection was high and significantly improved over time across measured visits, according to the PIN.

- Overall treatment acceptance in the CAB + RPV arm was high and remained high for the study duration according to the ACCEPT.

- "Life Satisfaction" and general health status were high at Baseline and remained high for both treatment groups.

Effective Date: [redacted]

Synopsis for Study 201585

Study Number: 201585

Title: A Phase III, randomized, multicenter, parallel-group, noninferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current INI- NNRTI-, or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed

Investigator(s): 114 investigators enrolled subjects

Study center(s): 115 centers in 13 countries (Argentina, Australia, Canada, France, Germany, Italy, Mexico, Korea, Russia, South Africa, Spain, Sweden, and the United States.)

Publication(s): None

Study Period: 28-OCT- 2016 to 29-MAY-2018

Phase of Development: III

Objectives:

Primary:

- To demonstrate the non-inferior antiviral activity of switching to IM CAB + RPV every 4 weeks (monthly) compared to continuation of CAR over 48 weeks in HIV-1 infected ART-experienced subjects.

Secondary:

- To demonstrate the antiviral and immunologic activity of switching to IM CAB + RPV every 4 weeks (monthly) compared to continuation of CAR;
- To evaluate the safety and tolerability of switching to CAB + RPV every 4 weeks (monthly) compared to continuation of CAR;
- To evaluate the effects of CAB + RPV every 4 weeks on fasting lipids over time compared to continuation of CAR over time;
- To assess viral resistance in subjects experiencing protocol-defined virologic failure;
- To assess the impact of Baseline third agent treatment class (INI, NNRTI, or PI) on efficacy, safety, tolerability, and viral resistance of CAB + RPV compared to continuation of CAR;
- To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability;

- To evaluate the antiviral and immunologic effects, safety, tolerability, and viral resistance of CAB + RPV for subjects during the Extension Phase;
  - For subjects randomized to CAB + RPV at Day 1;
  - For subjects electing to transition to CAB + RPV in the Extension Phase.
- To assess the acceptance of pain and injection site reactions following injections;
- To assess degree of HRQoL;
- To assess health status;
- To assess treatment satisfaction of CAB + RPV compared to continuation of CAR;
- To assess treatment acceptance;
- To assess tolerability of injections.

Methodology: Randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study

Number of subjects: 705 screened/618 randomized/616 exposed to study treatment (308 CAB + RPV, 308 CAR)

Diagnosis and main criteria for inclusion:

The main inclusion criteria were:

Aged 18 years or older (or ≥19 where required by local regulatory agencies) at the time of signing the informed consent;

Were on uninterrupted current regimen (either the initial or second ARV regimen) for at least 6 months prior to Screening. Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, had to occur due to tolerability/safety, access to medications, or convenience/simplification, and must NOT have been done for treatment failure (HIV-1 RNA ≥400 c/mL). Acceptable stable (initial or second) ARV regimens prior to Screening included 2 NRTIs plus:

- INI with the exception of ABC/DTG/3TC (either the initial or second CAR regimen);
- NNRTI (either the initial or second CAR regimen);
- Boosted PI (or atazanavir [ATV] unboosted) (had to be either the initial CAR regimen or 1 historical within-class switch was permitted due to safety/tolerability);

The addition, removal, or switch of a drug(s) that had been used to treat HIV based on antiretroviral properties of the drug constituted a change in ART with the following limited exceptions:

- Historical changes in formulations of ART drugs or booster drugs did not constitute a change in ART regimen if the data supported similar exposures and efficacy, and the change must have been at least 3 months prior to Screening;
- Historical perinatal use of an NRTI when given in addition to an ongoing HAART was not considered a change in ART regimen;
- A change in dosing scheme of the same drug from twice daily to once daily was not considered a change in ART regimen if data supported similar exposures and efficacy;

Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: 1 within the 6- to 12-month window, and 1 within 6 months prior to Screening;

Plasma HIV-1 RNA <50 c/mL at Screening.

Treatment administration:

Subjects were randomly assigned to receive treatment with oral CAB 30 mg + RPV 25 mg once daily for approximately 4 weeks during the Oral Lead-in Period, followed by CAB LA 600 mg + RPV LA 900 mg IM at Week 4b, CAB LA 400 mg + RPV LA 600 mg IM at Week 8 and Q4 weekly thereafter for 48 weeks, or to remain on their CAR.

Criteria for evaluation:

Primary Efficacy Assessments/Endpoints

- Proportion of subjects with Plasma HIV-1 RNA ≥50 copies/mL (c/mL) per the Snapshot Algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population).

Secondary Efficacy Assessments/Endpoints

- Proportion of subjects with Plasma HIV-1 RNA <50 copies/mL (c/mL) at Week 48 using the Snapshot Algorithm (Missing, Switch or Discontinuation = Failure, Intent-to-Treat Exposed [ITT-E] population).
- Proportion of subjects with plasma HIV-1 RNA <200 c/mL at Week 48 using the Snapshot algorithm (ITT-E population)
- Proportion of subjects with confirmed virologic failure (2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) at Week 48
- Absolute values and change from Baseline in plasma HIV-1 RNA (log_{10} c/mL) at Week 48.
- Absolute values and change from Baseline in CD4+ lymphocyte count at Week 48

- Incidence of disease progression (HIV-associated conditions, AIDS, and death over 48 Weeks

Pharmacokinetic Assessments/Endpoints

- To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability

Value Evidence and Outcomes Assessments/Endpoints

- To assess the acceptance of pain and injection site reactions following injections
  - Change from Week 5 in Dimension scores ("Bother of ISRs", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time using the Perception of iNjection questionnaire (PIN)
  - Proportion of participants considering pain and local reactions following injection to be extremely or very acceptable based on the acceptability score over time using the Perception of INjection questionnaire (PIN)
- To assess degree of health-related quality of life (HRQoL)
  - Change from Baseline in HR QoL using the HIV/AIDS-targeted quality of life questionnaire (HAT QoL) short form at Week 24, Week 48, Week 96 (or Withdrawal).
- To assess the health status
  - Change from Baseline in health status at Week 24, Week 48, and Week 96 (or Withdrawal) using the 12-item Short Form Survey (SF-12).
- To assess treatment satisfaction of CAB + RPV compared to continuation of current ART
  - Change from Baseline in total "treatment satisfaction" score, and individual items scores of the HIVTSQs at Weeks 4b, 24, 44, 96 (or Withdrawal)
  - Change in treatment satisfaction over time using the HIVTSQc at Week 48 (or Withdrawal)
- To assess treatment acceptance
  - Change from Baseline in treatment acceptance at Week 8, Week 24, Week 48, Week 96 (or Withdrawal) using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire
- To assess tolerability of injections
  - Change from Week 4b in tolerability of injection at Week 5, Week 40, Week 41, and Week 96 using the Numeric Rating Scale (NRS) within the CAB + RPV arm.

Viral Genotyping/Phenotyping Assessments/Endpoints

- To assess viral resistance in participants experiencing protocol-defined virologic failure
    - Incidence of observed genotypic and phenotypic resistance to current antiretroviral regimen and to CAB or RPV

Safety Assessments/Endpoints

- To evaluate the safety and tolerability of switching to CAB + RPV every 4 weeks (monthly) compared to continuation of current ART
    - Incidence and severity of adverse events (AEs) and laboratory abnormalities over time including Week 48
    - Proportion of participants who discontinue treatment due to AEs over time including Week 48
    - Absolute values and changes in laboratory parameters over time including Week 48
- To evaluate the effects of CAB + RPV every 4 weeks on fasting lipids over time compared to continuation of current ART over time.
    - Change from Baseline in fasting lipids over time including Week 48 and Week 96.

Other Assessments/Endpoints:

- To assess the impact of Baseline third agent treatment class (INI, NNRTI, or PI) on efficacy, safety, tolerability, and viral resistance of CAB + RPV compared to continuation of current ART

    1. <u>By Baseline third agent treatment class:</u>

    - Proportion of participants with a 'virologic failure' endpoint as per FDA Snapshot algorithm at Week 48 (Intent-to-Treat Exposed [ITT-E] population).
    - Proportion of participants with Plasma HIV-1 RNA <50 c/mL at Week 48 using the FDA Snapshot algorithm (Intent-to-Treat Exposed [ITT-E] population)
    - Incidence and severity of select AEs and laboratory abnormalities over time including Week 48
    - Proportion of participants who discontinue treatment due to AEs over time including Week 48
    - Absolute values and changes in select laboratory parameters over time including Week 48
    - Incidence of observed genotypic and phenotypic resistance to current antiretroviral regimen and to CAB or RPV for participants meeting confirmed virologic failure

- To evaluate the antiviral and immunologic effects, safety, tolerability, and viral resistance of CAB + RPV during the Extension Phase for participants randomized to CAB + RPV at Day 1 and for participants electing to transition to CAB + RPV in the Extension Phase

Statistical methods:

The primary analysis at Week 48 was performed after all participants had completed Week 48 or discontinued earlier.

Primary Efficacy Analyses

The primary analyses were based on the ITT-E population using the Snapshot method. The primary comparison was made at a 1-sided 2.5% level of significance. Treatment with CAB + RPV was to be declared non-inferior to CAR if the upper end of a 2-sided 95% confidence interval for the difference between the 2 groups ([CAB + RPV] - CAR) in the proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48 was below 6%.

For the primary comparison, adjusted estimates of the difference in the proportion of subjects with Snapshot HIV-1 RNA ≥50 c/mL between the 2 treatment groups were presented along with 95% CIs based on a stratified analysis using CMH weights. All CIs were 2-sided, and the analyses were stratified according to the Baseline third agent class (INI, NNRTI, or PI) and sex at birth. The INI strata was capped at 40%.

The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 groups.

The weighted least squares chi-squared statistic was used to test for 1-way homogeneity across the levels of each categorical variable, with each stratification factor considered separately. Following Lui and Kelly, 0.5 was added to each cell in any strata for which the stratum-specific rate estimates of either f_{la} or f_c were 0 or 1, and tests were 1-sided. Any heterogeneity found to be statistically significant was explored and if necessary, results were reported for each level of the categorical variable. Investigation of heterogeneity was confined to the primary endpoint using the Week 48 Snapshot analysis. Tests of homogeneity were assessed at the 1-sided 10% level of significance.

On-treatment data collected from extra visits within a window were included in the derivation of the Snapshot outcome.

The analyses for primary comparison were also performed using the PP population, and the results were compared for consistency with the results from the ITT-E population.

The proportion of virologic failures (HIV-1 RNA ≥50 c/mL per Snapshot algorithm) for each treatment group and the difference between the 2 groups at Week 48 were also summarized by subgroups (Baseline third agent class, sex at birth, age, race, country, Baseline CD4, Baseline CDC, and Baseline viral load). The 95% CIs for the differences

were calculated using both the normal approximation and an unconditional exact method with 2 inverted 1-sided tests, separately.

Secondary Analyses

Key Secondary Efficacy Analysis

A key secondary efficacy analysis evaluated the proportion of subjects with HIV-1 RNA <50 c/mL per Snapshot at Week 48 using a CMH test stratified by Baseline third agent class (INI, NNRTI, or PI) and sex at birth. A non-inferiority margin of -10% was used for this secondary comparison; if the lower limit of the 95% CI of the difference in responder rate between the 2 treatment groups was greater than -10%, then non-inferiority was demonstrated.

Similar subgroup analyses (as described for the primary efficacy endpoint) were also performed for the key secondary efficacy endpoint.

Other Efficacy Analysis

The proportion of subjects with plasma HIV-1 RNA <200 c/mL and <50 c/mL, respectively, for the ITT-E population over time was summarized using the Snapshot algorithm. The proportion of subjects with confirmed virologic failures was also summarized over time.

