Janssen Research & Development

Clinical Overview

Module 2.5

Rilpivirine (TMC278) Long-acting

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

abbreviation	description of abbreviated term
3TC	Lamivudine
ABC	Abacavir Sulfate
ACCEPT	General Treatment Acceptance Score
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate Aminotransferase
AUC(0-inf)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
BCRP	Breast cancer resistance protein
BMI	Body Mass Index
CAB	Cabotegravir
CAR	Continued/Current Antiretroviral Regimen
CD	Cluster of Differentiation Cells
CI	Confidence Interval
CK	Creatine Kinase
CL/F	Oral Clearance
Cmax	Maximum observed plasma drug concentration
c/mL	Copies per milliliter
CSF	Cerebrospinal Fluid
CSR	Clinical Study Report
Cτ	Trough plasma concentrations at the end of the dosing
CVF	Confirmed Virologic Failure
DDI	Drug-drug Interaction
DILI	Drug-induced Liver Injury
DTG	Dolutegravir
DTG/ RPV FDC	Dolutegravir and Rilpivirine Fixed-dose Combination
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
EU	European Union
FDC	Fixed-dose Combination
FTC	Emtricitabine
FOIA	Freedom of Information Act
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
HIVTSQc	HIV Treatment Satisfaction Questionnaire Change Version
HSR	Hypersensitivity Reaction
IFU	Instructions for Use
IM	Intramuscular
INSTI	Integrase Strand Transfer Inhibitor
ISE	Integrated Summary of Efficacy
ISR	Local Injection Site Reaction
ISS	Integrated Summary of Safety
ITTE	Intent-to-treat Exposed
Janssen	Janssen Sciences Ireland UC
L	Liter
LA	Long-acting Injectable, Extended Release Suspension for Injection, or Prolonged Release Suspension for Injection
LLQ	Lower limit of quantification
LOCF	Last Observation Carried Forward
LSC	Liver Stopping Criteria
LSLV	Last Subject Last Visit
LTFU	Long Term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
mm	Millimeter
MRHD	Maximum Recommended Human Dose
ms	millisecond
MVA	multivariable analysis
ng	Nanogram
nm	Nanometer
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NSAID	Nonsteroidal Anti-inflammatory Drugs
OLI	Oral Lead In
OR	odds ratio
PBMC	Peripheral blood mononuclear cell
Pgp	P-glycoprotein
PI	Protease Inhibitor
PIN	Perception of Injection
PK	Pharmacokinetics
PP	Per protocol
Q4W	Dosing once every 4 weeks
Q8W	Dosing once every 8 weeks
QTc	Corrected QT Interval

QTcB	Heart Rate-corrected QT Interval
QTcF	QT Interval Corrected using Fridericia's Formula
RAL	Raltegravir
RNA	Ribonucleic Acid
RPV	Rilpivirine (TMC278)
SAE	Serious Adverse Event
SC	Subcutaneous
SOC	Standard of Care
SVF	Suspected Virologic Failure
$T_{1/2}$	Terminal phase half-life
TDF	Tinofovir Disoproxil Fumarate
Tmax	Time of occurrence of Cmax
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper Limit of Normal
US	United States
Vc/F	Apparent volume of the central compartment

Confirmed virologic failure	Defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.
Continuation injection	Refers to the injections a patient receives following the initiation injection. In the clinical documents of clinical studies with CAB + RPV, reference is made to “maintenance dose” instead of “continuation injection”.
Initiation injection	Refers to the first injection a patient receives after the oral lead-in. In the clinical documents of clinical studies with CAB + RPV, reference is made to “loading dose” instead of “initiation injection”.

1. PRODUCT DEVELOPMENT RATIONALE

Rilpivirine (RPV) is part of a new 2-drug, monthly (Q4W) or every 2 months (Q8W), dosing regimen with cabotegravir (CAB) for the treatment of human immunodeficiency virus type 1 (HIV-1) infection. This application focuses on the RPV long-acting (LA) component of this 2-drug regimen. CAB is owned by ViiV Healthcare Company (further referred to as ViiV) and will be subject of a separate marketing authorization application.

1.1. Introduction

The overall objective of the CAB + RPV clinical program is to develop a novel, highly effective, well tolerated 2-drug LA injectable regimen. Such a regimen offers reduced dosing frequency (Q4W or Q8W) compared with daily oral antiretrovirals (ARVs). With less frequent dosing, the daily reminder of a patient's HIV status may be avoided and associated stigma related to taking oral treatment regimens may be lessened. A reduced dosing schedule holds promise for increased patient compliance with dosing requirements. This novel treatment option may result in improved overall satisfaction with treatment and longer retention in care for individuals with HIV infection. This nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen avoids exposure to this class of ARV therapy (ART) thereby avoiding possible NRTI-class-related resistance, and longer term NRTI-related toxicities. Given the parenteral route of administration, a 2-drug LA injectable regimen may result in fewer gastrointestinal adverse events (AEs), eliminates dosing restrictions with regard to food, and will have fewer drug-drug interactions (DDIs) at the level of the gastrointestinal tract.

When approved, this will be the first 2-drug LA injectable regimen for maintaining viral suppression (plasma HIV-1 ribonucleic acid [RNA] <50 copies [c]/mL). Current therapies and unmet medical need are discussed in Section 6.1.2.

RPV is a diarylpyrimidine derivative and a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) with in vitro activity against wild-type HIV-1 and specific NNRTI-resistant mutants, developed for the treatment of HIV-1 infection. Oral RPV is a globally available product marketed as EDURANT® 25 mg tablets and as part of several fixed dose combination (FDC) single tablet regimens (refer to Section 1.3). An RPV LA formulation was developed as extended release (also called prolonged release) suspension for intramuscular (IM) injection.

1.2. Summary of Clinical Development Program

Janssen in partnership with ViiV are developing the CAB + RPV regimen for the treatment of HIV-1 infection. Janssen is the sponsor of the RPV LA development and manufacturing program. ViiV is the sponsor of the CAB + RPV clinical program and manufacturer of the CAB oral and LA formulations.

An overview of the estimated cumulative exposure to RPV LA during the development program up to a cut-off date of [redacted] 20[redacted], except for ATLAS-2M which was calculated until [redacted] 20[redacted] (Week 48 last subject last visit), for subjects still on treatment at that time, is provided in Table 1.

Table 1 Estimated Cumulative Subject Exposure[a] From Clinical Studies

	Number of Subjects	Exposure (person-years)
RPV LA Injectable Nanosuspension Clinical Program (Janssen Conducted Studies)		
Non-HIV-infected subjects[b]		
RPV LA Injectable Nanosuspension (G001)[c]	185	-
CAB LA + RPV LA Clinical Program (ViiV Conducted Studies)		
HIV-infected subjects[d]		
CAB + RPV (oral and/or LA)[e]	2,141	-
RPV LA[f]	1,667	2,756
Non-HIV-infected subjects[g]		
RPV LA	19	-

CAB: cabotegravir; LA: long-acting; RPV: rilpivirine.

a. Exposure and person-time were calculated up to the point of the subject's last dose administered or until [redacted] 20[redacted] for subjects still on treatment at that time, except for study 207966 which was calculated until [redacted] 20[redacted] (Week 48 last subject last visit) for subjects still on treatment at that time. For injections, exposure can last for up to a year after the last injection.
b. Includes studies TMC278-TiDP15-C158, TMC278LAHTX1001 and TMC278LAHTX1002
c. Formulation proposed for commercial use.
d. Includes studies 201584, 201585, 207966, 200056, and LAI116482.
e. Number of subjects who received at least one dose of CAB + RPV oral and/or LA.
f. Number of subjects who received at least 1 dose of RPV LA.
g. Study LAI115428.

In addition, a Phase I Janssen-sponsored study with the RPV LA injectable nanosuspension formulation (G001; proposed for commercial use), was conducted in healthy subjects in support of the potential development of RPV LA as pre-exposure prophylaxis (study TMC278-MWRI-01). No safety issues were identified during this study and as data are not considered relevant for this submission, they are not further discussed in this Clinical Overview.

The summaries of efficacy and safety are based on the pooled primary (Week 48) analyses of the ongoing Phase III studies (201584 [FLAIR] and 201585 [ATLAS]) comparing Q4W dosing with oral standard of care (SOC) and the Week 48 analysis of the ongoing Phase IIIb study (207966 [ATLAS-2M]) comparing Q8W dosing with Q4W dosing. The Phase III/IIIb randomized studies represent the proposed regimen and dosages intended for commercial use and enable an assessment of benefit-risk based on the comparative efficacy and safety data from these 3 studies. Supportive efficacy and safety information are provided from further analyses of the Phase III studies (201584 and 201585) and from the Phase II studies (LAI116482 [LATTE] and 200056 [LATTE-2]) (see Table 2).

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocols. The CAB + RPV clinical studies were sponsored by ViiV and were undertaken in accordance with standard operating procedures of ViiV and the GlaxoSmithKline Group of Companies, which comply with the principles of GCP. All studies were conducted with the approval of Ethics Committees or Institutional Review Boards. Informed consent was obtained for all subjects, and the studies were performed in accordance with the version of the Declaration of Helsinki that applied at the time the studies were conducted. Where required, regulatory approval was obtained from the relevant health authority.

Table 2 Summary of Key Clinical Studies

Study	Study Design	Population	Treatment Details
201584 (FLAIR) Status: Ongoing; Week 48 and Week 96/100[a] CSRs completed LSLV Cut-off date: [redacted] 20[redacted]	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 and Week 96 CSRs completed LSLV Cut-off date: [redacted] 20[redacted]	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 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 LSLV Cut-off date: [redacted] 20[redacted]	Open-label, randomized, Phase IIIb study to demonstrate non-inferiority of CAB LA + RPV LA Q8W compared with CAB LA + RPV LA Q4W	HIV-1 infected ART-experienced adult subjects who are virologically suppressed on a stable ARV regimen	**Maintenance Phase (52 weeks):** CAB + RPV Q4W group: CAB LA 600 mg + RPV LA 900 mg loading 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 loading dose*, CAB LA 600 mg + RPV LA 900 mg second loading dose* administered 4 weeks after the initial loading 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 loading doses. Those transitioning from CAB + RPV Q4W received OLI and loading 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.

[a] Note that this time point is further referred to as 'Week 96'

Study	Study Design	Population	Treatment Details
200056 (LATTE-2) Status: Ongoing; Week 48, Week 96, and Week 160 CSRs 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 loading dose, CAB LA 400 mg + RPV LA 600 mg every 4 weeks CAB + RPV Q8W group: CAB LA 800 mg + RPV LA 900 mg loading dose, CAB LA 600 mg second loading 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**: If on CAB LA + RPV LA, continue from Maintenance Phase (either Q4W or Q8W). If on oral CAB + ABC/3TC, transition to chosen optimized IM dosing regimen (CAB LA + RPV LA Q4W or Q8W)
LAI116482 (LATTE) Status: Completed; Week 24, Week 96, Week 144 and Final (EOS) CSRs completed	Open-label, randomized, 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
LAI115428 Status: Completed; CSR completed	Open-label, randomized, repeat dose escalation, Phase I trial to determine the safety, tolerability, and PK profile of IM and SC injections of CAB LA alone and in combination with RPV LA	Healthy adult subjects	**Cohort 2 (4 months):** Loading dose of CAB LA 800 mg IM at month 1, followed by CAB LA 200 mg IM at months 2-4 + RPV LA 1200 mg IM at month 3 and RPV LA 900 mg IM at month 4 **Cohort 3 (4 months):** Loading dose of CAB LA 800 mg IM at month 1 followed by CAB LA 400 mg IM at months 2-4 + RPV LA 1200 mg IM at month 3 and RPV LA 600 mg IM at month 4 Details of the run-in period, and Cohorts 1 and 4 (CAB LA alone) are described in the CSR.
LAI116181 Status: Completed; CSR completed	Open-label, repeat dose, three-period, single-sequence, Phase 1 drug-drug interaction trial: Cohort 2 evaluated coadministration of oral RPV with oral CAB	Healthy adult subjects	CAB 30 mg once daily for 12 days alone followed by a 14-day washout, and then RPV 25 mg once daily for 12 days alone, immediately followed by CAB 30 mg + RPV 25 mg once daily for 12 days

1.3. Regulatory History

The CAB + RPV development program has been formally discussed with different regulatory agencies (including FDA and EMA) at various milestones throughout development (see Mod1 [Administrative Information and Prescribing Information]).

Authorization Applications for the combination regimen of CAB LA + RPV LA have been submitted and are under review in several countries/regions. At the time of the writing of the CO, the regimen was approved in several countries/regions, including in the EU on 17 December 2020 (RPV LA: REKAMBYS®, MAH JCI NV; and CAB LA: Vocabria®, MAH ViiV HC BV) and, as a co-packaged product, in both Canada and the US (Cabenuva®, ViiV HC BV MAH) on 18 March 2020 and 21 January 2021, respectively.

Oral 25-mg RPV tablets (EDURANT) have been approved for the treatment of HIV-1 infection in ARV treatment-naïve patients ≥12 years of age in multiple countries worldwide including the US, EU, and Canada. In most countries, the indication is restricted to patients with plasma HIV-1 RNA ≤100,000 copies/mL (c/mL).

1.4. Claimed Indication and Dosage

RPV LA injection (REKAMBYS®) is indicated in combination with CAB injection (Vocabria®), for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) and have no known or suspected resistance to either RPV or CAB.

RPV LA injections should be administered by a healthcare professional.

Oral RPV (EDURANT) is recommended for approximately 1 month (at least 28 days) in virologically suppressed patients prior to the initiation of RPV LA to assess tolerability to RPV (hereafter referred to as "oral lead-in" [OLI]).

Table 3 Recommended Every 1 Month Dosing Schedule in Adult Patients

	Oral Lead-in	IM Initiation Injections	IM Continuation Injections
Drug	**During Month 1**	**At Month 2**	**Month 3 Onwards**
Rilpivirine	25 mg once daily	3 mL (900 mg)	2 mL (600 mg) monthly
Cabotegravir	30 mg once daily	3 mL (600 mg)	2 mL (400 mg) monthly

IM=intramuscular injection
Note: In study 201584 and study 201585 protocols, the 3 mL injections were referred to as “First Injections (Loading Dose)” and the 2 mL injections were referred to as “Maintenance Injections.”

Table 4 Recommended Every 2 Months Dosing Schedule in Adult Patients

Drug	Oral Lead-in	IM Initiation Injections (1 month apart)	IM Continuation Injections (2 months apart)
	During Month 1 (at least 28 days)	At Month 2 and Month 3	Month 5 Onwards
Rilpivirine	25 mg once daily	3 mL (900 mg)	3 mL (900 mg)
Cabotegravir	30 mg once daily	3 mL (600 mg)	3 mL (600 mg)

IM=intramuscular injection

2. OVERVIEW OF BIOPHARMACEUTICS

The proposed commercial formulation of RPV LA and the approved commercial formulation of oral RPV were used in all clinical studies included in this application.

The sterile, neutral nanosuspension RPV LA formulation provides extended release of the active moiety after IM injection.

For detailed information on biopharmaceutic data described in this section, refer to Mod2.7.1 (Summary of Biopharmaceutic Studies and Associated Analytical Methods).

2.1. Formulation Development

During the development of the parenteral LA formulation, RPV LA as the poloxamer-338 (P-338)-containing formulation G001 (300 mg/mL Extended Release Suspension for Injection) was selected for further development and registration. This formulation was used in all Phase I studies in healthy volunteers included in this submission and in all clinical trials with HIV-infected subjects.

RPV LA (G001) is formulated as a free base with median particle size of [redacted]nm and is provided as a sterile white to off-white suspension containing 300 mg/mL of RPV. RPV LA is packaged in a single use 4-mL USP Type I glass vial with a 13-mm grey stopper and aluminum seal. Each vial contains a nominal fill of 2.0 mL or 3.0 mL (Table 3) and does not require dilution prior to administration. Each sterile, single-use vial of RPV LA 300 mg/mL is intended to provide a dose of 600 mg/2 mL or 900 mg/3 mL for IM administration.

For detailed information on the development of the RPV LA formulation, refer to Mod3.2.P.2.2.1/Formulation Development.

2.2. In Vitro Dissolution Data

For detailed information on the RPV LA in vitro release method and an overview of its development, refer to Mod3.2.P.5.2/Analytical Procedure in Vitro Release Method (DS-TMD-22525) and Mod3.2.P.2.2.3/Physicochemical and Biological Properties, respectively.

In vitro release testing results for relevant clinical G001 batches are included in Mod3.2.P.5.4/Batch Analyses (DS-TEC-132046).

2.3. Analytical Methods

The bioanalytical methods used to measure concentrations of RPV in human plasma, in the absence and presence of CAB, were selective, accurate and reproducible (Mod2.7.1/Sec1.5).

2.4. Biopharmaceutic Studies

The results of study TMC278LAHTX1001 confirmed that RPV LA (G001) should be stored in the refrigerator at 2°C to 8°C (Mod2.7.1/Sec2.1.1).

The results of study TMC278LAHTX1002 showed that the particle size distribution of the RPV LA formulation influenced the pharmacokinetic (PK) profile (ie, the release rate) after IM injection, with a similar rank order of release rates in vitro and in vivo (Mod2.7.1/Sec2.1.2).

More details on the biopharmaceutic studies for RPV LA are presented in Mod2.7.1/Sec2.

The oral RPV 25 mg tablets used in the CAB + RPV clinical program, were the same as the commercial tablets, marketed as EDURANT.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Main conclusions from the clinical pharmacology studies conducted with RPV are discussed in this section.

The clinical pharmacology characteristics of RPV LA were determined based on studies with the CAB + RPV regimen and studies with RPV LA alone. In addition, studies with oral RPV that determined the clinical pharmacology of RPV, and are relevant for RPV LA, are discussed where applicable and study reports are resubmitted with this application. These studies include a mass balance study, a study in mild and moderate hepatic impaired subjects, TQT studies and DDI studies. These studies are described in detail in Mod2.7.2/App/Tab1 and Mod2.7.2/App/Tab2.

3.1. Absorption, Distribution, Metabolism, and Elimination

Table 5 Key Pharmacokinetic Characteristics of RPV After IM Administration of RPV LA

	Rilpivirine LA
Absorption	
t_{max} [a]	3 - 4 days
Distribution	
% bound to human plasma proteins [b]	99.7
Blood-to-plasma ratio [c]	0.67
Cervical tissue-to-plasma ratio [d]	0.42 - 0.77
Vaginal tissue-to-plasma ratio [d]	0.44 - 0.72
Rectal tissue-to-plasma ratio [d]	1.10 - 1.22
CSF-to-plasma ratio [e]	0.01
Metabolism	
Metabolism [f]	CYP3A

	Rilpivirine LA
Elimination	
Major route of elimination	Metabolism
CL/F [g]	5.08 L/h
$t_{1/2}$ [h]	90 - 200 days (13 - 28 weeks)
% of dose excreted as total radioactivity (unchanged drug) in feces [i]	85.1 (25.5)
% of dose excreted as total radioactivity (unchanged drug) in urine [i]	6.1 (<1.0)

a. t_{max} presented as median; Data Source: Mod5.3.3.5/RPV LA PopPK report Q4W
b. Plasma protein binding based on average values for oral RPV; Data Source: Mod2.6.4/Sec4.2.
c. Data Source: Mod2.6.4/Sec4.2.
d. Tissue-to-plasma ratios presented as range of overall median values for single doses of RPV LA 300, 600 or 1200 mg IM; Data Source: Jackson 2014, McGowan 2016.
e. CSF-to-plasma ratio presented as median. Data Source: Mod5.3.4.2/200056 CSF Sub-study CSR/Tab3.2 and Tab3.6.
f. Data Source: Mod2.4/Sec3.5
g. CL/F presented as estimate from the PopPK analysis; Data Source: Mod5.3.3.5/RPV LA PopPK report Q4W/Sec6.
h. RPV LA exhibits absorption rate limited PK, which is reflected in a long apparent $t_{1/2}$ following IM administration compared with oral RPV administration. 90 days (13 weeks) is the estimated mean $t_{1/2}$ from Phase I studies in healthy volunteers (Data Source: Mod5.3.1.2/TMC278LAHTX1002 CSR/Tab4; Mod5.3.3.1/TMC278-C158 CSR/Att/PK08) and 200 days (28 weeks) is the estimated mean $t_{1/2}$ based on the RPV LA PopPK model (Data Source: Mod5.3.3.5/RPV LA PopPK report Q4W/Sec6).
i. Data obtained following oral RPV human radiolabeled study. Data Source: Mod2.7.2/App/Tab2/TMC278-C119. The mean total recovery of radioactivity in urine and feces was 91.2% of the administered dose.