The proportion of subjects without virologic (ERDF) or virologic/tolerability (TRDF) failure was estimated using the Kaplan-Meier nonparametric method based on the time to the event (events including CVF or treatment related/efficacy related discontinuation such as drug-related AE, intolerability of injection, protocol defined safety stopping criteria, or lack of efficacy). Subjects without any of these events were censored. The estimate of the standard error used to derive 95% CIs for the difference in proportions between treatment groups was based on Greenwood's formula. The estimated proportion of subjects without any of these events at Week 48 for each group, the difference, and its 95% CI between 2 groups were presented. Absolute values and change from Baseline in plasma HIV-1 RNA and CD4+ lymphocyte count were summarized over time. The incidence of HIV-1 disease progression (AIDS and death) was presented. Data from low level of HIV-1 RNA quantification were summarized at Baseline and Week 48.

Safety Analysis

The safety analyses were performed on the Safety population.

The proportion of subjects reporting AEs was tabulated for each treatment group. The following summaries of AEs were provided:

- Incidence and severity of all AEs;
- Incidence and severity of treatment related AEs;
- Incidence and severity of AEs leading to withdrawal;
- Incidence of SAEs;

- Injection site reaction AEs at the event level and subject level, separately.

The incidence and severity of treatment related AEs, SAEs, and AEs leading to withdrawal were also assessed by Baseline third agent class.

The extent of exposure was summarized for each treatment group. The adherence to the monthly dosing schedule in relation to the projected date was assessed.

Changes from Baseline in laboratory (including fasting lipids) and vital signs data were summarized by visit and treatment group. In addition, the number and proportion of subjects with graded laboratory toxicities (based on DAIDS categories) were summarized by treatment group. The number and proportion of subjects with graded laboratory toxicities and the change from Baseline in fasting lipids were also assessed by Baseline third agent class.

Viral Genotyping/Phenotyping Analyses

The incidence of observed genotypic and phenotypic resistance to CAR, CAB or RPV was summarized for subjects meeting CVF criteria (i.e., CVF population).

Pharmacokinetics Analyses

Plasma CAB and RPV concentrations were summarized by visit for the subjects switching to CAB + RPV during the Maintenance Phase.

The statistical analysis of plasma steady state concentration was performed for CAB and RPV separately.

Pharmacokinetics/ Pharmacodynamics Analyses

The relationship between plasma CAB and RPV concentrations and the efficacy measure (i.e., Snapshot HIV-1 RNA ≥50 c/mL at Week 48) was analyzed. In addition, the relationship between plasma CAB and RPV concentrations and the following safety measures during Maintenance Phase was assessed:

- Maximum Change from Baseline (CFB) in ALT/Total Bilirubin;
- 2 hours post dose QTc at Week 4b and Week 48;
- The maximum toxicity grades of the top 5 most common non-ISR AEs.

Health Outcomes Analyses

The following endpoints were summarized for the Observed Case values by visit during the Maintenance Phase. In addition, these endpoints were also summarized by visit with missing values imputed by LOCF.

- Change from Week 5 in Dimension Scores and proportion of subjects considering pain and local reactions following injection using PIN (Perception of Injection Questionnaire) (CAB + RPV group only);
- Change from Baseline in health-related quality of life using HATQoL;

- Change from Baseline in health status using SF-12;
- Change from Baseline in treatment acceptance using ACCEPT;
- Change from Week 4b in tolerability of injection (NRS) (CAB + RPV group only);
- Change from Baseline in total treatment satisfaction score, and individual item scores of the HIV Treatment Satisfaction Status (HIVTSQs);
- Total treatment Satisfaction Score Change, and individual item scores of the HIV Treatment Satisfaction Score Change (HIVTSQc) for CAB + RPV group only;
- Patients' treatment preference at Week 48 (CAB + RPV group only);
- Patient reported reasons for willingness to switch therapies.

A statistical comparison between the 2 treatment groups was performed at each visit for HATQoL, HIVTSQs, ACCEPT, and SF-12 using an ANCOVA model with covariates (treatment, age, Baseline third agent class, sex at birth, and race and Baseline score value) included in the model.

Summary:

The purpose of this study was to evaluate the safety and efficacy of the 2-drug regimen of IM CAB + RPV for the treatment of HIV-1 infection in ARV-experienced adult subjects, with viral load suppressed to <50 c/mL, after switching from their current 3-drug oral ART regimen. The overall objective of the CAB + RPV clinical development program is to develop a highly effective, well tolerated, 2-drug, long-acting injectable regimen which has the potential to offer improved treatment convenience, compliance and improved quality of life for individuals with HIV compared with current standard of care. The Week 48 data from this study support the proposition that CAB + RPV monthly is an effective and well tolerated regimen for the maintenance of HIV-1 suppression.

One of the goals of this study was to enroll at minimum 25% women, who are typically underrepresented in HIV clinical studies. This goal was exceeded, with 34% female subjects in the CAR group and 32% female subjects in the CAB + RPV group. In addition, those 50 years of age or older accounted for 31% of subjects in the CAR group while 21% of subjects in this age group were randomized into the CAB + RPV treatment group. The 2 treatment groups were otherwise well balanced with regards to demographic and Baseline characteristics. The diverse demographics of the study population broadens the applicability of the data across HIV-1 treatment-experienced patients. The CAB + RPV regimen was assessed across a wide range of body types based on BMI.

This study has shown CAB + RPV to be non-inferior to a 3-drug CAR regimen containing NRTIs on the primary endpoint of plasma HIV-1 RNA ≥50 c/mL through 48 weeks per the Snapshot Algorithm. For the key secondary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 per the Snapshot Algorithm, CAB + RPV also demonstrated non-inferiority to the CAR regimens. Low rates of CVF were observed in both the CAB + RPV group (<1%) and in the daily oral CAR (1%) group through Week 48. The overall safety profile (apart from injection site reactions) was comparable between CAB

+ RPV and CAR. Although there are some limitations to the assessment of safety due to the open-label design, the results provide support for the use of CAB + RPV Q4W in treatment-experienced subjects with suppressed plasma HIV-1 RNA. Importantly, this study did not identify an increased loss of viral suppression or ART resistance selection with the use of this novel 2-drug regimen in treatment-experienced subjects relative to those subjects on the CAR group.

Efficacy

A novel, NRTI-sparing, monthly injectable 2-drug regimen of CAB + RPV demonstrated high efficacy through Week 48 and was non-inferior to the continuation of daily oral CAR in virologically-suppressed HIV-1-infected adults. Subjects adhered well to the planned treatment schedule for CAB + RPV administration with few injections administered outside of the allowable treatment window and no injections were missed without coverage by a planned oral bridging strategy.

The primary efficacy analysis demonstrated that once-monthly CAB + RPV is non-inferior to CAR at Week 48 for the proportion of subjects with plasma HIV-RNA greater than or equal to 50 c/mL per Snapshot algorithm in the ITT-E Population, meeting the predefined non-inferiority margin of 6%. In addition, the key secondary analysis demonstrated that CAB + RPV is non-inferior to CAR for the proportion of subjects with <50 c/mL plasma HIV-1 RNA at Week 48 based on the Snapshot algorithm for the ITT-E Population, meeting the predefined non-inferiority margin of -10%. Importantly, results for the primary and key secondary analyses were consistent for the PP population, from which 30 subjects from the ITT-E population were excluded, primarily due to violation of protocol entry requirement (25 subjects). Non-inferiority in the primary endpoint was also supported across randomization factors (Baseline third agent class and sex at birth).

Analysis of the treatment difference within other subgroups (demographic factors, Baseline CDC stage of disease, Baseline viral load, Baseline CD4+ lymphocyte count, and participating countries) were also examined. No statistically significant difference between two treatment arms were observed for the proportion of subjects with HIV-1 RNA≥50 (Snapshot algorithm) at 48 Weeks in any of these subgroups.

The numerical higher proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48 in CAB + RPV arm (3/47, 6.4%) in Russia compared to CAR (1/59, 1.7%) was observed. The relatively small sample size in this subgroup also limits the ability to make a robust conclusion.

Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA >/=50 c/mL at Week 48 (Maintenance Phase) – Snapshot Analysis – (ITT-E and PP Populations)

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
CAB + RPV	308	5 / 308 (1.6)	0.6 (-1.1, 2.4)	0.6 (-1.2, 2.5)
CAR	308	3 / 308 (1.0)		
PP Population				
CAB + RPV	294	4/294 (1.4)	0.3 (-1.4, 2.1)	0.3 (-1.4, 2.1)
CAR	292	3/292 (1.0)		

a: Difference: Proportion on CAB + RPV - Proportion on CAR.
b: Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: sex at birth (Male, Female) and Baseline third agent class (PI, NNRTI, INI).

The efficacy results of this study are similar for those observed for other recent integrase inhibitor switch studies in virologically suppressed subjects, such as Study 201636, Study 201637, GS-US-380-1844, GS-US-380-1878 and consistent with Week 48 results observed in the Phase IIb trial, Study 200056 investigating once-monthly CAB + RPV. The current study is the first Phase III trial to demonstrate high levels of sustained suppression through Week 48 with a long-acting injectable regimen comparable to 3-drug oral standard of care regimens.

The Snapshot efficacy analysis demonstrated similar outcomes between treatment groups and across categories for lack of virologic success. This includes data in window not below virologic threshold of 50 copies/mL, discontinuations due to lack of efficacy and discontinued for other reason while not below virologic threshold. Under the Snapshot category of "No Virologic Data", there were more subjects who discontinued due to AE or death in the CAB + RPV group (11 subjects) compared with the CAR group (5 subjects). The main reasons for this difference included 4 subjects on the CAB + RPV group who discontinued due to injection intolerability, and 4 additional subjects with acute viral hepatitis meeting liver stopping criteria. No other trends were observed for reasons for withdrawal.

Sensitivity analyses of the key secondary endpoint were also conducted. The PP population results were consistent with the ITT-E (primary) study population results. Also, Kaplan-Meier estimates of the proportion of subjects without treatment related discontinuation = failure (TRDF) at Week 48 were high and similar between treatment groups. The proportion of subjects without efficacy related discontinuation = failure (ERDF) was also high and similar between treatment groups.

In summary, the primary and secondary efficacy results of this study provide evidence to support the non-inferiority of once-monthly CAB + RPV to CAR for the treatment of HIV-1 infection in ARV-experienced adult subjects with viral load suppressed to <50 c/mL.

Safety

An important secondary objective of this study was to evaluate the safety and tolerability of switching to a novel 2-drug, "NRTI-sparing" monthly injectable regimen (CAB + RPV) compared with continuation of CAR. Safety and tolerability were evaluated through the Week 48 LSLV and will continue beyond the current 48-week analyses for subjects remaining in the Extension Phase to more fully assess the impact of this 2-drug injectable regimen in the longer term.

The incidence of subjects developing at least 1 SAE was low and similar between treatment groups (CAB + RPV 4%; CAR 5%). There were no discernible patterns of SAEs by preferred term as each SAE in the CAB + RPV group was reported in a single subject, and there were no SAEs considered drug-related to CAB + RPV. Of 14 subjects in the CAB + RPV group who had drug-related Grade 3-4 AEs, 11 had drug-related Grade 3 ISRs. The few additional drug-related Grade 3-4 events reported for CAB + RPV were diverse across system organ class and did not demonstrate any patterns of clinical concern.

Through the cut-off date of this report, inclusive of the Maintenance and Extension Phases, five subjects in the CAB + RPV group and one subject in the CAR group met liver stopping criteria due to acute viral hepatitis events. The increased number of events for the CAB + RPV group is likely explained by chance occurrence in this randomized trial, as there is no known systematic link or mechanism between CAB + RPV injections and acute viral hepatitis events.

Greater proportions of subjects in CAB + RPV group compared with those in the CAR group reported AEs (95% vs. 71%), with injection site pain (75%) reported as the most common AE among those receiving LA injections. Non-ISR drug-related AEs consisted primarily of Grade 1-2 events and were reported more frequently for CAB + RPV (29%) compared to CAR (3%). Excluding ISRs, the most common AEs observed in this study were nasopharyngitis, headache, upper respiratory tract infections, diarrhea, fatigue, back pain, pyrexia, influenza, viral respiratory tract infections, and cough. With the exception of viral RTIs these AEs were reported at higher frequencies for subjects in the CAB + RPV group. The most frequently reported non-ISR drug-related AEs during the Maintenance Phase in the CAB + RPV group were fatigue (4%), pyrexia (4%), headache (4%), and nausea (4%).

An important caveat to consider in comparing the safety data between treatment groups in this open-label study is that all enrolled subjects were stable on medication for at least 6 months prior to study entry. The mean duration of the ART regimen at Baseline was over 5 years. Adverse events reported subjectively by participants within unblinded trials have the potential to be biased by anticipation of adverse events potentially associated with a novel intervention and investigators may be more likely to diagnose and report AEs that could be considered likely related to the investigational product.

An OLI of CAB + RPV was included in this study to evaluate the potential in each subject for ADRs which would preclude IM dosing. Overall, oral CAB + RPV was well tolerated and less than 1% of subjects withdrew due to AEs that were considered drug-related. Reported AEs and laboratory abnormalities primarily consisted of

mild/moderate (Grade 1-2) events. There were no hypersensitivity events, no cases of DILI or subjects meeting hepatobiliary abnormality criteria, and no patterns for AEs or chemistry/hematology abnormities of clinical concern observed during the OLI.

Overall, injections with CAB + RPV were well tolerated. ISRs were reported frequently and most commonly comprised of mild (Grade 1 or 2) short-lived and self-resolving pain events. Few ISRs (5%) lasted more than 14 days. ISRs seldom led to discontinuation and overall health outcomes data demonstrated consistent and high levels of acceptability of injections. A majority of subjects had ISRs at the initial 3 mL loading injections; however, the incidence of ISRs decreased over time through Week 48. In addition, all ISRs reported after Week 24 were mild/moderate (Grades 1 or 2). Nevertheless, the potential for more severe Grade 3 or 4 ISRs occurring albeit in a small proportion of subjects, especially early in therapy, warrants that health care providers are familiar with best practices for administration of injections and monitor patients for ISRs following administration of CAB + RPV.

There were no notable findings for AEs related to rash (including hypersensitivity reaction) or other skin and subcutaneous disorders; hepatobiliary disorders; musculoskeletal and connective tissue disorders; cardiovascular disorders; or metabolism and nutrition disorders. Based on the association of other NNRTIs such as EFV, NVP and ETV, with severe skin rash and some observations of rash with oral RPV (mainly Grade 1 and Grade 2) reported in clinical studies, skin reactions are considered an important potential risk for RPV. Rash is labelled as an ADR for oral RPV.

Hepatic adverse events were categorized as adverse events of special interest for the current study. There were no liver findings that raised a concern for the CAB + RPV regimen and there were no DILI events. All of the subjects in the study who met liver stopping criteria on the CAB + RPV group had acute viral hepatitis infections.

No clinically relevant differences were observed in clinical laboratory abnormalities, for either chemistry or hematology, between the CAB + RPV and CAR groups. No clinically significant differences were observed for graded abnormalities for any of the following parameters: ALT, AST, bilirubin, or lipase.

There were no reported events of rhabdomyolysis associated with any of the transient Grade 1 to 4 elevations of CPK. One subject in the CAB + RPV group had a grade 2 myositis which was considered related to treatment along with a grade 4 CPK elevation. CPK elevations were generally explained by subject exertion or activity.

Fasting lipid NCEP categories at Week 48 versus Baseline were similar in the 2 treatment groups. No clinically relevant patterns of change in NCEP fasting lipids from Baseline to maximum post Baseline category were observed in either treatment group.

Overall, the incidence of psychiatric disorders was similar across both treatment groups. Assessment of potential treatment-emergent suicidality through the electronic version of the C-SSRS demonstrated no signals for increased suicidal and self-injury AEs upon switching to CAB + RPV relative to continuation of CAR based on prior history of depression, anxiety, or suicidal ideation.

In summary, in the current Phase III multinational patient population study, CAB + RPV was well tolerated with few discontinuations due to adverse events. Relative to prior Phase IIb trials for CAB + RPV, Study 200056 and Study LAI116482, no additional safety issues of clinical concern have been identified.

Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

Following completion of the 4-week oral lead-in, Week 4b CAB concentrations were consistent with oral dosing of CAB 30 mg once daily. Similarly, Week 4b RPV concentrations were consistent with historical data on oral dosing of RPV 25 mg once daily.

Following the initial CAB LA injection at Week 4b, geometric mean [95% CI] Week 8 CAB concentration was 1.23 [1.13, 1.33] μg/mL, similar to that of 1.18 [0.395, 3.50] μg/mL observed in oral switch subjects (n=7) receiving an initial dose of 600 mg IM in the optimized Q4W regimen of the Study 200056 Extension Phase. Geometric mean [95% CI] Week 48 CAB trough concentration was 2.84 [2.68, 3.01] μg/mL, more than double the value observed following the initial injection and similar to that of 2.58 μg/mL observed at Week 48 of Study 200056. Geometric mean [95% CI] Week 41 CAB concentration obtained 3 to 10 days following the W40 injection was 3.39 [3.18, 3.61] μg/mL, similar to Cmax,ss of 3.5 [3.3, 3.8] μg/mL observed in Study 200056. Using evaluable trough concentrations collected within 24 to 32 days of the prior injection, steady state was confirmed by W44; this is similar to Study 200056 where steady state was confirmed by W40 for the Q4W regimen.

Following the first RPV LA dose, geometric mean [95% CI] Week 8 RPV concentration was 38.6 [36.0, 41.4] ng/mL, similar to that of 40.3 [28.4, 57.2] ng/mL observed in the oral switch subjects (n=7) receiving an initial dose of 900 mg IM in the optimized Q4W regimen of the Study 200056 Extension Phase. Geometric mean [95% CI] Week 48 RPV trough concentration was 90.3 [84.9, 96.0] ng/mL, more than double the value observed following the initial injection and higher than that achieved following oral RPV 25 mg once daily at the end of the oral lead-in (75.4 [70.8, 80.2]). Geometric mean Week 41 RPV concentration obtained 3 to 10 days following the W40 injection was 110 [103, 118] ng/mL, approaching the geometric mean Cmax of 127 [118, 136] ng/mL observed for the Q4W regimen in Study 200056. RPV steady state was not yet confirmed by Week 48; whereas steady state was confirmed by W36 for the Q4W regimen in Study 200056.

Given the few subjects who experienced CVF on CAB + RPV and the high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it is difficult to establish a relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. Other factors may be associated with the occurrence of virologic failure.

No relationships between CAB or RPV concentrations and safety parameters of interest were identified.

Biomarkers

Biomarkers were collected as an exploratory endpoint to analyze potential changes associated with bone and renal disorders in HIV-1 infected adults.

A numerical decrease from Baseline for the median urine retinol binding protein and urine protein/creatinine ratio in the CAB + RPV group with numerical increases in these renal function markers in the CAR group supports additional future investigation to determine whether there is a possible favorable effect of the switch to CAB + RPV on renal tubular function.

Within the current study, CAB, an analogue of dolutegravir, in combination with RPV through 48 Weeks demonstrated reductions from Baseline in bone biomarkers including BSAP, osteocalcin, P1NP, and CTX. Significant interactions between treatment group and Baseline third agent class, and significant interaction between treatment group and whether ART regimens contained TDF at Baseline again suggests that the switch from CAR to a 2-drug NRTI sparing regimen is associated with a comparative reduction in bone turnover.

Viral Genotyping and Phenotyping

Protocol defined CVF through Week 48 was rare in the study and was distributed evenly between the 2 treatment groups, with 7 subjects meeting CVF: 3 subjects in the CAB + RPV group and 4 subjects in the CAR group. In the CAB + RPV group, the 3 CVF subjects all had RPV RAMs at position E138 at the time of SVF leading to decreased virus susceptibility to the study drug, RPV. RAMs at this position were also present in the HIV-1 viral DNA of 2 of the 3 subjects at Baseline. One subject also had INI substitution, L74I, present at both Baseline and at SVF. The INI RAM, N155H, was present in the plasma RNA of another CVF subject in the CAB + RPV group at the time of virologic failure and was not in the Baseline viral DNA sample. This subject's ART history included raltegravir. This RAM resulted in low level resistance to CAB (FC = 2.7) and resistance to raltegravir and elvitegravir, but the virus remained sensitive to dolutegravir. This subject also had the INI substitution, L74I, present at both Baseline and SVF. Another CVF subject in the CAB + RPV group had NNRTI RAM, V108I which was present as a mixture of V108V/I in Baseline PBMC DNA and could contribute to the in vitro resistance seen to rilpivirine. The PI mutation, N88N/S, also seen in this subject at the virologic failure timepoint and Baseline, is an accessary mutation and did not have any effect on PI drug sensitivity. Comparison of the plasma HIV-1 RNA and PBMC HIV-1 DNA genotype results must be viewed with the caveat that resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing. As such, HIV-1 DNA resistance testing is exploratory and its primary value is in showing whether resistance is present, and it is less definitive at showing that resistance is not present. Since all subjects entered the study suppressed, only PBMC viral DNA could be genotyped at Baseline. No phenotype analysis is performed on virus isolated from PBMCs.

In the CAR group, 1 subject had NRTI RAM, M184I, at virologic failure with a corresponding decrease in susceptibility to emtricitabine (FC>97.2) which was part of the subject's ART. The Baseline viral DNA for this subject did not have this RAM. Another

subject had NRTI RAM, M184V, and NNRTI RAM, G190S, at virologic failure. The phenotypic assay failed for this subject. Baseline viral DNA did not have the G190S RAM, but did have the NRTI RAM, M184M/I, which usually emerges before M184V, but is outcompeted by M184V within several weeks. This subject also had the INI substitution, L74I, at Baseline and SVF, but no decrease in INI susceptibility was observed. One subject had the NNRTI RAM, M230M/I at virologic failure and did not have any decreased susceptibility to their study ART. Baseline viral DNA did not contain the M230M/I RAM. Another subject had no RAMs present either at virologic failure or in Baseline viral DNA.

Health Outcomes

PRO instruments included in this study examined the following concepts of patients' experience:

- Treatment Satisfaction with CAB + RPV compared with CAR using the HIVTSQs and HIVTSQc.
- Treatment Acceptance with CAB + RPV compared with CAR using the General Acceptance dimension of the ACCEPT
- Acceptability of injections and ISRs with CAB + RPV over time using the PIN
- Quality of life in patients receiving CAB + RPV compared with CAR using three out of nine dimensions of the HAT-QoL ("Life Satisfaction", "Disclosure worries" and "HIV Medication")
- Health status in patients receiving CAB + RPV compared with CAR using the SF-12
- Preference for CAB + RPV compared with daily oral treatment prior to study entry using a single item preference question
- Reason for switch of study medication with a single item question.

Treatment satisfaction was one of the key secondary endpoints in the 201585 study. At Baseline, subjects in both treatment groups reported high scores for the HIVTSQs. Patients in the CAB + RPV group reported statistically significant improvements in treatment satisfaction from Baseline at Weeks 24 and 44, compared with subjects in the CAR group. In addition, the difference in treatment satisfaction between treatment groups at Weeks 24 and 44 was also found to be clinically meaningful (mean increase of 6.12 (95% CI: 5.21-7.03) in the CAB + RPV group by Week 44. These results indicate that subjects on the CAB + RPV group were more satisfied with the novel monthly injectable treatment for HIV compared with subjects receiving CAR.