3.1.1. Absorption

Following IM injection of RPV LA into the gluteus medius muscle, RPV is slowly absorbed into the systemic circulation. The median observed time to reach the maximum RPV plasma concentration was approximately 3-4 days after injection. The release of the drug starts as early as Day 1 and may last for a year or longer. The RPV PK profile after IM injection is characterized by absorption rate limited elimination (i.e., flip-flop PK) with a prolonged apparent terminal half-life (Mod2.7.2/Sec3.2.6.1).

After IM administration, RPV disposition was described by an open, one compartment model with linear elimination. The population PK model was parameterized in terms of Vc and Kel. The absorption of RPV from the injection site was best described by 2 parallel absorption pathways: a fast absorption route describing the initial RPV peak and a second slow absorption route determining the terminal part of the RPV concentration vs time curve, reflecting the flip-flop kinetics after IM administration. From the population PK (PopPK) model (based on Phase I data as well as long-term data in HIV-infected patients from Phase II/III), the estimated apparent terminal half-life (ln2/*KA1*) for RPV after IM administration is 200 days (28 weeks).

From Phase I studies in healthy volunteers, the estimated mean apparent terminal half-life was ~90 days (13 weeks). This apparent discrepancy with the PopPK analysis can likely be explained by limitations of an extended sampling period after injection in healthy volunteer studies; although 6 to 9 months follow-up was implemented in the RPV LA Phase I studies, this may not have been long enough to describe the RPV elimination. This

is also confirmed by the observed plasma concentration-time profiles in the Phase III studies, which showed that steady-state was not yet reached after 1 year (~4 times the estimated apparent terminal half-life of 90 days).

Absorption from the IM depot into the systemic circulation is near complete following RPV LA injection, and the bioavailability of RPV LA after IM injection was similar to that after administration of an oral immediate release RPV solution (Mod5.3.1.2/TMC278LAHTX1002 CSR).

3.1.2. Distribution

Based on PopPK analysis, the typical apparent volume of the central compartment (Vc/F) for RPV after IM administration was estimated to be 132 L, reflecting a moderate distribution to peripheral tissues (Mod2.7.2/Sec3.2.6.2).

The RPV blood-to-plasma concentration ratios were 0.67 and 0.66 at RPV concentrations of 100 and 1,000 ng/mL, respectively (TMC278-NC112, Mod2.6.4/Sec4.2).

The in vitro plasma protein binding of RPV, determined by equilibrium dialysis, was on average 99.7%, irrespective of the RPV concentration (10-3000 ng/mL). RPV was extensively bound to human albumin and to a lesser extent to α1-acid glycoprotein. A very limited fraction of RPV was distributed to the plasma water compartment (0.003). The fraction of RPV distributed to plasma proteins was 0.773 and the fraction distributed to blood cells was 0.224 (TMC278-NC112, Mod2.6.4/Sec4.2).

RPV distributes into compartments other than plasma (cerebrospinal fluid [CSF], genital tract secretions). Following RPV LA doses of 300, 600, and 1200 mg, cervicovaginal tissue concentrations were ~65% of plasma concentrations after 7 and 14 days, ~85% of plasma concentrations after 28 days, and ~300% of plasma concentrations after 56 days; and rectal tissue concentrations in males were ~90 to 98% of plasma concentrations after 7 and 14 days [Jackson, 2014]. In another study [McGowan, 2016], with RPV LA doses of 600 mg and 1200 mg, vaginal and ectocervical tissue-to-plasma ratios were 0.44 to 0.72 for vaginal tissue and 0.42 to 0.77 for ectocervical tissue for 112 days post-dose. Rectal tissue-to-plasma RPV ratios were 1.10 to 1.22. RPV concentrations in rectal tissue were comparable in men and women. RPV concentrations in all tissues correlated with RPV plasma concentrations at the same time point.

A CSF PK sub-study was performed in study 200056, including 18 subjects (n=3 in Q4W and n=15 in Q8W), with paired CSF and plasma samples taken 7 (±3) days after injection at steady-state. The RPV plasma concentrations ranged from 83 to 378 ng/mL, and the CSF RPV concentrations ranged from below the detection limit (1 ng/mL) to 2.90 ng/mL. Median RPV total CSF concentrations were 1.07 to 1.32% of the paired total RPV plasma concentrations. RPV total CSF concentrations and CSF/plasma ratios were similar for Q4W and Q8W dosing. The RPV total CSF concentrations were higher than the in vitro IC50 for wild-type HIV-1 virus (0.066 to 0.081 ng/mL). Similar values have been reported after oral administration of RPV, with a mean CSF/plasma ratio of 1.4% [Mora-Peris, 2014].

3.1.3. Metabolism

RPV metabolism is mainly catalyzed by CYP3A enzymes, which also play the major role in the biotransformation of RPV in vitro (Mod2.6.4/Sec5.1.4).

A major metabolic pathway of RPV, representing the main in vitro biotransformation, was aromatic hydroxylation at the pyrimidinyl moiety (to metabolite 42), followed by glucuronidation (to metabolite 25). Another major metabolic pathway was aliphatic hydroxylation at one of the methyl groups of the cyanoethenyl-2,6-dimethylphenyl moiety (to metabolite 33), followed by dehydration to form a tricyclic metabolite (metabolite 27).

The metabolites of ^{14}C-RPV were determined in feces, urine, and plasma collected from healthy adults after a single oral dose of 150 mg ^{14}C-RPV (TMC278-C119, Mod2.7.2/Sec3.2.6.3). The most abundant metabolite originated from oxidation at the 5-position of the pyrimidinyl moiety (metabolite 42) and accounted for 16.1% of the RPV-related radioactivity in feces. Three other metabolites each accounted for 2.2 to 3.0% of RPV. In urine, apart from the carboxylic acid metabolite (metabolite 30, 0.03%), the other metabolites were phase-2 metabolites (glucuronides or glutathione derived conjugates) including 2 glycine conjugates (metabolites 13 and 14) and a mercapturic acid conjugate (metabolite 18). Unchanged drug accounted for the major part of the total radioactivity in plasma (76% based on C_{max}, 51% based on AUC_{last}). Several minor plasma metabolites were detected, including the glucuronide of RPV (metabolite 15, ≤10.2% of the sample radioactivity), the tricyclic metabolite (metabolite 27, ≤9.7% of the sample radioactivity), and hydroxymethyl RPV (metabolite 33, ≤5.1% of the sample radioactivity); others (glucuronide of hydroxymethyl RPV and of hydroxylated RPV) were only present in trace amounts.

3.1.4. Excretion

A mass balance trial (TMC278-C119, Mod2.7.2/Sec3.2.6.4) showed that most of the ^{14}C-RPV-related radioactivity from a single 150-mg dose administered as an oral solution was excreted in feces. At 168 h after dosing, a mean of 85.1% of the administered radioactivity was recovered in feces, and a mean of 6.1% of the administered radioactivity was recovered in urine. Unchanged RPV accounted for a mean of 25.5% of the dose in feces. Only trace amounts (<1%) of unchanged RPV were detected in urine.

From the PopPK model, the apparent plasma clearance (CL/F) of RPV after IM administration of RPV LA in healthy subjects was calculated to be 5.08 L/h.

The apparent terminal elimination t1/2 of RPV after oral administration is approximately 50 h. After IM injection, the apparent terminal t1/2 is determined by the absorption rate limited elimination (i.e., flip-flop PK) and was estimated to be approximately 90 days (13 weeks) (from Phase I studies) – 200 days (28 weeks; from RPV PopPK model).

From the PopPK analysis, following discontinuation of the RPV LA Q4W regimen (administered to steady-state), 87% of patients overall were predicted to have quantifiable plasma RPV concentrations (>LLQ [1 ng/mL]) 3 years after the last IM injection and 5% of patients overall were predicted to have quantifiable plasma RPV concentrations 4 years after the last IM injection (Mod5.3.3.5/RPV LA PopPK Report Q4W/Sec5.6.8). Observed RPV plasma concentrations for HIV-infected subjects that discontinued CAB+RPV and

entered the 12-month long-term follow-up are summarized in Mod2.7.2/Sec2.1.2.1 (ATLAS), Sec2.1.2.2 (FLAIR), Sec2.1.2.3 (ATLAS-2M) and Sec2.1.2.4 (LATTE-2).

3.2. Pharmacokinetics in Healthy Subjects and Target Patient Populations

Based on accumulated data, there appears to be no significant difference in the PK of RPV between healthy and HIV-infected subjects (Mod2.7.2/Sec3.2.1).

The proposed Q4W and Q8W CAB + RPV regimens achieve RPV plasma concentrations similar to those achieved with the approved oral RPV 25 mg once daily dosing (Table 6).