Closely related to treatment satisfaction, preference for the CAB + RPV compared to daily oral ART was also high. 97% (266/273) of responders preferred CAB + RPV at Week 48 compared with the daily oral treatment they received at study entry. In the treatment acceptance measure (3 items of the General Acceptance dimension), subjects in both treatment groups reported high scores at Baseline. A statistically significant improvement in change from Baseline in General Acceptance score was found in CAB + RPV compared with CAR as Weeks 24 and 48. Treatment acceptance

significantly improved at Week 48 compared to Baseline with an improvement of 13.3 points at Week 48 from 75.9 at Baseline (18% increase from Baseline) in CAB+RPV group. These data also show that subjects receiving monthly injections with CAB + RPV considered their treatment as more acceptable compared with subjects on the CAR group in terms of the overall advantages and disadvantages with adjusted difference of 10.7 at Week 48 between the two groups.

Acceptability of injections and ISRs was measured only in patients receiving CAB + RPV using the PIN. Overall, injections and ISRs were found to be acceptable; most subjects considering them "totally acceptable" or "very acceptable" at Weeks 5, 41 and 48. Acceptability of the injections of CAB + RPV statistically significantly improved over time up to Week 48. Consistent with the "Acceptance of ISRs" dimension, numerical improvements were also observed in the remaining dimensions of the PIN ("Bother from ISRs, "Sleep" and "Leg movement") as well as in individual items ("Anxiety Before" injection, "Anxiety After" injection, "Satisfaction" with the injection system and "Willingness" to receive injectable HIV treatment), allowing us to conclude that the overall experience from injections improved over time; In addition, there were only 4 of 26 withdrawals associated with ISRs further suggesting that patients tolerated the injections on a monthly basis. Notably ISRs also diminished overtime in the trial duration.

Quality of life domains and general health status were assessed with selected dimensions of the HAT- QoL (Life Satisfaction, HIV Medication, Disclosure Worries) and the SF-12. In the HAT-QoL and the SF-12, Baseline scores were high for both treatment groups upon study entry and remained high for the study duration. These Baseline scores were consistent with other clinical trials in similar HIV population and roughly equivalent to the general US population.

In the dimension "Disclosure Worries" of the HAT-QoL, both treatment groups reported numerically improved scores compared with Baseline, reaching statistical significance only at Week 24. This could be due to confounding factors which may be partially attributed to study participation itself (e.g., additional support offered during clinic visits). "Life Satisfaction" dimension did not show any significant differences between treatment groups at Weeks 24 and 48. The third dimension, "HIV Medication", showed small but statistically significant difference between treatment groups in adjusted mean change from Baseline at Weeks 24 and 48.

Conclusions

- The switch to a novel 2-drug injectable regimen of CAB + RPV demonstrated high efficacy and was non-inferior to the continuation of CAR in virologically suppressed HIV-1-infected adults. This 2-drug regimen administered monthly maintained HIV-1 suppression through the 48 Week primary endpoint equally as well as the oral 3-drug ART regimens taken daily. The safety profiles of the injectable regimen demonstrated that the monthly regimen was well tolerated and (with the exception of ISR events) comparable to the CAR group.

- CAB + RPV offers the option to switch subjects to a well-tolerated ART regimen, without an increased risk of virologic failure.

Efficacy

- The primary efficacy analysis demonstrated that CAB + RPV is non-inferior to CAR and provided good clinical efficacy based on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 for the ITT-E and PP populations. The adjusted treatment difference between CAB + RPV and CAR met the non-inferiority criterion, set below 6%.

- The key secondary analysis (HIV-1 RNA <50 c/mL) also demonstrated that CAB + RPV is non-inferior to CAR according to the Snapshot Algorithm (Missing, Switch or Discontinuation = Failure) for the ITT-E, and PP populations. The adjusted treatment difference between CAB + RPV (93% responders) and CAR (95% responders) met the non-inferiority criterion, set above -10%.

- Non-inferiority in the primary and secondary endpoints were also supported across randomization factors (Baseline third agent class and sex at birth).

- The analysis of treatment difference within other subgroups (demographic factors, Baseline CDC stage of disease, Baseline viral load, Baseline CD4+ lymphocyte count, and participating countries) were also examined. No statistically significant difference between the two treatment groups was observed for either the primary or secondary endpoints at Week 48 in any of these subgroups.

- Non-inferiority in the primary and secondary endpoints is supported across demographic subgroups (age, race and sex at birth), Baseline CD4+ lymphocyte count, and Baseline third agent treatment class.

- The 2-drug once monthly injectable regimen effectively maintained virologic suppression, with few Snapshot virologic failures and no increased risk for on-treatment development of resistance compared with CAR through 48 Weeks. Rates of CVF in Study 201585 study were 1.0% in the CAB + RPV group and 1.3% in the daily oral CAR group through Week 48.

- Taken together, these results indicate that the CAB + RPV 2-drug injectable regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure.

Safety

- Over 48 weeks, the safety data from this randomized, open-label Phase III study of subjects switching to CAB + RPV is favorable and consistent with prior Phase II trials. No new adverse drug reactions of clinical concern were observed.

- Greater proportions of subjects in CAB + RPV group compared with those in the CAR group had AEs. Differences between the groups were primarily driven by

ISRs in the CAB + RPV group, as would be expected. There were no drug-related SAEs reported for CAB + RPV.

- The difference between treatment groups in AEs leading to withdrawal was driven by ISRs and acute hepatitis infections in the CAB + RPV group.

- The Oral Lead-in period for CAB + RPV was well tolerated with no patterns observed for clinical adverse events or laboratory abnormalities, and few subject withdrawals.

- Overall, injections with CAB + RPV were well tolerated, generally mild and of short duration. Injection site pain was the most frequently reported ISR (75% subjects) however ISRs resulted in few withdrawals (1%).

- For adverse events of special interest including hepatotoxicity, hypersensitivity reactions, rash, QTc prolongation, neuropsychiatric events, seizures and seizure-like events, weight gain, rhabdomyolysis, pancreatitis, and events related to impact on creatinine and safety in pregnancy, there was no evidence for increased occurrence, severity or clinical concern for CAB + RPV compared with CAR.

- No clinically relevant patterns in changes in NCEP fasting lipids from Baseline category to maximum post Baseline category for the Maintenance Phase were observed in either treatment group for triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, or total cholesterol/HDL ratio.

Pharmacokinetics and Pharmacokinetics/Pharmacodynamics

- Geometric mean CAB and RPV concentrations were consistent with those observed in Phase II studies. CAB LA steady state was confirmed by Week 48.

- Given the few subjects who experienced CVF on CAB + RPV and the fact that there is a high proportion of subjects with virologic success while having similar CAB and RPV concentrations as those observed in subjects with CVF, it is difficult to establish a causal relationship between CAB and RPV plasma concentrations and the occurrence of virologic failure. Other factors may be associated with the occurrence of virologic failure.

- No associations between CAB or RPV concentrations and safety findings of interest were identified.

Biomarkers

- CAB + RPV was associated with reductions from Baseline in bone biomarkers including BSAP, osteocalcin, P1NP, and CTX. Statistically significant interactions between treatment group and Baseline third agent class, and statistically significant interaction between treatment group and whether ART regimens contained TDF at Baseline suggests that the switch to CAB + RPV is associated with a reduction in bone turnover relative to continuation of CAR.

Viral Genotyping and Phenotyping

- CVF was rare, with 3 subjects in the CAB + RPV group and 4 subjects in the CAR group.
- All 3 CVFs in the CAB + RPV group had on-treatment RPV resistance mutations at the virologic failure timepoint.
- One of the CVFs in the CAB + RPV group had INI resistance mutation in N155H; this subject had a history of raltegravir use.

Global Health Outcomes

- Subjects receiving CAB + RPV reported significantly greater satisfaction for their HIV treatment compared with subjects receiving CAR across all measured visits, according to HIVTSQs.
- For most subjects receiving CAB + RPV, acceptance of ISRs following their first injection was high and significantly improved over time across measured visits, according to the PIN.
- Most subjects receiving CAB + RPV reported being "not at all" or "a little" bothered from ISRs following their first injection. "Bother from ISRs" also improved over time across all measured visits, consistent with the "Acceptance of ISRs" (assessed with the PIN).
- Subjects receiving CAB + RPV reported a significant improvement in "HIV Medication" dimension of the HAT-QoL and a greater overall treatment acceptance, according to the ACCEPT, compared with subjects receiving CAR across all measured visits.
- Out of the responders, 97% selected CAB + RPV over daily oral as their preferred HIV treatment at Week 48.
- "Life Satisfaction" and general health status were high at Baseline and remained high for both treatment groups.

Effective Date: [redacted]-[redacted]-20[redacted]

Synopsis for Study 205162

Cabotegravir (CAB) is primarily metabolized by UDP-glucuronosyltransferase 1A1 (UGT1A1) with a minor contribution from UDP-glucuronosyltransferase 1A9 (UGT1A9). The objective of this meta-analysis was to evaluate effects of *UGT1A1* and *UGT1A9* genotypes on oral CAB pharmacokinetics (PK) measures (Cτ, AUCτ, and Cmax) and tolerability (liver function chemistries) using data from consenting subjects enrolled in phase I and phase II studies. Genetically predicted UGT1A1 activity was significantly associated with steady-state oral 30mg CAB PK parameters Cτ, AUCτ, and Cmax, with mean values of Cτ, AUCτ, and Cmax being ~1.5, 1.4 and 1.3-fold, respectively, higher in subjects with low versus normal predicted enzyme activity. Based on the cumulative CAB PK and safety data collected to date, this magnitude of increase in CAB exposure is not anticipated to have a clinically relevant impact and does not change the understood benefit-risk profile of 30mg oral CAB. UGT1A1 predicted activity status was significantly associated with changes from baseline in total bilirubin (TBL), but not alanine aminotransferase (ALT). All subjects (N=5) who experienced on-treatment TBL ≥1.5x upper limit of normal (ULN) carried one or more genetic alleles that confer reduced UGT1A1 enzyme activity. Genetically predicted UGT1A9 activity was not associated with any PK endpoints analyzed or ALT, but was moderately associated with TBL. After accounting for genetically predicted UGT1A1 activity within the model, UGT1A9 genetically predicted activity was no longer significantly associated with change from baseline in TBL, which indicates that the association between UGT1A9 and TBL may be due to the correlation between genetic variation in *UGT1A1* and *UGT1A9.*

Effective Date: [redacted]

Synopsis for Study 207966

Title: A Phase IIIb, Randomized, Multicenter, Parallel-group, Non-inferiority, Open-label Study Evaluating the Efficacy, Safety, and Tolerability of Long-acting Cabotegravir Plus Long-acting Rilpivirine Administered Every 8 Weeks or Every 4 Weeks in HIV-1-infected Adults who are Virologically Suppressed.

Investigator(s): Multicenter study

Study center(s): This was a multicenter study conducted in 13 countries: Australia, Argentina, Canada, France, Germany, Italy, Mexico, Russia, South Africa, South Korea, Spain, Sweden, and the United States.

Publication(s): None at the time of this report.

Study Period (Week 48 Analysis): The first subject was screened on 27-OCT-2017. The last subject last visit for the Week 48 analysis was 06-JUN-2019. This study is ongoing.

Phase of Development: IIIb

Objectives:

Primary Objective

- To demonstrate the non-inferior antiviral activity of long-acting injectable cabotegravir and rilpivirine (CAB LA + RPV LA) every 8 weeks (Q8W) compared to CAB LA + RPV LA every 4 weeks (Q4W) over 48 weeks in suppressed human immunodeficiency virus (HIV-1) infected antiretroviral therapy (ART)-experienced subjects

Secondary Objectives

- To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks
- To evaluate the safety and tolerability of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks
- To assess viral resistance in subjects experiencing protocol-defined confirmed virologic failure
- To characterize CAB and RPV concentrations and population pharmacokinetics (PK) and identify important determinants of variability
- To assess preference for CAB LA + RPV LA every 8 weeks or CAB LA + RPV LA every 4 weeks LA compared to oral antiretroviral (ARV)

- To assess preference for CAB LA+ RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks

- To assess patient reported health-related quality of life, treatment satisfaction, injection tolerability, and treatment acceptance.

Methodology:

Study 207966 is an ongoing Phase IIIb, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study designed to assess the antiviral activity and safety of intramuscular (IM) CAB + RPV Q8W compared to IM CAB + RPV Q4W in HIV-1 infected adult subjects.

Subjects in Study 207966 were enrolled from the ongoing 201585 Study (ATLAS) with additional subjects receiving ART standard of care (SOC) included in order to support a targeted total sample size of approximately 1020 subjects.

All subjects completed a Screening Phase of up to 35 days prior to randomization. Eligible subjects were randomized (1:1) to receive either CAB + RPV Q8W or CAB + RPV Q4W for at least 100 weeks. Randomization was stratified by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks). Two groups of subjects were randomized:

<u>Group 1: Subjects randomized from current ART SOC therapy:</u>

Subjects randomized from current ART SOC therapy, including those enrolled to the current ART (CAR) arm of Study 201585 (following completion of the Week 52 visit at minimum), received oral lead-in with CAB 30 mg + RPV 25 mg once daily at Baseline (Day 1) for 28 days (±3 days) followed by IM CAB + RPV Q8W or IM CAB + RPV Q4W thereafter.

For subjects on SOC transitioning from Study 201585, eligibility for this study was determined once the final central lab results from Study 201585 were available and safety parameters had been reviewed.

<u>Group 2: Subjects currently receiving IM CAB+ RPV Q4W in Study 201585:</u>

At Baseline (Day 1), subjects entering Study 207966 from Study 201585 and currently receiving IM CAB + RPV Q4W (including both those who were originally randomized to Q4W in the Maintenance Phase of Study 201585 and those who transitioned from SOC to the Q4W regimen within the Extension Phase of Study 201585) were randomized 1:1 to either continue IM CAB + RPV Q4W or transition to IM CAB + RPV Q8W.

The first injection visit for Study 207966 was performed once the final central lab results from Study 201585 were available and safety parameters had been reviewed, and the Study 201585 Week 52 visit (at minimum) has been completed. Subjects continued to receive IM CAB + RPV Q4W as scheduled within Study 201585 until their eligibility for Study 207966 was evaluated and the subject was re-randomized

(Q8W or Q4W). If determined to be ineligible for Study 207966, subjects could elect to continue participation in Study 201585 or withdraw from Study 201585.

Any subject who received at least a single dose of IM CAB and/or RPV and discontinued the regimen for any reason entered a 52-week Long-Term Follow-up (LTFU) Phase. Subjects were to remain on suppressive highly active antiretroviral therapy (HAART) for at least 52 weeks after the last dose of IM CAB and/or RPV.

Number of subjects: A total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W 524 subjects; Q4W 525 subjects). Four subjects were randomized but did not receive study treatment (2 subjects in each of the Q8W and Q4W groups).

Diagnosis and main criteria for inclusion: This study recruited HIV-1 infected virologically suppressed (HIV-1 RNA <50 c/mL) subjects on stable ART including subjects who had completed, at minimum, Week 52 of Study 201585. Male and female (non-pregnant, non-lactating and practicing adequate contraception) subjects, aged ≥18 were eligible.

Treatment administration: Two groups of subjects were randomized in a 1:1 ratio to:

Group 1: Subjects currently receiving ART SOC, including those enrolled to the CAR arm of Study 201585 (following completion of the Week 52 visit at minimum).

oral CAB 30 mg + RPV 25 mg once daily for 28 days (± 3 days) followed by IM injections of CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4b, IM CAB 400 mg + RPV 600 mg at Week 8 and every 4 weeks thereafter). Subjects were to receive IM injections of CAB + RPV for at least 96 Weeks, or;

oral CAB 30 mg + RPV 25 mg once daily for 28 days (±3 days) followed by IM injections of CAB + RPV (IM CAB 600 mg + RPV 900 mg at Week 4b and Week 8 and every 8 weeks thereafter). Subjects were to receive IM injections of CAB + RPV for at least 96 Weeks.

Group 2: Subjects currently receiving IM CAB+ RPV Q4W in Study 201585 (following completion of the Week 52 visit at minimum).

IM CAB 600 mg + RPV 900 mg Q8W for at least 100 Weeks, or:

IM CAB 400 mg + RPV 600 mg Q4W for at least 100 Weeks.

Criteria for evaluation: Endpoints relevant to the 48 Week analysis are listed here.

Objectives	**Endpoints**
Primary	
To demonstrate the non-inferior antiviral activity of CAB LA + RPV LA every 8 weeks (every two months) compared to CAB LA + RPV LA every 4 weeks	Proportion of subjects with plasma HIV-RNA greater than or equal to 50 copies/mL as per Food and Drug Administration (FDA) Snapshot algorithm at Week 48

Objectives	Endpoints
(monthly) over 48 weeks in suppressed HIV-1 infected ART-experienced subjects	(Intent-to-Treat Exposed [ITT-E] population)
Secondary	
To demonstrate the antiviral and immunologic activity of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Proportion of subjects with plasma HIV-1 RNA <50 c/mL (c/mL) at Week 24, Week 48 and Week 96 using the FDA Snapshot algorithm (ITT-E population) Proportion of Subjects with protocol-defined confirmed virologic failure (CVF) through Week 24, Week 48 and Week 96 Absolute values and changes from Baseline in viral load and CD4+ cell counts over time including Week 48 and Week 96

Objectives	Endpoints
To evaluate the safety and tolerability of CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Incidence and severity of AEs and laboratory abnormalities over time including Week 24, Week 48 and Week 96 Proportion of Subjects who discontinue treatment due to AEs over time including Week 24, Week 48 and Week 96 Change from Baseline in laboratory parameters over time including Week 48 and Week 96
To assess viral resistance in Subjects experiencing protocol-defined confirmed virologic failure	Incidence of treatment emergent genotypic and phenotypic resistance to CAB, RPV through Week 24, Week 48 and Week 96
To characterize CAB and RPV concentrations and population pharmacokinetics and identify important determinants of variability	Plasma PK parameters for CAB LA and RPV LA (when evaluable, $C_{trough,}$ concentrations post dose [~Cmax], and area under the curve [AUC]) Demographic parameters including, but not limited to, age, sex, race, body weight, body mass index (BMI), and relevant laboratory parameters will be evaluated as potential predictors of inter- and intra-subject variability for PK parameters
To assess preference for CAB LA + RPV LA every 8 weeks or CAB LA + RPV LA every 4 weeks LA compared to oral ARV therapy To assess preference for CAB LA+ RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks	Preference for CAB LA + RPV LA every 8 weeks and CAB LA + RPV LA every 4 weeks compared to oral ARV and preference for CAB LA + RPV LA every 8 weeks compared to CAB LA + RPV LA every 4 weeks will be assessed using a preference questionnaire at week 48 (or Withdrawal).
To assess patient reported health-related quality of life, treatment satisfaction, injection tolerability, and treatment acceptance.	Change from Baseline (Day 1) in Health-related Quality of Life (HRQoL) at Week 24 and Week 48 (or Withdrawal) Change from baseline (Day 1) in total "treatment satisfaction" score, and individual item scores of the HIV Treatment Satisfaction Status Questionnaire (HIVTSQs) at Week 24, and

Objectives	Endpoints
	48, (or Withdrawal) Change in treatment satisfaction over time using the HIV Treatment Satisfaction Change Questionnaire HIVTSQc at Week 48 (or Withdrawal). Change from Week 8 in Dimension scores ("Bother of injection site reactions [ISRs]", "Leg movement", "Sleep", and "Injection Acceptance") and individual item scores assessing pain during injection, anxiety before and after injection, willingness to be injected in the future and overall satisfaction with mode of administration over time will be assessed using the Perception of Injection questionnaire (PIN) at Weeks 8, 24, and 48 (or Withdrawal) Change from Baseline (Day 1) in treatment acceptance at Week 24 and Week 48 (or Withdrawal) will be assessed using the "General acceptance" dimension of the Chronic Treatment Acceptance (ACCEPT) questionnaire

Statistical methods:

A sample size of 510 subjects per treatment group was planned to show noninferiority at Week 48 for the primary endpoint and key secondary endpoints. The Week 48 endpoint is the primary analysis.

Analysis populations are listed below.

Population	Definition / Criteria	Analyses Evaluated
Screened	• Comprised of all subjects screened for inclusion in the study. • Subjects may be re-screened once, for which they will receive a new subject number. • For disposition displays, except for the listing of subjects who were rescreened, only the latest re-screening data will be included. All screening data will be summarized or listed for other displays.	• Study Population
Randomized	• All subjects who were randomly assigned to treatment in the study.	• Study Population

Population	Definition / Criteria	Analyses Evaluated
	• In this study, the randomized population includes all enrolled participants, i.e. the randomized population is equivalent to the enrolled population. • This population will be based on the treatment the participant was randomized to.	
Safety	• All randomized subjects who received at least one dose of study treatment. • Participants will be assessed according to actual treatment received.	• Safety
Intent-to-Treat Exposed (ITT-E)	• All randomized subjects who received at least one dose of study treatment. • Subjects will be assessed according to their randomized treatment, regardless of the treatment they received.	• Study Population • Efficacy • Health Outcomes
Per-Protocol (PP)	• All subjects in the ITT-E population with the exception of major protocol violators. • Protocol deviations that would exclude participants from the PP population are defined in the study RAP (Protocol Deviation Management and Definitions for Per Protocol Population).	• Efficacy (Sensitivity Analysis)
Pharmacokinetic (PK)	• All subjects who received CAB and / or RPV and underwent PK sampling during the study and provide at least 1 non-missing CAB and / or RPV plasma concentration value (Non-quantifiable [NQ] values will be considered as non-missing values).	• PK
Confirmed Virologic Failure (CVF)	• All subjects in the ITT-E population who met Confirmed Virologic Failure (CVF) criteria.	• Virology • Efficacy
Long-term Follow-up (LTFU)	• All subjects receiving at least one dose of CAB LA and/or RPV LA who have discontinued the CAB LA + RPV LA regimen and have either at least one Long-term Follow-up phase clinic visit (i.e. have at least one long-term follow-up visit shown in the study database, LTFU month 1, LTFU month 3, etc) or have filled out the LTFU phase conclusion form.	• Safety • Study Population
Oral Lead-in (OLI)	• All subjects who received at least one dose of study treatment during the oral lead-in period in ATLAS-2M study.	• Safety • Study Population • Efficacy
Q4W ATLAS	• All subjects in the ITT-E population who were randomized to Q4W arm in ATLAS.	• Health Outcomes
SOC	• All subjects in the ITT-E population who either were randomized to SOC arm in ATLAS or did not participate in ATLAS.	• Health Outcomes

Source: Study 207966 RAP.

Analyses for Week 48 endpoints were conducted according to methods outlined in the Study Reporting and Analysis Plan (RAP).