Table 6 Summary of RPV PK Parameters Following Administration of Proposed CAB + RPV Regimen in HIV-infected Subjects

Dosing Phase	Dose Regimen	Geometric Mean (5th; 95th Percentile)[a]		
		$AUC_{(0\text{-}tau)}$[b] (ng•h/mL)	C_{max} (ng/mL)	C_{tau}[b] (ng/mL)
Oral Lead-In[c]	25 mg once daily	2,083 (1,125; 3,748)	116 (48.6; 244)	79.4 (31.8; 177)
Initial Injection[d]	900 mg IM initial dose	44,842 (21,712; 87,575)	144 (93.9; 221)	41.9 (21.7; 78.9)
Monthly Injection[e]	600 mg IM monthly	67,703 (39,029; 117,472)	120 (68.2; 208)	84.9 (49.4; 146)
Every 2 Months Injection[e]	900 mg IM every 2 months	132,450 (76,638; 221,783)	138 (80.6; 228)	68.9 (38.0; 1198)

Data Source: Mod5.3.3.5/RPV LA PopPK report Q4W/TabA2 and Mod5.3.3.5/RPV LA PopPK report Q8W/TabES2

[a] Pharmacokinetic parameter values based on individual post hoc estimates from RPV popPK model (pooled data from FLAIR, ATLAS and ATLAS-2M [subjects with no prior rilpivirine exposure]), except for oral rilpivirine *(see footnote c)*.

[b] tau is dosing interval: 24 hours for oral administration; 1 month for monthly RPV LA IM injections, 2 months for every 2 months RPV LA IM injections.

[c] Oral lead-in pharmacokinetic parameter values represent steady-state. For oral RPV 25 mg once daily, C_{tau} values are observed values from FLAIR, ATLAS and ATLAS-2M (subjects with no prior rilpivirine exposure); $AUC_{(0\text{-}tau)}$ is based on population pharmacokinetic estimates from pooled Phase III trials with oral RPV (EDURANT); C_{max} is based on observed data from a PK sub-study in pooled Phase III trials with oral RPV (EDURANT).

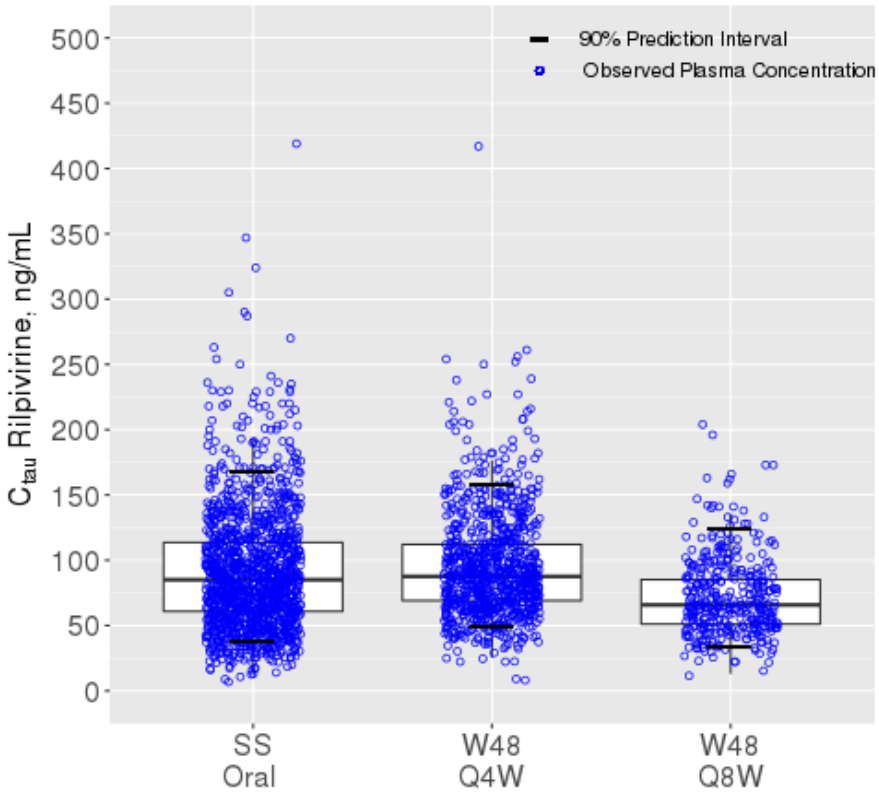
[d] Initial injection C_{max} value primarily reflects oral dosing because the initial injection was administered on the same day as the last oral dose; however, the $AUC_{(0\text{-}tau)}$ and the C_{tau} value at Week 4 reflects the initial injection.

[e] Monthly and every 2 months injection pharmacokinetic parameter values represent Week 48 data.

The plasma exposure of RPV after monthly 600 mg IM injections (pooled Phase III studies 201584 and 201585) and every 2 months 900 mg IM injections (Phase IIIb study 207966) is in range with that observed after daily 25 mg oral RPV (see Figure 1). This supports extrapolation of data (e.g., DDIs, TQT, hepatic impairment) generated with oral RPV (25 mg or supratherapeutic doses) to RPV LA.

Figure 1: Similar RPV Exposures with Daily Oral Dosing or Monthly or Every 2 Months IM Dosing

Simulated and observed predose RPV plasma concentrations at steady-state with oral RPV 25 mg once daily and 48 weeks of RPV LA 600 mg Q4W (with initial dose 900 mg) and 48 weeks of RPV LA 900 mg Q8W (with initial two 900 mg doses separated by 1 month).



Pooled data 201585, 201584, and 207966 (only subjects without prior CAB LA + RPV LA exposure)

Data Source: Mod5.3.3.5/RPV LA PopPK report Q4W/Fig34 and Module 5.3.3.5/RPV LA PopPK report Q8W/Fig13

In general, plasma RPV exposures increased in proportion to or slightly less than in proportion to the RPV LA dose following IM administration (Mod2.7.2/Sec3.2.2).

Based on PopPK modeling (Mod2.7.2/Sec3.2.3), the accumulation ratio for RPV based on AUC is 4.2 for a 4-weekly RPV LA 600 mg dose and 2.4 for a 8-weekly RPV LA 900 mg dose. With the RPV LA dosing regimen evaluated in the Phase III/IIIb studies (900 mg initial dose with 600 mg monthly continuation doses thereafter, or two 900 mg initial doses separated by 1 month with 900 mg every 2 months continuation doses thereafter), full steady-state for RPV is anticipated to be reached after 2.2 years. Nevertheless, ~80% of the RPV steady-state exposure is reached by Week 48: 79-83% after 48 weeks, 90-94% after 1.5 years and 95-98% after 2 years for monthly - every 2 months dosing, respectively.

Based on PopPK modeling, there is no indication of time-dependent RPV PK after IM administration of RPV LA (Mod2.7.2/Sec3.2.4).

From the RPV PopPK modeling, the inter-individual variability on model parameters was found to be moderate for exposure-related parameters and moderate to large for absorption-related parameters (Mod2.7.2/Sec3.2.5).

3.3. PK in Special Populations

Clinical studies to evaluate RPV PK in special populations were conducted using the oral RPV formulation. RPV PK following oral administration in special populations can be extrapolated to the LA formulation because the active drug moiety is the same in oral and injectable formulations and exposures are comparable with oral RPV and RPV LA. In addition, select intrinsic and extrinsic factors were evaluated in the RPV LA population PK model to identify potential covariates affecting RPV PK. Refer to Mod2.7.2/Sec3.2.7 for details.

3.3.1. Hepatic Impairment

RPV LA may be administered without dose adjustment in patients with mild or moderate hepatic impairment (Child-Pugh A and B) (Mod2.7.2/Sec3.2.7.1). The effect of severe hepatic impairment (Child-Pugh C) on RPV (oral or LA) has not been studied.

RPV is primarily metabolized and eliminated by the liver (Mod2.7.2/Sec3.2.7.1). The impact of hepatic impairment on the PK of RPV was evaluated during the development of oral RPV and is independent of administration route. The results from study TMC278-TiDP6-C130 with RPV 25 mg once daily in subjects with mild (Child-Pugh score A, n=8) or moderate hepatic impairment (Child-Pugh score B, n=8) indicated that no RPV dose adjustment is needed; the multiple dose exposure of RPV was 47% higher in subjects with mild hepatic impairment and 5% higher in subjects with moderate hepatic impairment, which is not considered clinically relevant.

RPV concentrations in subjects on RPV LA who were HCV antibody positive at baseline were similar to the overall study population. In addition, popPK analysis indicated that hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection had no clinically relevant effect on the RPV exposure after oral RPV intake.

3.3.2. Renal Impairment

RPV LA may be administered without dose adjustment in patients with mild to moderate renal impairment (Mod2.7.2/Sec3.2.7.2). RPV LA should be used with caution in patients with severe renal impairment or end stage renal disease and increased monitoring for AEs is recommended.

In view of the negligible renal excretion of RPV, a specific trial to investigate the exposure to RPV in subjects with renal impairment has not been conducted (Mod2.7.2/Sec3.2.7.2). Any impact of renal function on RPV PK would be independent of administration route. PopPK analysis during the development of oral RPV indicated that RPV exposure was similar in subjects with mild renal impairment relative to subjects with normal renal function. There is limited or no information regarding the PK of RPV in patients with severe renal impairment or in patients with end stage renal disease, and RPV concentrations may be increased due to alternation of drug absorption, distribution, and metabolism secondary to renal dysfunction. As RPV is highly bound to plasma proteins, it is unlikely

that it will be significantly removed by renal replacement therapies, such as hemodialysis or peritoneal dialysis.

3.3.3. Covariates Evaluated in Population PK Analysis

RPV LA may be administered without dose adjustment in adults regardless of age, gender, race, and body size (weight, body mass index [BMI]) (Mod2.7.2/Sec3.2.7.3) as none of these covariates were found to have a clinically relevant effect on the RPV PK after IM administration. The PK of RPV after IM administration of RPV LA has not been studied in adolescents and children (<18 years of age).