Summary:

Subject Disposition

Table: Summary of Subject Accountability: Maintenance Phase Conclusion Record (ITT-E Population)

	Q8W (N=522)	Q4W (N=523)
Subject Status		
Ongoing, n (%)	486 (93)	481 (92)
Completed, n (%)	0	0
Withdrawn, n (%)	36 (7)	42 (8)
Primary Reason/ Subreason for Study Withdrawal		
Adverse Event (AE) [a]	12 (2)	13 (2)
Lack of efficacy	9 (2)	3 (<1)
Protocol Defined CVF	8 (2)	2 (<1)
Insufficient viral load response	1 (<1)	1 (<1)
Protocol deviation	1 (<1)	1 (<1)
Prohibited medication use	0	1 (<1)
Non-compliance with study treatment	1 (<1)	0
Non-compliance with protocol procedures	1 (<1)	0
Protocol specified withdrawal criteria met	1 (<1)	3 (<1)
Pregnancy	1 (<1)	3 (<1)
Lost to follow-up	2 (<1)	0
Physician decision	5 (<1)	1 (<1)
Patient has developed resistance to rilpivirine [b]	1 (<1)	0
Subject had pulmonary tuberculosis, on long term follow-up	1 (<1)	0
Physician discretion with reason=positive pregnancy test with no confirmation of intrauterine pregnancy	1 (<1)	0
Subject was taking zidovudine lamivudine efavirenz abacavir atazanavir ritonavir before study start and was randomized in error but later early withdrawn during oral lead in phase	1 (<1)	0
The overall status of the subject including subject's significant cardiovascular history	0	1 (<1)
Subject required long term anticoagulant therapy	1 (<1)	0
Withdrawal by subject	6 (1)	21 (4)
Anxiety related to suicidality assessment	0	1 (<1)
Subject relocated	0	5 (<1)
Due to business subject cannot continue to participate in the study	0	1 (<1)
New safety updates a concern for patient wanting to	0	1 (<1)

	Q8W (N=522)	Q4W (N=523)
have a baby in the future		
Subject was incarcerated	0	1 (<1)
Subject planning to become pregnant	1 (<1)	0
Burden of travel or lack of access to travel	0	1 (<1)
Subject wanted to switch to a non-integrase inhibitor regimen due to potential weight gain side effect	1 (<1)	0
Burden of procedures	1 (<1)	3 (<1)
Intolerability of injections	1 (<1)	4 (<1)
Frequency of injections	0	1 (<1)
Frequency of visits	3 (<1)	6 (1)
Depressive syndrome and pain at site injection	0	1 (<1)
Family problems	0	1 (<1)
Problems with work due to study schedule and injection site reactions; no other visits will be done	0	1 (<1)
The patient will move to other country	0	1 (<1)

Note: Subjects may have only 1 primary reason for withdrawal. Percentages for subreasons may sum to more or less than 100%. Subjects may have more than 1 subreason underneath a single primary reason. Subjects are not required to indicate subreasons.

All of the AEs leading to withdrawal were nonfatal. One fatality occurred during the study and is discussed in detail in the Safety results.

Subject did not meet CVF at Week 48; the investigator withdrew the subject based on a viral load of 1038 c/mL at Week 56.

Demographic Characteristics

Demographic characteristics were generally similar between the 2 treatment groups. Although the majority of subjects were male, the study enrolled 27% females. Almost half of all subjects were ages 35 to <50 years (46%) with a median (range) of 42 (19 to 83) years. Over a quarter of the population (27%) was at least 50 years of age. The predominant race was White/Caucasian/European heritage (72%). Median BMI was 25.8 kg/m^2 and similar between the two groups. The largest proportion of subjects were from the United States (28%).

Table: Summary of Demographic Characteristics (ITT-E Population)

Demographic Characteristic	Q8W (N=522)	Q4W (N=523)
Age (y), n		
Mean	42.7	42.3
Standard Deviation (SD)	11.16	10.58
Median	42.0	42.0
Minimum (Min)	20	19
Maximum (Max)	83	75
Age group (years), n (%)		
<35	137 (26)	145 (28)
35 to <50	242 (46)	239 (46)
≥50	143 (27)	139 (27)
Sex at birth, n (%) [a]		
Female	137 (26)	143 (27)
Male	385 (74)	380 (73)
Reported gender, n (%) [a]		
Female	142 (27)	146 (28)
Male	380 (73)	377 (72)
Race, n (%)		
White	370 (71)	393 (75)
Non-White	152 (29)	130 (25)
American Indian or Alaska Native	17 (3)	11 (2)
Asian-Central/South Asian Heritage	1 (<1)	1 (<1)
Asian-East Asian Heritage	20 (4)	12 (2)
Asian-Japanese Heritage	0	2 (<1)
Asian-South East Asian Heritage	8 (2)	7(1)
Black or African American	101 (19)	90 (17)
Native Hawaiian or Other Pacific Islander	3 (<1)	1 (<1)
White-Arabic/North African Heritage	2 (<1)	4 (<1)
White-White/Caucasian/European Heritage	368 (70)	388 (74)
Mixed White	0	1 (<1)
Multiple	2 (<1)	6 (<1)
Ethnicity, n (%)		
Hispanic or Latino	71 (14)	65 (12)
Not Hispanic or Latino	451 (86)	458 (88)
BMI (kg/m^2) at Baseline		
Mean	26.677	26.782
SD	5.2023	5.7877
Median	25.724	25.923
Min	17.75	16.57
Max	48.27	77.52

Prior Exposure to CAB + RPV

Subjects in Study 207966 included subjects from the ongoing 201585 Study (Q4W or CAR) and additional ART SOC subjects. Subjects randomized from current ART SOC or transitioning from the CAR arm of Study 201585 had no prior exposure to CAB + RPV. Subjects transitioning from the IM CAB + RPV Q4W arm in Study 201585 and subjects who transitioned from CAR to the Q4W arm within the Extension Phase of Study 201585 and then transitioned to Study 207966 had prior exposure to CAB + RPV. Prior exposure to CAB + RPV was similar between the 2 treatment groups.

Table: Prior Exposure to CAB + RPV (ITT-E Population)

Prior Exposure to CAB + RPV (Weeks)	Q8W (N=522) n (%)	Q4W (N=523) n (%)
0 Weeks	327 (63)	327 (63)
1-24 Weeks	69 (13)	68 (13)
>24 to ≤48 Weeks	0	1 (<1)
>48 Weeks	126 (24)	127 (24)

Note: Prior exposure to CAB + RPV was calculated based on the prior CAB and/or RPV taken in Study 201585, as recorded in electronic case report form (eCRF).

Subjects adhered well to the planned treatment schedule for CAB + RPV administration with few injection visits outside of the allowable (±7-day) treatment window (Q8W, n=78 [98%]; Q4W, n=108 [99%]). No injection visits were missed without coverage by a planned oral therapy strategy for both the Q8W and Q4W regimens (Q8W, n=1; Q4W, n=7).

Efficacy

The primary efficacy analysis demonstrated that Q8W CAB LA + RPV LA was non-inferior to Q4W CAB LA + RPV LA in maintaining virologic suppression in HIV-1 infected subjects at Week 48. The upper bound of 95% confidence interval (CI) for the adjusted treatment difference between Q8W and Q4W was 2.2%, which was less than the pre-defined non-inferiority margin of 4%, with few subjects having plasma HIV-1 ribonucleic acid (RNA) ≥50 c/mL at Week 48 per the Snapshot Algorithm in either group for the ITT-E population (Q8W, n=9 [1.7%]; Q4W, n=5 [1.0%]). Results for the PP population were similar to those for the ITT-E Population.

Table: Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA ≥50 c/mL at Week 48 (Maintenance Phase) Snapshot algorithm (ITT-E Populations)

Treatment	N	Number of HIV-1 RNA ≥50 c/mL/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
ITT-E Population				
Q8W	522	9 / 522 (1.7)	0.8 (-0.6, 2.2)	0.8 (-0.6, 2.2)
Q4W	523	5 / 523 (1.0)		
PP Population				
Q8W	516	7 / 516 (1.4)	0.4 (-0.9, 1.7)	0.4 (-0.9, 1.7)
Q4W	514	5 / 514 (1.0)		

a. Difference: proportion on CAB + RPV Q8W – proportion on CAB + RPV Q4W.
b. Based on CMH stratified analysis adjusting for the following Baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

Note: The 2 subjects with HIV-1 RNA ≥50 c/mL in the Q8W group that were excluded from the PP Population had the following protocol deviations: One did not meet eligibility criteria and another did not have study treatment administered per protocol.

Study outcomes based on plasma HIV-1 RNA 50 c/mL threshold at Week 48 (Snapshot algorithm) were similar between treatment groups.

Table: Summary of Study Outcomes (Plasma HIV-1 RNA 50 c/mL Threshold) at Week 48 (Maintenance Phase) Snapshot algorithm (ITT□E Population)

Outcome	Q8W (N=522) n (%)	Q4W (N=523) n (%)
HIV-1 RNA <50 c/mL	492 (94.3)	489 (93.5)
HIV-1 RNA ≥50 c/mL	9 (1.7)	5 (1.0)
Data in window not below threshold	3 (0.6)	2 (0.4)
Discontinued for lack of efficacy	6 (1.1)	2 (0.4)
Discontinued for other reason while not below threshold	0	1 (0.2)
Change in background therapy	0	0
No virologic data	21 (4.0)	29 (5.5)
Discontinued study due to AE or death[a]	9 (1.7)	13 (2.5)
Discontinued study for other reasons[b]	12 (2.3)	16 (3.1)
On study but missing data in window	0	0

a. 2 deaths were reported: One during Maintenance Phase and another during Screening (subject did not receive study drug).
b. Q8W: lost to follow up, 2 subjects; withdrawal by subject, 4 subjects; protocol deviation, 1 subject; Investigator decision, 4 subjects, lack of efficacy, 1 subject. Q4W: protocol specified withdrawal criteria met (pregnancy), 3 subjects; withdrawal by subject, 12 subjects; protocol deviation, 1 subject.

Treatment differences for the primary endpoint (proportion of subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 [Snapshot Algorithm]) for each randomization

stratification stratum (prior exposure to CAB + RPV: 0 weeks, 1-24 weeks, and >24 weeks) support the non-inferiority of Q8W vs. Q4W. The test of evidence against homogeneity of the treatment difference was not statistically significant for prior exposure to CAB + RPV (p=0.346).

The proportion of Q8W subjects with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot Algorithm) was similar between those with no prior exposure to CAB + RPV (1.5%) and those with prior exposure to CAB + RPV (2.1%). Within the Q4W group, no subjects previously treated with CAB + RPV and 1.5% of subjects with no prior exposure had HIV-1 RNA ≥50 c/mL at Week 48.

Treatment differences on the primary endpoint (proportion of subjects with HIV-1 RNA≥50 at Week 48 (Snapshot algorithm)] were generally consistent across the strata within the following subgroups: demographic factors (age, gender, race, BMI), Baseline Centers for Disease Control (CDC) stage of disease, Baseline viral load, Baseline CD4+ lymphocyte count, and participating countries. The proportion of Snapshot virologic failures was numerically higher in the Q8W arm compared with the Q4W arm in female subjects (5/137 [3.6%] and 0/143 [0%] in females vs 4/385 [1.0%] and 5/380 [1.3%] in males, respectively) as well as in subjects with BMI ≥30 kg/m2 (6/113 [5.3%] for Q8W and 2/98 [2.0%] for Q4W in BMI ≥30 kg/m2 vs 3/409 [0.7%] for Q8W and 3/425 [0.7%] for Q4W in BMI <30 kg/m2).

The secondary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) was similar for both treatment groups. The majority of subjects in both treatment groups in the ITT-E Population remained suppressed (plasma HIV-1 RNA <50 c/mL: Q8W: 94%; Q4W: 93%). Results for the PP Population were similar to those for the ITT-E Population.

Stratification of the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 by prior exposure to CAB + RPV or by subgroups representing demographic and Baseline characteristics produced no statistically significant differences among subgroups or between treatment groups.

The proportion of subjects with CVF (2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL) through Week 48 (including subjects with dosing beyond Week 48) was 1.5% (8 subjects) for the Q8W group and <1% (2 subjects) for the Q4W group.

Subjects randomized in this study were to be virologically suppressed at Screening. No clinically relevant differences in absolute values and changes from Baseline in viral load through Week 48 were observed across the treatment groups

Mean and median lymphocyte (CD4+ and CD8+) cell counts remained stable from Baseline in both treatment groups over time and were similar between treatment groups when analysed by subgroups.

Kaplan-Meier estimates of the proportion of subjects without treatment related discontinuation = failure (TRDF) at Week 48 were 96.9% (95% CI: 95.0, 98.1) in the Q8W group and 97.1% (95% CI: 95.2, 98.2) in the Q4W group. The proportion of

subjects without efficacy related discontinuation = failure (ERDF) at Week 48 were 98.4% (95% CI: 96.9, 99.2) in the Q8W group and 99.6% (95% CI: 98.4, 99.9) in the Q4W group.

Safety

Unless otherwise specified, safety results presented are for the Maintenance Phase (including OLI and data collected for subjects with dosing beyond Week 48). For the purposes of this report the Maintenance Phase covers the period from the first dose of study treatment to the start of LTFU ART. The LTFU Phase starts after the last dose of the study treatment. Therefore, AEs starting after the last dose of study treatment and before the start of LTFU ART would be considered in both the Maintenance Phase and LTFU Phase.

Adverse Events

The proportion of subjects reporting any AE was similar between the 2 treatment groups (Q8W, 91%; Q4W, 92%). The distribution of common AEs (≥5%) was similar throughout the duration of the Maintenance Phase. The incidence of drug-related AEs was similar between the 2 treatment groups (Q8W, 77%; Q4W, 76%). The proportion of subjects reporting Grade 2 to 5 AEs was similar in both treatment groups (Q8W, 52%; Q4W, 55%). The incidence of serious adverse events (SAEs) and AEs leading to withdrawal was low and similar between the treatment groups. There were 2 fatal SAEs; hemorrhage from a cerebral aneurysm in 1 subject during Screening (not included in the Safety Population) and sepsis as a result of complications of acute pancreatitis in a subject in the Q8W group during the Maintenance Phase, which occurred 98 days after the final study injection. The death from the cerebral hemorrhage was not considered related to study drugs. The acute pancreatitis was considered related to study treatment by the investigator but the Sponsor did not consider this event to be related to study drugs due to a prior history of pancreatitis and length of time on treatment. The subject had previously received CAB + RPV on Study 201585.

Table: Overall Summary of Adverse Events - Maintenance Phase (Safety Population)

	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Any AE	473 (91)	482 (92)
Drug-related AEs	400 (77)	399 (76)
Any Grade 2 to 5 AEs	272 (52)	287 (55)
Drug-related Grade 2 to 5 AEs	156 (30)	164 (31)
AEs leading to withdrawal	12 (2)	13 (2)
Drug-related AEs leading to withdrawal	8 (2)	11 (2)
Any SAE	27 (5)	19 (4)
Drug-related SAEs[a]	3 (<1)	1 (<1)
Fatal SAEs [b]	1 (<1)	0
Drug-related fatal SAEs	0	0

c. Drug related SAEs were injection site abscess, presyncope, and acute pancreatitis in the Q8W group and hypersensitivity in the Q4W group.
d. The fatal SAE was sepsis. The death was not considered related to study drug.
Note: AEs in this table include ISRs.

The proportion of subjects reporting any AE was similar between the 2 treatment groups. The most frequently reported AE in both treatment groups was injection site pain.

Table: Summary of Common AEs (≥5% in Either Treatment Group) - Maintenance Phase (Safety Population)

Preferred Term	Q8W (N=522) n (%)	Q4W (N=523) n (%)
Any event	473 (91)	482 (92)
Injection site pain	371 (71)	363 (69)
Nasopharyngitis	71 (14)	74 (14)
Injection site nodule	54 (10)	89 (17)
Upper respiratory tract infection	50 (10)	71 (14)
Injection site induration	41 (8)	39 (7)
Injection site discomfort	36 (7)	41 (8)
Pyrexia	28 (5)	44 (8)
Headache	35 (7)	36 (7)
Diarrhea	33 (6)	37 (7)
Injection site swelling	32 (6)	27 (5)
Back pain	28 (5)	29 (6)
Injection site pruritus	27 (5)	25 (5)
Cough	17 (3)	29 (6)
Fatigue	13 (2)	33 (6)
Gastroenteritis	16 (3)	28 (5)
Pharyngitis	16 (3)	28 (5)

Most of the drug-related AEs were ISRs and the most frequently reported drug-related AE was injection site pain in both treatment groups. The most frequently reported non-ISR, drug-related AE was pyrexia, with similar frequency between treatment groups (Q8W: 4%, Q4W: 5%).

The majority of drug-related AEs were Grade 1 or 2 with drug-related Grade 3 to 4 AEs reported for 16 (3%) subjects in the Q8W group and 26 (5%) subjects in the Q4W group. There were no Grade 5 drug-related AEs.

The majority of AEs overall in both treatment groups were Grade 1 or 2. The overall incidence of Grade 3 to 5 AEs was low (Q8W: 41 [8%] subjects; Q4W: 49 [9%] subjects) and attributed primarily to ISRs. The only Grade 5 AE reported was 1 event of sepsis in the Q8W group, which occurred after study drug discontinuation.

A total of 12 (2%) subjects in the Q8W group and 13 (2%) subjects in the Q4W group had AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase. Except for fatigue, abnormal dreams, and hyperhidrosis, all occurring in the Q4W group, no individual AE term resulted in withdrawal/permanent discontinuation of study drug in >1 subject per treatment group.

The frequency of SAEs was similar in the 2 treatment groups (Q8W, 5% vs. Q4W, 4%). No patterns of clinical concern for non-fatal SAEs were noted as individual SAEs occurred across diverse system organ classes and preferred terms for both treatment groups. Drug related SAEs resulting in withdrawal were reported by 3 subjects in the Q8W group (injection site abscess, presyncope [and suspected partial IV administration of RPV], acute pancreatitis) and 1 subject in the Q4W group (hypersensitivity [and suspected partial IV administration of RPV]). Four additional subjects had SAEs (not drug related) leading to withdrawal/permanent discontinuation of study drug, 2 in the Q8W group (acute hepatitis B, diffuse large B-cell lymphoma) and 2 in the Q4W group (acute hepatitis B, glioblastoma).

One death was reported in the Q8W group during the Maintenance Phase. The subject presented with severe acute pancreatitis 2 weeks after the Week 16 visit and was withdrawn from study treatment. The subject required a prolonged hospital admission over 14 weeks, during which he experienced multiple serious complications, 10 of which were also reported as SAEs, culminating in death from sepsis. The event of sepsis occurred 98 days after the last dose of study medication. This subject had a history of pancreatitis before study enrollment. The Sponsor assessed the death was not related to study drug.

Another death was reported during Screening and the subject had not received a dose of study drug. The cause of death was a hemorrhage from a cerebral aneurysm.

Overall, injections with CAB + RPV were well tolerated. Local ISRs were reported frequently and most commonly comprised of mild (Grade 1 or 2), short-lived, and self-resolving pain events. Grade 3 ISRs accounted for 3% and 4% of ISRs in the Q8W and Q4W groups, respectively, and there were no Grade 4 or 5 ISRs. Few ISRs lasted more than 14 days (median duration 3 days). ISRs seldom led to withdrawal (Q8W: 5 [<1%] subjects and Q4W: 5 [<1%] subjects). Additionally, 1 subject in the Q8W group

and 6 subjects in the Q4W group withdrew consent from the study due to injection intolerability. One ISR in the Q8W group was reported as a SAE (Grade 3 right gluteal abscess) and resulted in withdrawal from the study. The event of right gluteal abscess was considered possibly related to RPV because the gluteal abscess appeared on the same site where RPV was administered by intramuscular injection.

Hepatotoxicity was categorized as an adverse event of special interest (AESI) for the current study. There were no adverse liver findings that raised concern for the CAB + RPV regimens. Five subjects met LSC during the Maintenance Phase of the study (2 on Q8W, 3 on Q4W); 3 of the subjects continued treatment with CAB + RPV. 3 additional subjects warranted monitoring based on liver chemistries. 4 subjects who met LSC had acute viral hepatitis and 1 subject was using melanotan II and continued treatment with CAB + RPV after discontinuing melanotan II.

One subject (Q4W group) had possible drug-induced liver injury (DILI) during OLI that was considered to be related to CAB + RPV. No cases of DILI were reported with CAB LA + RPV LA.

Other AESIs were reported at low frequencies and were similar between treatment groups. There were no notable findings for AEs related to rash (including hypersensitivity reaction) or other skin and subcutaneous disorders; however, 1 subject who had fever and prominent injection site reactions soon after injections discontinued from the study, although this event was not considered to be true delayed-type hypersensitivity reaction. There were no notable findings for AEs related to hepatobiliary disorders; musculoskeletal and connective tissue disorders; cardiovascular disorders; or metabolism and nutrition disorders.

Two subjects had suspected inadvertent partial IV administration of RPV LA that resulted in SAEs (presyncope, Q8W group, and hypersensitivity, Q4W group) and the subjects were withdrawn from the study.

AEs and laboratory abnormalities reported during the OLI primarily consisted of mild/moderate (Grade 1 or 2) events. Overall, oral CAB + RPV was well tolerated with 2 subjects in each treatment group (<1%) withdrawing due to AEs during OLI. Four of the 5 AEs that were reported for 4 subjects were considered to be possibly drug related.

Clinical Laboratory Evaluations and Other Safety Assessments

No clinically relevant patterns nor differences were observed in clinical laboratory values, for either chemistry or hematology, between the CAB LA + RPV LA groups. No clinically significant differences were observed for graded abnormalities for any of the following parameters: ALT, AST, bilirubin, or lipase. Grade 1 to 4 elevations of CPK were transient and commonly associated with recent exercise. Fasting lipid categories at Week 48 versus Baseline were similar in the 2 treatment groups. No clinically relevant patterns of change in fasting lipids from Baseline to maximum post Baseline category were observed in either treatment group. Median weight increases were minimal at 1.0 kg for both treatment groups.

Pharmacokinetics:

The CAB + RPV Q8W regimen was noninferior to the Q4W regimen for PK/PD parameters evaluated. Q8W achieves lower trough concentrations than the Q4W regimen. There was no clear relationship between Week 48 HIV RNA ≥50 c/mL and CAB or RPV exposures for subjects receiving the Q8W regimen.

Week 8 CAB pre-dose concentrations for subjects with no prior exposure to CAB were similar between treatment arms, in line with the same initial injection dose for the 2 regimens. Geometric mean Week 48 CAB pre-dose concentrations (regardless of prior exposure) were 1.67 μg/mL for the Q8W group and 2.74 μg/mL for the Q4W group.

Week 8 RPV pre-dose concentrations for subjects with no prior exposure to RPV were similar between treatment arms, in line with the same initial injection dose for the 2 regimens. Geometric mean Week 48 RPV pre-dose concentrations (regardless of prior exposure) were 73.1 ng/mL for the Q8W group and 97.5 ng/mL for the Q4W group.