To evaluate the impact of different intrinsic factors on the RPV PK after IM administration of RPV LA, a covariate analysis was performed (Mod2.7.2/Sec3.2.7.3). As no clinically relevant covariates were identified for the disposition of RPV after oral administration, the current covariate analysis focused on the impact of covariates on absorption parameters for RPV after IM administration of RPV LA. The covariates included in the analysis were gender, age, race, body weight, BMI, patient status and needle length.

- There was no clinically relevant impact of body composition (weight, BMI) on the RPV PK after IM administration. As expected, based on the absence of such impact of body composition, there was also no clinically relevant difference in RPV exposure when different needle lengths were used for the RPV LA IM injections.
- There was no clinically relevant difference between genders in the RPV PK after IM administration.
- Age was statistically significantly associated with the RPV fast first-order absorption PK parameter (KA2), with some impact on RPV C_{max} after IM injection. The effect of age was however considered not clinically relevant, as there was only a limited impact on RPV AUC.
- There was no clinically relevant difference between races in the RPV PK after IM administration.

3.4. RPV LA Drug-drug Interactions

Given the pathways of metabolism and elimination of RPV are independent of formulation and route of administration, results from DDI studies with oral RPV can be used to inform the recommendations for RPV LA, when used with CAB LA (Mod2.7.2/Sec3.2.8). DDIs that are specific for oral RPV only (ie, at the level of the gastrointestinal tract) are considered not to have an impact on RPV LA given as IM injection and therefore are not further discussed.

- RPV LA is contraindicated with the CYP3A inducers rifampicin, rifabutin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, systemic dexamethasone (more than single dose), and St John's wort due to potential for loss of therapeutic effect and development of resistance.
- RPV LA should be used with caution when coadministered with a drug that is known to have a risk of Torsade de Pointes.

- There are no significant DDIs between CAB and RPV, the 2 components of the CAB + RPV regimen.
- Because of the low DDI liability for RPV as perpetrator, there are no co-medications that require dose adjustment when given together with RPV LA and there are no DDI limitations to the ARV regimens that can be given after discontinuation of RPV LA.
- No dose adjustments are needed for RPV LA when coadministered with CYP3A inhibitors.

3.5. Pharmacodynamics

There was no clinically relevant QT interval corrected for heart rate (QTc) prolongation with oral RPV 25 mg once daily. Proposed doses of RPV LA achieve RPV concentrations within a range that does not produce QT prolongation.

In a study of healthy subjects, supratherapeutic doses of oral RPV 75 mg once daily and 300 mg once daily have been shown to prolong the QTc of the electrocardiogram (ECG). The mean RPV steady-state C_{max} for the recommended 600 mg monthly dose of RPV LA is 143 ng/mL, which is, respectively, 4.4-fold and 11.6-fold lower than the mean steady-state C_{max} of the supratherapeutic oral RPV doses of 75 mg once daily and 300 mg once daily. The mean steady-state RPV C_{max} for the recommended 900 mg every 2 months dose of RPV LA is 155 ng/mL, which is 4.1-fold and 10.7-fold lower than the mean steady-state C_{max} of the supratherapeutic oral RPV doses of 75 mg once daily and 300 mg once daily, respectively (Mod2.7.2/Sec3.2.8.1).

The mean steady-state C_{max} for oral RPV 25 mg once daily, which is not associated with a clinically relevant effect on QTc, was 247 ng/mL. The RPV plasma concentrations with CAB LA + RPV LA Q4W or Q8W are in line with those observed with oral RPV 25 mg once daily.

The pharmacodynamic studies are described in Mod2.7.2/Sec2.5.4.

PK/PD for efficacy and safety are discussed in Section 4.11 and Section 5.9, respectively.

3.6. Clinical Pharmacology Conclusions

The proposed Q4W and Q8W RPV regimens achieve plasma concentrations similar to those with the approved oral RPV 25 mg once daily regimen. The following conclusions apply to the entire CAB + RPV regimen.

- 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.
- RPV LA may be administered without dose adjustment in patients with mild and moderate hepatic impairment (Child-Pugh A and B), mild and moderate renal impairment, and regardless of age (≥18 years of age), gender, race, and body size (weight, BMI).
- RPV LA is contraindicated with CYP3A inducers rifampicin, rifabutin, rifapentine, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, systemic dexamethasone

(more than single dose), and St John's wort due to potential for loss of therapeutic effect and development of resistance.

- Because absorption is prolonged following IM administration of RPV LA, RPV can be detected in plasma for more than a year after stopping treatment with RPV LA in some individuals. Alternative highly active ART (HAART) should be initiated as soon as feasible, no later than one month following discontinuation of monthly RPV LA and no later than 2 months following discontinuation of every 2 months RPV LA, to maintain suppression of viral load and so reduce the chance of any RPV resistance emerging while concentrations are waning.

4. OVERVIEW OF EFFICACY

The pivotal studies supporting the efficacy of RPV injection, in combination with CAB injection for the treatment of HIV-1 are Phase III studies 201584 and 201585 and Phase IIIb study 207966. Results from these studies indicate that monthly CAB + RPV dosing is non-inferior to SOC and that every 2 months dosing is non-inferior to monthly dosing for the treatment of HIV-1 infection in adults, with no known or suspected resistance to RPV or CAB.

For a full presentation of efficacy results, see Mod2.7.3 (Summary of Clinical Efficacy). For a full presentation of the resistance analyses, see Mod2.7.2.4 (Special Studies).

4.1. Rationale for Dose Selection in Clinical Development

The proposed commercial dosing regimens for CAB + RPV (Table 3) were used in the pivotal Phase III studies, 201584 (monthly) and 201585 (monthly), and in the Phase IIIb study 207966 (monthly and every 2 months). The CAB + RPV doses for Phase III/IIIb were selected on the basis of 2 Phase IIb studies (LAI116482 for oral CAB and RPV, and 200056 for CAB LA and RPV LA: Table 3 and Table 4).

An OLI of CAB 30 mg + RPV 25 mg was included in the Phase III/IIIb studies 201584, 201585, and 207966, and the Phase IIb study 200056 to evaluate tolerability to the individual components prior to starting LA dosing. The same CAB and RPV doses are used for periods of oral therapy to cover planned missed IM injections. If a patient plans to miss a scheduled injection by more than 7 days, oral therapy may be used to replace up to 2 consecutive monthly CAB + RPV injection visits or 1 every 2 months CAB + RPV injection visit.

The RPV dose (25 mg once daily) for OLI and oral therapy for missed IM injections to be taken with CAB is the commercially approved dose (EDURANT; Section 1.3).

Study 200056 was a Phase IIb 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 RPV LA was based on maintaining efficacious plasma RPV concentrations beginning with the first injections and throughout the course of therapy. Initial and steady-state exposures of RPV following IM injection were predicted based on population PK modeling of healthy and HIV-infected subject data and supported by the lack of DDI between CAB and RPV following concomitant administration.

The dose and dosing frequency of RPV LA in study 200056 was based on maintaining plasma concentrations within the range of mean exposures following the marketed RPV

25 mg once daily oral dose. Mean steady-state RPV plasma concentrations were predicted to be approximately 115 ng/mL and 65 ng/mL following Q4W and Q8W dosing, respectively (Mod5.3.4.2/200056 W96 CSR/Sec1.9.4). Results from study 200056 indicated that plasma RPV geometric mean trough concentrations for both Q4W and Q8W regimens were within the range of Cτ values associated with oral RPV 25 mg once daily.

Both CAB LA + RPV LA Q4W and Q8W regimens demonstrated high and comparable rates of viral suppression compared with oral CAB + 2 NRTIs at Week 32 and Week 48 (study 200056, Mod2.7.3/App1). However, a higher rate of virologic non-response of 7% in the Q8W group compared with <1% in the Q4W group was observed at Week 48.

As such, results from study 200056 through Week 48 supported progression of the Q4W dosing regimen with maintenance 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 group (Mod2.7.3/Sec4.1). Using population PK modeling, the initiation dose strategy was optimized for Phase III studies to simplify and align the number of injections at each dosing visit and to achieve higher RPV exposures early on without impacting steady-state drug levels (Mod5.3.5.1/201584 W48 CSR, Mod5.3.5.1/201585 W48 CSR). An initiation dose of 900 mg (a single 3 mL IM injection) was introduced to maintain higher plasma RPV concentrations during the early phase.

Q8W dosing of CAB + RPV has been evaluated in the ongoing Phase IIIb study 207966. The selected doses and dosing regimen of RPV LA used for Q8W and Q4W dosing, in combination with CAB LA, were selected based on the Week 96 results from Phase IIb study 200056 (Mod2.7.3/Sec4.1.2.2). Additional details around Q8W dose optimization are discussed in Mod2.7.2 and in Mod5.3.5.3/207966 207966 W48 CSR.

4.2. Clinical Trial Methodology and Design

Both study 201584 and study 201585, are ongoing, pivotal, Phase III, efficacy studies with a randomized, multicenter, active-controlled, parallel-arm, open-label, non-inferiority design, evaluating the monthly CAB + RPV dosing regimen compared with SOC (Table 2). The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely. Week 96 data are also available for both studies. As the majority of subjects in study 201585 transitioned to study 207966 after completing the Maintenance Phase at Week 52, populations in the Week 96 analysis for study 201585 are limited and data are not described into detail in this Clinical Overview (Mod5.3.5.1/201585 W96 CSR).

The Phase IIIb study 207966 is an ongoing, randomized, multicenter, parallel-group, open-label, non-inferiority study evaluating the monthly CAB + RPV dosing regimen compared with the every 2 months dosing regimen (Table 2). The majority of subjects in study 207966 were enrolled from the ongoing Phase III study 201585. The primary analysis was conducted after all subjects completed their Week 48 visit or discontinued the study prematurely.

4.3. Selection of Patient Populations

Study 201584 enrolled HIV-1 infected, ARV treatment-naïve subjects who achieved virologic suppression (<50 c/mL) after 20 weeks of induction therapy with ABC/DTG/3TC (or DTG + 2 NRTIs if HLA-B*5701 positive). Subjects were then

randomized on Day 1 to either continue CAR (ABC/DTG/3TC) or switch to LA therapy. Subjects randomized to the LA group would proceed with 4 weeks of CAB + RPV OLI before receiving Q4W CAB + RPV.