Pharmacokinetic/ Pharmacodynamic Analysis

The following factors were evaluated in a logistic regression analysis: Treatment (dosing regimen), age, race, sex, Baseline CD4+ cell count, Baseline HIV-1 RNA, derived Baseline CDC Stage, Baseline BMI, Baseline third agent class, Week 8 RPV predose concentration, Week 8 CAB predose concentration, length of first RPV injection needle, and length of first CAB injection needle. In both the univariable and the multivariable regression analyses for the overall population, Baseline CDC stage of disease, Baseline BMI, and Week 8 CAB plasma concentration at the end of the dosing interval following the first injection were identified as statistically significant predictors of having a Week 48 HIV RNA ≥50 c/mL. In the multivariable logistic regression analysis for subjects without prior exposure, the strongest predictor of Snapshot HIV-1 RNA ≥50 c/mL was BMI.

Health Outcomes

Study subjects reported very high levels of treatment satisfaction with Q4W and Q8W dosing at Week 48, irrespective of prior CAB + RPV exposure. For subjects with prior CAB + RPV exposure, Baseline treatment satisfaction (i.e. satisfaction with Q4W dosing) was high (at around 62 out of possible 66 points in the HIVTSQs) and remained high across all time points, without significant differences between Q4W and Q8W dosing. For subjects without prior exposure to CAB + RPV, a significant increase from Baseline in treatment satisfaction was observed for both treatment groups across all timepoints, significantly favoring the Q8W group compared to the Q4W group. Supportive to HIVTSQs results, similar trends are observed in the General Acceptance scores across all timepoints. High rates of preference for the Q8W dosing (179/191 [94%]) were reported compared with Q4W dosing (6/191 [3%]) and daily oral dosing (4/191 [2%]) of CAB + RPV. The most common reasons supporting their preference were frequency of administration and convenience in terms of ease to integrate into their daily life. Acceptance of ISRs significantly improved from first injection through Weeks 24 and 48 for both treatment groups, with similar scores and no significant differences

between Q4W and Q8W at any timepoint. In the HAT-QoL dimensions, no significant differences were reported overall in change from Baseline within each treatment group, or between groups stratifying by prior CAB + RPV exposure, at Week 48.

Viral Genotyping:

CVF was uncommon in the study overall; 8 subjects in the Q8W group and 2 subjects in the Q4W group met CVF criteria.

RPV resistance-associated mutations were identified in 5/10 CVFs in Baseline PBMCs and 7/10 CVFs at the SVF timepoint. RPV mutations that arose on treatment included K101E (2), K101E + M230L, and E138E/K. In vitro phenotypic resistance to RPV was observed in 9/10 CVFs at the SVF time point. Two subjects did not have any RPV resistance-associated mutations, but still had reduced susceptibility to RPV (FC=2.4 and >119.2). Both subjects had virus that harboured other NNRTI substitutions and the association of those with decreased sensitivity to RPV is being investigated.

INSTI resistance-associated mutations occurred in 1/10 CVF subject in PBMCs at Baseline and 7/9 CVFs at the SVF timepoint. The INSTI mutation that was present at Baseline was G140G/R. CAB mutations that arose on treatment were Q148R, Q148R + E138E/K, Q148Q/R + N155N/H (2), N155H (2), and N155N/H. CAB resistance (in vitro phenotypic analysis) was observed in 4/8 CVF subjects at the SVF timepoint. INSTI substitutions, L74I and T97T/A, were present in some subjects but do not reduce INSTI susceptibility by themselves. All subjects, with phenotype data at the SVF time point, retained susceptibility to dolutegravir and bictegravir.

CVF subjects in this study harboured Subtype A (n=4), B (n=4), and C (n=2) viruses. This is in contrast to the CVF subjects from the CAB LA +RPV LA group in Study 201584 (FLAIR) and Study 201585 (ATLAS), where viral subtypes were either A, A1 or AG.

Conclusions:

Administration of CAB LA 600 mg + RPV LA 900 mg every 8 weeks demonstrated high efficacy and was non-inferior to CAB LA 400 mg + RPV LA 600 mg every 4 weeks in virologically suppressed HIV-1-infected adults. The current study results indicate that the 2-drug regimen, administered every 8 weeks, maintained HIV-1 suppression through the Week 48 primary endpoint comparatively to Q4W administration while adding the convenience of less frequent dosing. In addition, subjects in the current study expressed a higher rate of preference for the Q8W regimen compared with prior experience on CAB + RPV treatment (oral and/ or Q4W regimen).

The safety profiles demonstrated that the Q8W regimen was well tolerated and had similar types and frequency of ISRs compared to the Q4W regimen.

Results from the current study support the option for HIV-1 infected subjects who are virologically suppressed to switch to Q8W CAB LA + RPV LA IM injections for continued maintenance therapy.

Efficacy

The primary efficacy analysis demonstrated that CAB LA + RPV LA administered every 8 weeks is non-inferior to CAB LA + RPV LA administered every 4 weeks and provided good clinical efficacy based on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 for the ITT-E and PP populations. The adjusted treatment difference between Q8W and Q4W met the non-inferiority margin, set below 4%.

The key secondary analysis (HIV-1 RNA <50 c/mL) also demonstrated that Q8W CAB LA + RPV LA is non-inferior to Q4W CAB LA + RPVL LA according to the Snapshot Algorithm (Missing, Switch or Discontinuation = Failure) for the ITT-E, and PP populations. The adjusted treatment difference between Q8W (94% responders) and Q4W (93% responders) met the non-inferiority criterion, set above -10%.

The results within the stratification groups for duration of prior treatment exposure to CAB + RPV (0, 1-24, and >24 weeks) support the overall conclusions of non-inferiority in the primary and secondary endpoints.

Treatment differences for HIV-1 RNA ≥ 50 c/mL were observed in females with 5/137 (3.6%) above the threshold for Q8W compared with 0/143 in the Q4W group. Multivariable modeling for predictors of HIV-1 RNA ≥50 c/mL demonstrated that for the total study population, a BMI ≥30 kg was associated with an odds ratio of 5.0 for Snapshot HIV-1 RNA ≥50 c/mL. Results within this subgroup analysis should be interpreted with caution due to small sample size and the potential for confounding factors or other potentially important factors that were not taken into account.

The analysis of treatment difference within other subgroups (age, race, Baseline 3rd agent class, Baseline CD4+ lymphocyte count, and participating countries) were also examined. No statistically significant difference between the two treatment groups was observed for either the primary or secondary endpoints at Week 48 in any of these subgroups.

The Q8W regimen effectively maintained virologic suppression, with few Snapshot virologic failures and no overall increased risk for on-treatment development of resistance compared with the Q4W regimen through 48 weeks. Rates of CVF were 1.5% and 0.4% in the Q8W and Q4W groups, respectively.

Taken together, these results indicate that switching to Q8W CAB LA + RPV LA 2-drug injectable regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. Overall, this regimen, enabling 6 injection visits per year, demonstrated no increased risk of virologic failure relative to the Q4W regimen.

Safety

Over 48 weeks, the safety data from this randomized, open-label Phase III study of subjects switching to Q8W CAB LA+ RPV is favorable and consistent with prior Phase II and III trials examining the Q4W and Q8W regimens.

A similar proportion of subjects in Q8W group compared with those in the Q4W group had AEs. The increased frequency of reported common adverse events (occurring

with a frequency of ≥5%) for the Q4W group are most likely attributable to the increased number of clinical visits associated with Q4W injections. The most common AEs experienced by both treatment groups were injection site reactions, of which injection site pain was the most commonly reported.

SAEs reported as possibly drug-related occurred with a frequency of <1% in both arms and each type of SAE was reported once.

Two deaths occurred during the study: one death occurred during Screening (hemorrhage from cerebral aneurysm) and another death occurred in a subject in the Q8W group during the Maintenance Phase. The latter death was reported 98 days after the subject's last dose of study drug. The cause of death was sepsis as a result of complications of acute pancreatitis. Based upon the long latency period and these possible confounders the Sponsor does not believe the evidence supports the study drugs being causative in this instance.

The rate of AEs leading to withdrawal was low (2%) with no distinct patterns of AEs between treatment groups.

Overall, injections for Q8W CAB LA + RPV LA were well tolerated. ISRs were generally mild and of short duration, were similar in frequency and type to Q4W injections, and resulted in few withdrawals (1%).

For AEs of rash and myalgia, there was no evidence for increased occurrence, severity or clinical concern for Q8W injections compared with Q4W injections.

Review of adverse events of special interest potentially related to QTc prolongation, seizures and seizure-like events, rhabdomyolysis, pancreatitis, and events related to impact on creatinine and safety in pregnancy did not identify any safety concerns.

No cases of DILI were reported for subjects receiving CAB LA + RPV LA.

Subjects in both treatment groups had a median weight gain of 1.0 kg during the study.

Neuropsychiatric events of depression, anxiety, and sleep disorders occurred between 2 to 7% in each treatment group, with few events leading to withdrawal.

The OLI period for CAB + RPV was well tolerated with no new patterns observed for clinical adverse events or laboratory abnormalities and few subject withdrawals. One possible case of DILI was reported during OLI.

2 cases of suspected partial IV administration of RPV were associated with SAEs that led to discontinuation from the study.

No clinically relevant patterns in changes for chemistry, hematology, or lipids from Baseline category for the Maintenance Phase through Week 48 were observed in either treatment group.

PK and PK/PD Conclusions

Steady state was confirmed for CAB by Week 48 regardless of stratification by prior exposure. Following Q8W dosing, CAB predose concentrations increased from Week 8 to Week 48 in subjects with 0 prior exposure and decreased from Day 1 to Week 48 in subjects with >24 weeks prior exposure on the Q4W regimen.

Following Q8W dosing, RPV predose concentrations increased from Week 8 to Week 48 in subjects with 0 prior exposure and from Week 8 to Week 48 in subjects with >24 weeks prior exposure on the Q4W regimen, in line with the apparent half-life of RPV LA of 28 weeks.

Following Q4W dosing, CAB and RPV concentrations were similar to those observed in Phase IIb/III studies. Following Q8W dosing, CAB and RPV concentrations were similar to those observed in Phase IIb studies.

Health Outcomes Conclusions

High levels of treatment satisfaction with CAB+RPV were observed for both treatment groups across all study visits. Significant increase from Baseline in treatment satisfaction was reported among subjects without prior exposure to CAB + RPV at Weeks 24 and 48 for both treatment groups, significantly favoring the Q8W group compared with the Q4W group.

Of respondents randomised to the Q8W arm with prior exposure to CAB + RPV, preference for Q8W was higher (94%) compared with the Q4W (3%) and oral CAB + RPV (2%); the most common reasons were frequency of administration and convenience in terms of ease to integrate into one's daily life.

High rates of acceptance of ISRs that improved over time for both treatment groups from Week 8 to Week 48 were observed.

Virology Conclusions

CVFs were infrequent in the study with 8 subjects (1.5%) in the Q8W arm and 2 subjects (0.4%) in the Q4W arm. Virus subtypes observed in CVF subjects were A or A1 (n=4), B (n=4) or C (n=2).

RPV resistance-associated mutations were found in 5/10 CVF subjects in Baseline PBMCs and 7/10 subjects at SVF time point.

At the SVF time point, in vitro phenotypic resistance to RPV occurred in 9/10 CVF subjects.

INSTI resistance-associated mutations were present in 1/10 subjects in Baseline PBMCs and 7/9 subjects at SVF time point.

At the SVF time point, in vitro phenotypic CAB resistance occurred in 4/8 CVF subjects.

INSTI substitution, L74I, was present in 5 subjects at Baseline and 4 subjects at the SVF time points.

No dolutegravir or bictegravir resistance was observed in the CVF subjects.

Effective Date: [redacted] 20[redacted]