Study 201585 enrolled HIV-1 infected subjects, virologically suppressed (<50 c/mL; >6 months prior to Screening) without history of virologic failure (ie, ≥400 c/mL) on uninterrupted first or second CAR regimen (ie, 2 NRTIs plus an INSTI, NNRTI, or PI). Median [range] treatment duration prior to enrollment was 4.3 [0.6 - 21.4] years (Mod5.3.5.1/201585 W48 CSR/Tab1.31). Subjects were then randomized on Day 1 to either continue CAR or switch to LA therapy. Subjects randomized to the LA group would proceed with 4 weeks of CAB + RPV OLI before receiving Q4W CAB + RPV.

Study 207966 enrolled HIV-1 infected subjects, virologically suppressed (<50 c/mL; >6 months prior to Screening) on stable ART including subjects who completed, at minimum, Week 52 of study 201585 (Mod5.3.5.1/201585 W48 CSR). In addition to subjects rolled over from study 201585, additional subjects on SOC treatment were screened to supplement enrollment such that the study could be appropriately statistically powered. Subjects received 4 weeks of CAB + RPV OLI and then transitioned to either monthly or every 2 months CAB LA + RPV LA dosing regimen.

In studies 201584, 201585, and 207966, HIV-1 infected subjects with any evidence of primary resistance based on the presence of any known major INSTI or NNRTI RAM, except for K103N, were excluded.

4.4. Efficacy Endpoints and Statistical Considerations of Efficacy Analyses

In studies 201584, 201585, and 207966, the primary efficacy endpoint was the proportion of subjects with plasma HIV-1 RNA ≥50 c/mL (i.e., virologic failure) at Week 48 using the Snapshot algorithm. Additional efficacy endpoints are described in Mod2.7.3/Sec1.1.1.2.

Efficacy analyses were performed for the Intent-to-treat Exposed (ITT-E) population, which consisted of all randomly assigned subjects who received at least 1 dose of study drug. Sensitivity analyses of the primary efficacy endpoint were conducted based on the Per Protocol (PP) population.

Standard analysis methods were applied (refer to Mod2.7.3/Sec1.1.1.3.4 and Sec1.1.2.3). Stratification factors applied at randomization were induction Baseline HIV-1 RNA (<100,000, ≥100,000 c/mL) and gender at birth for study 201584, and maintenance Baseline third agent class (PI, INSTI, or NNRTI) and gender at birth for study 201585. In study 207966, subjects were stratified at randomization by prior CAB + RPV exposure (0 weeks, 1-24 weeks, >24 weeks).

To assess the generalizability of the primary analysis results, consistency of the treatment difference was explored within subgroups. One-way homogeneity across the strata of each variable used to stratify randomization was tested. In addition, potential treatment-by-subgroup interactions were evaluated via the assessment of summaries of the treatment

differences across subgroups (i.e., age, race, country, Baseline CD4+ group, Baseline CDC Stage).

4.5. Subject Disposition and Baseline Characteristics

In the pooled Phase III analysis (studies 201584 and 201585) through Week 48, a total of 591 subjects were randomized and treated with CAB + RPV and 591 subjects were randomized and treated with CAR (Mod2.7.3/Sec3.1.1). Similar proportions of subjects in each treatment group withdrew from the study (9% on CAB + RPV; 7% on CAR). The most common reasons for withdrawal were AE (4% on CAB + RPV; 2% on CAR) and withdrew consent (1% on CAB + RPV; 2% on CAR) (Mod2.7.3/Sec3.1.1).

In study 207966, a total of 1049 subjects were randomized 1:1 into the Maintenance Phase (Q8W: 524 subjects; Q4W: 525 subjects) (Mod2.7.3/Sec3.1). Of these, 253 subjects (Q8W, 126 subjects; Q4W, 127 subjects) enrolled from the Q4W group of study 201585 and 4 subjects (2 in each group) were randomized but not treated. Similar proportions of subjects in each treatment group withdrew from the study (Q8W: 7%; Q4W: 8%) (Mod2.7.3/Sec3.1.1). The most common reasons for withdrawal were AE (Q8W: 2%; Q4W: 2%) and withdrew consent (Q8W: 1%; Q4W: 4%).

Demographic and Baseline characteristics were similar across treatment groups in studies 201584 and 201585 (m2.7.3/Sec3.1.2). Of note, 27% and 28% of subjects in the pooled analysis were women for the CAB LA + RPV LA and CAR groups, respectively. Further 17% and 21% of subjects in the pooled analysis were 50 years of age or older for the CAB LA + RPV LA and the CAR groups, respectively.

In study 207966, demographic and Baseline characteristics were generally similar between the 2 treatment groups (Mod2.7.3/Sec3.1.2). Although the majority of subjects were male, the study enrolled 27% females (sex at birth). Almost half (46%) of all subjects were ages 35 to <50 years, with a median (range) of 42 (19 to 83) years. Further, 27% of subjects were ≥50 years of age in both the Q4W and Q8W groups.

Additional details of Baseline characteristics for each study are presented in Mod2.7.3/Sec3.1.2.2.

4.6. Efficacy Results

4.6.1. Primary Efficacy Results

In the pooled Phase III analysis (studies 201584 and 201585) using a pre-specified non-inferiority margin of 4%, monthly CAB + RPV is non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects, with <2% of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot algorithm in either treatment group (adjusted difference 0.2 [-1.4, 1.7], Table 7). Primary endpoint results were consistent between study 201584 and study 201585, allowing both study data sets to be pooled and subgroup analyses to be based upon the pooled data set. Results for the PP population were similar to those for the ITT-E population (Mod2.7.3/Sec3.2.1).

Treatment differences between CAB + RPV and CAR in the rates of HIV-1 RNA ≥50 c/mL per Snapshot were consistent between study 201584 and study 201585 suggesting that the

duration of CAR treatment prior to the initiation of monthly CAB + RPV does not impact the overall rates of HIV-1 RNA ≥50 c/mL (Mod2.7.3/Sec3.2.1).

Longer term data from the Week 96/100 (further referred to as 'Week 96') analysis of study 201584 support the durability of the CAB + RPV regimen (Mod2.7.3/Sec5.1). The secondary efficacy analyses demonstrated that monthly CAB + RPV continued to be non-inferior to CAR in maintaining virologic suppression in HIV-1 infected subjects at Week 96, with few additional subjects (3.2% [9/283] in each treatment group) having plasma HIV-1 RNA ≥50 c/mL between the Week 48 and Week 96 analysis time points (ITT-E and PP Populations). The majority of subjects remained suppressed with HIV-1 RNA <50 c/mL at Week 96 (86.6% on CAB + RPV; 89.4% on CAR). At Week 96 of study 201585, 23/23 (100%) subjects in the CAB + RPV group had plasma HIV-1 RNA <50 c/mL (Mod5.3.5.1/201585 W96 CSR/Tab12.9) and 28/29 (97%) subjects in the Extension Switch to CAB + RPV had plasma HIV-1 RNA <50 c/mL (Mod5.3.5.1/201585 W96 CSR/Tab12.10).

In study 207966, the primary efficacy analysis demonstrated that CAB + RPV administered every 2 months was non-inferior to monthly CAB + RPV in maintaining virologic suppression in HIV-1 infected subjects at Week 48, with <2% of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot algorithm in either treatment group for the ITT-E population (Mod2.7.3/Sec3.2.1). The upper bound of the 95% 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% (Table 7). Results for the PP population were similar to those for the ITT-E population (Mod2.7.3/Sec3.2.1).

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 Populations)**

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: Mod5.3.5.3/209522 Output Tables & Figures/Tab2.01 and Mod5.3.5.3/207966 W48 CSR/Tab2.1.

a. In the Data Source tables, for studies 201584 and 201585: the CAB + RPV group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC.
b. For studies 201584 and 201585: 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 for Baseline stratification factor of prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks).

4.6.1.1. Subgroup Analysis of the Primary Endpoint: Subjects with Plasma HIV-1 RNA ≥50 c/mL

In each of the Phase III studies (201584 and 201585) and in the pooled analysis of both studies, 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 (eg, by age, sex at birth, body mass index ([BMI], race) and there were no statistically significant differences in treatment effect between the 2 treatment groups in any subgroup analyses (Mod2.7.3/Sec3.3). 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 (Mod2.7.3/Sec3.2.1.1.1).

In study 207966, 9/522 (1.7%) subjects in the Q8W group and 5/523 (1%) subjects in the Q4W group had HIV-1 RNA ≥50 c/mL at Week 48 (Mod2.7.3/Sec3.2.1). 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 (Mod2.7.3/Sec3.2.1.1.2). 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 to CAB + RPV had HIV RNA ≥50 c/mL at Week 48.

The relatively small number of subjects with HIV-1 RNA ≥50 c/mL limits the ability to make a robust conclusion regarding subgroup analyses in study 207966. Treatment differences for the primary endpoint (proportion of subjects with HIV-1 RNA ≥50 c/mL at Week 48 [Snapshot algorithm]) were generally 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 (Mod2.7.3/Sec3.3.4.1). The proportion of Snapshot virologic failures was numerically higher in the Q8W group compared with the Q4W group in female subjects (5/137 [3.6%] and 0/143 [0%]) vs in males (4/385 [1.0%] and 5/380 [1.3%]) and in subjects with BMI ≥30 kg/m^2 (6/113 [5.3%] and 2/98 [2.0%]) vs in subjects with BMI <30 kg/m^2 (3/409 [0.7%] and 3/425 [0.7%]). These differences in proportions are not considered clinically relevant.

4.6.2. Secondary Efficacy Results

4.6.2.1. Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis)

In the pooled Phase III analysis (studies 201584 and 201585), high rates of plasma HIV-1 RNA <50 c/mL were observed in both treatment groups (93% on CAB + RPV and 94% on CAR) (Table 8) meeting the definition of non-inferiority (lower bound above -10%) (Mod2.7.3/Sec3.2.2.1). These results are consistent with the conclusions drawn from the primary efficacy analysis.

In study 207966, the majority of subjects in both treatment groups in the ITT-E Population remained suppressed (plasma HIV-1 RNA <50 c/mL) at Week 48 (Q8W: 94%; Q4W: 93%), and the non-inferiority criterion was met for this secondary endpoint (Table 8)

(Mod2.7.3/Sec3.2.2.1). Results for the PP Population were consistent with those for the ITT-E Population. These results are consistent with the conclusions drawn from the primary efficacy analysis.

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 (ITT-E Populations)

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 (95)		
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)		
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: Mod5.3.5.3/209522 Output Tables & Figures/Tab2.08 and Mod5.3.5.3/207966 W48 CSR/Tab2.8.
Note: In the Data Source tables, for studies 201584 and 201585: 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. For studies 201584 and 201585, Difference: Proportion on CAB + RPV (Q4W IM) – CAR (unadjusted). For study 207966, Difference: Proportion on CAB + RPV Q8W – Proportion on CAB + RPV Q4W.
c. Based on Cochran-Mantel Haenszel 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).

Additional sensitivity analyses of the secondary efficacy endpoint of proportion of subjects with HIV-1 RNA <50 c/mL are described in Mod2.7.3/Sec3.2.2.1.1 (by randomization strata) and Mod2.7.3/Sec3.2.2.1.2 (by visit). Results for the sensitivity analyses were consistent with the overall results for each of the Phase III/IIIb studies.

4.6.2.2. Study Outcomes at Week 48: Snapshot Outcomes

Snapshot outcomes at Week 48 for studies 201584 and 201585, the pooled analysis (201584 and 201585), and study 207966 are shown in Table 9. Snapshot outcomes at Week 48 for subjects receiving the monthly CAB + RPV Q4W regimen in Phase III studies 201584 and 201585 are consistent with results observed in the every 2 months and monthly CAB + RPV treatment groups in Phase IIIb study 207966.

Table 9 Snapshot Outcomes at Week 48 – Study 201584, Study 201585, Studies 201584 and 201585 (Pooled Data), and Study 207966 (ITT-E Populations)

Outcome	201584		201585		201584 and 201585 (Pooled Data)		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: Mod5.3.5.3/209522 Output Tables & Figures/Tab2.05 and Mod5.3.5.3/207966 W48 CSR/Tab2.3.
Note: In the Data Source tables: for studies 201584 and 201585, the CAB + RPV group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC.

4.7. Visits That Exceeded Injection Dosing Window

Oral therapy (CAB 30 mg + RPV 25 mg) is permitted to cover missed injection visits as per proposed labeling.

In study 201584, a total of 47 injection visits for CAB + RPV subjects (out of 3,577 total injection visits, representing 1.3%) were more than 7 days after the planned injection date (Mod5.3.5.1/201584 W48 CSR/Tab3.6). Of these, 5 injection visits were more than 14 days after the planned injection visit. One subject missed an injection visit without oral therapy.

In study 201585, a total of 59 injection visits for CAB + RPV subjects (out of 3,343 total injection visits, representing 1.8%) were more than 7 days after the planned injection date (Mod5.3.5.1/201585 W48 CSR/Tab3.6). Of these, 5 injection visits were more than 14 days after the planned injection visit. No subjects missed an injection visit without oral therapy.

In study 207966, some injection visits occurred more than 7 days after the planned injection visit (33/3719, representing <1.0% in Q8W; 58/7346, representing <1.0% in Q4W). No subjects missed an injection visit without oral therapy.

No cases of CVF were reported for subjects who missed injection visits in any of the Phase III/IIIb studies.

4.8. Oral Lead-in

Within the pivotal Phase III studies 201584 and 201585, 591 subjects received CAB + RPV OLI dosing to assess subject's tolerability before starting LA therapy. Only 1 subject during CAB + RPV OLI met CVF criteria (Mod5.3.5.1/201584 W48 CSR/Other Data Listings/Lis34). 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 phase (Mod5.3.5.3/207966 W48 CSR/Tab1.8 and Mod5.3.5.3/207966 W48 ICH Data Listings/Lis4). These findings, combined with the Week 96 results of study LAI116482, provide support that short treatment with oral CAB 30 mg + RPV 25 mg is effective at maintaining virologic suppression prior to initiation of LA dosing. Refer to Section 5.6.7 for a summary of safety during OLI.

4.9. Oral Therapy (Bridging)

Oral therapy (CAB 30 mg + RPV 25 mg) was permitted in the Phase II and Phase III/IIIb studies to address pre-planned missed CAB LA + RPV LA dosing visits.

The overall efficacy and safety of oral CAB + RPV are supported by exposures across the CAB + RPV development program. A summary of the total exposure to oral CAB + RPV is presented in Table 10. The totality of the oral clinical data presented in Table 10 and the simulations discussed in Mod2.7.2/Section 3.1.4.1 support the use of oral therapy with CAB + RPV. When implemented as recommended, oral therapy should provide plasma RPV concentrations below safety thresholds.

Table 10 Summary of Exposure to Oral CAB 30 mg + Oral RPV 25 mg (Study 201584, Study 201585, Study 207966, Study 200056, Study LAI116482)

Treatment	# of Subjects	Person Time (years)
CAB 30 mg once daily oral	1909	1171
RPV 25 mg once daily oral [a]	1873	904

Data Source: Mod5.3.5.3/209522 Output Tables & Figures/Tab4.5.
Note: Person time was calculated up to the point of the subject's last dose administered or until [redacted] 20[redacted], except for study 207966, which includes the full Week 48 data, for subjects still on treatment at that time.
a. For subjects that subsequently take oral therapy after starting LA, their time on oral therapy is also included in their total duration on oral.

In the Phase III studies up to Week 48, a total of 18 subjects received oral therapy, for durations ranging from 3 days to approximately 2 months to cover missed injection(s) (Mod2.7.3/Sec4.3). All but 2 subjects resumed IM dosing. No cases of CVF were observed during a period of oral therapy or following resumption of IM dosing.

In the Phase IIIb study 207966 at Week 48, a total of 4 subjects in the Q8W group and 7 subjects in the Q4W group received oral therapy for durations ranging from 2 to 64 days (Mod2.7.3/Section 4.3).

In the Phase IIb study 200056, 8 subjects received oral therapy for a duration ranging from 17 to 56 days (Mod2.7.3/Sec4.3). All subjects resumed IM dosing and no cases of CVF were observed during a period of oral therapy or following resumption of IM dosing.

In addition to the use of oral therapy in studies 201584, 201585, 207966, and 200056, results from study LAI116482 provide evidence for the safety and efficacy of oral CAB 30 mg + oral RPV 25 mg once daily for >5 years, supporting the use of oral therapy for an extended duration (Mod5.3.4.2/LAI116482 W96 CSR).

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 permitted to cover missed injection visits as per proposed labeling. Oral therapy should be initiated at the time of the planned missed injection. Injection dosing should be resumed on the same day oral dosing completes, and as recommended in Table 11 and Table 12.

Table 11 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy for the Monthly CAB + RPV Dosing Regimen

Time Since Last Injection	Recommendation
≤2 months	Continue with the monthly 2-mL injection dosing schedule as soon as possible
>2 months	Re-initiate the patient on the 3-mL dose, and then continue to follow the monthly 2-mL injection dosing schedule

Table 12 Recommendations for Resuming Injection Dosing After Missed Injections or After Oral Therapy for the Every 2 Months CAB + RPV Dosing Regimen

Missed Injection Visit	Time Since Last Injection	Recommendation (all injections are 3 mL)
Injection 2 (Month 3)	≤2 months	Resume with the 3-mL (900 mg) injection as soon as possible and continue with every 2 months injection dosing schedule.
	>2 months	Re-initiate the patient on the 3-mL (900 mg) dose, followed by a second 3-mL (900 mg) initiation injection one month later. Then follow the every 2 months injection dosing schedule.
Injection 3 or later (Month 5 onwards)	≤3 months	Resume with 3-mL (900 mg) injections as soon as possible and continue with every 2 months injection dosing schedule.
	>3 months	Re-initiate the patient on the 3-mL (900 mg) dose, followed by a second 3-mL (900 mg) initiation injection one month later. Then follow the every 2 months injection dosing schedule.

4.10. Virology

4.10.1. Confirmed Virologic Failure

CVF was defined by 2 consecutive plasma HIV-1 RNA levels ≥200 c/mL after prior suppression to <200 c/mL.

In the pooled Phase III analysis (studies 201584 and 201585), few subjects (7/591 [1.2%] subjects in both treatment groups) met CVF criteria through Week 48 (Mod2.7.3/Section 3.2.2.3). All subjects with CVF were offered an alternative fully active oral ARV therapy (ART) regimen and consenting subjects were entered into LTFU. The majority (4/7) of subjects with CVF who entered into LTFU were successfully re-suppressed after switching to an alternative oral ART regimen (Mod2.7.2.4/Sec6.1).

In study 201584, no CVFs occurred between Week 48 and 96 in the CAB + RPV Q4W treatment group. 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. In study 201585, no CVFs occurred between Week 48 and 96 (Mod2.7.3/Sec5.1.3 and Sec5.2.2).

In study 207966, the proportion of subjects with CVF through Week 48 (including subjects with dosing beyond Week 48) was 1.5% (8/522 subjects) for the Q8W group and 0.4% (2/523 subjects) for the Q4W group (Mod2.7.3/Sec3.2.2.3). All subjects with CVF were offered a fully active oral ART regimen and entered into LTFU. 9/10 subjects with CVF who entered the LTFU study had HIV-1 RNA <50 c/mL at their last available visit (Mod5.3.5.3/207966 W48 CSR/Other Data Listings/Lis10).

4.10.2. Resistance

In the CAB + RPV group of the pooled Phase III studies, CVF cases were infrequent through Week 48 (n=7): 4 occurred in study 201584 and 3 in study 201585. All CVFs were subtype A1 or AG (subtype A1: study 201584 [3/283], study 201585 [2/308]); subtype AG: study 201584 [1/283], study 201585 [1/308]), with pre-treatment archived RPV resistance mutations in some patients (Mod2.7.2.4/Sec4.3.1).

In study 201584, 5 additional subjects with subtype A1 maintained viral suppression (HIV-1 RNA <50 c/mL) per Snapshot algorithm at Week 48 (Mod2.7.2.4/Sec4.3.1.2). 0.7% (4/591) of subjects had CVF with phenotypic resistance to CAB and 0.8% (5/591) of subjects had CVF with resistance

to RPV (Mod2.7.2.4/Sec4.3.1). Among these 5 subjects, phenotypic cross-resistance was observed against efavirenz (n=4), etravirine (n=3), and nevirapine (n=4). Three subjects developed dual resistance to CAB + RPV (Mod2.7.2.4/Sec4.5).

Two of the 4 CVFs in study 201584 had treatment-emergent INSTI RAM Q148R while 1 of the 3 had G140R, all associated with reduced phenotypic susceptibility to CAB. All 3 CVFs had a treatment-emergent RPV RAM: K101E, E138E/A/K/T or E138K, and 2 of the 3 showed reduced phenotypic susceptibility to RPV.

One of the 3 CVFs in the CAB + RPV group of study 201585 carried the INSTI RAM N155H at failure with reduced CAB phenotypic susceptibility. All 3 CVFs carried one RPV RAM at failure: E138A, E138E/K, or E138K, and showed reduced phenotypic susceptibility to RPV. In 2 of these 3 CVFs, the RPV RAMs observed at failure were also observed on Day 1 in PBMC HIV-1 DNA.

The seventh CVF (study 201584) never received an injection dose.

During the Extension Phase of study 201584, 1 additional CVF was identified in the CAB + RPV Q4W group at Week 108. This subject developed resistance to both RPV and CAB.

In study 207966, CVFs were infrequent with 8 subjects (1.5%) in the Q8W group and 2 subjects (0.4%) in the Q4W group (Mod2.7.2.4/Sec4.2.1.3). Virus subtypes observed in CVF subjects were A or A1 (n=4), B (n=4) or C (n=2). RPV RAMs were found in 5/10 CVF subjects at baseline and 7/10 subjects at failure. In vitro phenotypic resistance to RPV occurred in 9/10 CVF subjects at failure. INSTI RAMs were present in 1/10 CVF subjects at baseline and 7/9 CVF subjects at failure. In vitro phenotypic CAB resistance occurred in 4/8 CVF subjects at failure. INSTI substitution, L74I, was present in 5 subjects at baseline and 4 subjects at failure.

The RPV RAMs which may affect the activity of RPV, whether delivered as EDURANT or RPV LA, include: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, M230L, and the combination of L100I+K103N (Mod2.7.2.4/Sec4.4.3).

As a result of the extended release of RPV from depots after IM administration, plasma concentrations of RPV can be detected for more than a year in some subjects. To minimize the risk of developing viral resistance, it is essential to adopt an alternative, fully suppressive ART regimen no later than 1 month after the final injection of RPV LA when dosed monthly and no later than 2 months after the final injection of RPV LA when dosed every 2 months (Mod2.7.2/Sec3.1.6).

A summary of nonclinical and clinical virology can be found in Mod2.7.2.4, where virology analyses from the Phase IIb, III (including Week 96 data), and IIIb studies are discussed.

4.11. Pharmacokinetic – Pharmacodynamic Relationship: Efficacy

In the pooled analysis of studies 201584 and 201585, as well as in study 207966, the rate of CVF was low (<2%) across all treatment groups at Week 48 (Section 4.10.1). For subjects with CVF, CAB and RPV plasma concentrations at failure overlapped with plasma concentrations of subjects with HIV-1 RNA <50 c/mL at the corresponding visit (Mod2.7.2/Sec3.1.1.2). In studies 201584, 201585, and 207966, CAB and RPV concentration-time profiles for subjects with Snapshot HIV-1 RNA ≥50 c/mL at Week 48 were generally below the median while the majority were within the 5th and 95th percentile of observed data for the remainder of the population (Mod2.7.2/Sec2.1.3.1).

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

Post hoc multivariable analyses (MVA) and baseline factors analyses were conducted on pooled study data 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 analysis population, 1,039 HIV-infected subjects who were naïve to CAB + RPV were pooled from Phase III and IIIb Studies 201584, 201585, and 207966 (Week 48 analyses). Subjects from Study 207966 who had transferred from the CAB + RPV arm of Study 201585 were excluded from these analyses. Of the 17 subjects from the 3 Phase III and IIIb studies who did not maintain virologic suppression through their first 48 weeks of CAB + RPV treatment (monthly or every 2 months) and who met CVF criteria, 4 were excluded from the analysis population (3 due to prior exposure to CAB + RPV in Study 201585 prior to transferring to Study 207966 and 1 due to 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). Overall, 13 (1.25%) of the 1,039 subjects included in the analysis population met CVF criteria while receiving CAB + RPV (Mod2.7.3/Sec4.4.2).

In the MVA, 4 of the examined covariates were significantly associated with increased risk of CVF ($p<0.05$ for each adjusted odds ratio [OR]):

- Archived 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 C_{trough} 4 weeks following initial injection dose (per halving concentration) (in model as Log2 of post hoc Week 8 RPV through concentration).
- BMI (per unit increase in kg/m^2) (associated with CAB PK).

Overall, a high proportion of subjects (n=1,531 [94%]) continued to maintain viral suppression in the Phase III/IIIb studies, thus limiting the predictive value of these identified covariates, particularly in isolation.

A significant association with CVF was not observed for the other 6 variables included in the analysis:

- Pre-specified INSTI mutation (excluding L74I non-M mixture) at Baseline.
- NNRTI RAM(s) (excluding RPV RAMs) at Baseline.
- Log_2 of post hoc Week 8 CAB trough concentration (CAB C_{trough} 4 weeks following initial injection dose).
- L74I (non-M mixture) INSTI mutation at Baseline.
- Female at birth.

- Q4W vs Q8W regimen.

Although the L74I polymorphism and CAB trough concentration at Week 8 (4 weeks following initial injection dose) did not have a significant association with CVF, they are correlated with factors that did have a significant association with CVF, specifically HIV Subtype A6/A1 and BMI, respectively.

Additionally, although the factor for dosing regimen (ie, 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).

Overall, the results of the MVA analysis indicate that no covariate alone is associated with a higher likelihood of experiencing CVF. Only 2 of 13 subjects with CVF had <2 factors associated with CVF; 46% of subjects (n=6) had 4 factors (Mod2.7.3/Sec4.4.2).

In the baseline factors analysis, the same covariates as in the MVA were explored, with the exception of PK parameters. Archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and BMI ≥30 kg/m^2 were selected ($p<0.05$) by the stepwise model selection procedure (Mod2.7.3/Sec4.4.2).

The majority of CVF cases (9 of 13; 69.2%) were multifactorial (≥2 baseline factors present). 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 developing CVF. In fact, even in the presence of 2 or more baseline factors, 25/35 (71%) subjects maintained virologic suppression at Week 48 via the Snapshot algorithm. The CVF rate through Week 48 was <0.5% when 0 or 1 baseline factor(s) were present. Details of this analysis are presented in Mod2.7.3/Sec4.4.2 and Mod5.3.5.3/MVA Report.

In conclusion, results of the post hoc MVA and baseline factors analyses showed that CVF is an infrequent multifactorial event, with a rate of ~1% in the LA arms across the 3 Phase III and IIIb studies (201584, 201585, and 207966) through Week 48. Rilpivirine C_{trough} (4 weeks following initial injection dose [per halving concentration]), archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and higher BMI (≥30 kg/m^2) had a statistically significant association with virologic failure. Regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%), and no baseline factor (archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and higher BMI) when present in isolation was predictive of virologic failure.

4.12. Global Health Outcomes

Subjects' views of their treatment were assessed with several patient-reported outcome measures in studies 201584, 201585, and 207966. In order to compare the novel LA treatment regimen with the SOC of daily oral ART, tolerability and perception of the injections as well as satisfaction and acceptance of the treatments were included as secondary outcome measures.

In the context of Global Health Outcomes (GHO), review of key subject demographic and clinical characteristics at Baseline demonstrates that subject populations are measurably different among the studies with regard to age, sex, time since diagnosis, and number of years on previous ART (Mod2.7.3/Sec3.1.2). Subjects in study 201584 were naïve to treatment prior to enrolling in the study while those in study 201585 were on average 5.6 years on their previous ART, and many

subjects in study 207966 were previously enrolled in study 201585. These differences in subject population, especially regarding the length of time on prior oral ART, may be relevant factors to consider when interpreting GHO data from the individual studies. Therefore, the evaluation of GHO data from Phase III both as pooled analysis and within each individual study remains important.

4.12.1. HIVTSQs and HIVTSQc

In study 201585, the CAB + RPV group demonstrated a statistically significant and clinically meaningful improvement in total treatment satisfaction using HIVTSQs compared with the CAR group at each timepoint (Mod2.7.3/Sec3.4.1).

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 in study 201584 (Mod5.3.5.1/201584 W48 CSR/Tab6.21 and Tab7.22), indicating ceiling effects with this measure. To account for this ceiling effect, the HIVTSQc change version was used at Week 48 for study 201584. The HIVTSQc, administered at a single point in time (Week 48), assessed subjects' experience with their treatment compared with their treatment at Baseline. In study 201584, subjects in the CAB + RPV group reported a statistically significant improvement in treatment satisfaction compared with subjects in the CAR group when compared with the Induction Phase (Mod2.7.3/Sec3.4.2).

In study 207966, subjects reported very high levels of satisfaction with Q4W and Q8W dosing at Week 48. For subjects with prior CAB + RPV exposure, Baseline treatment satisfaction (i.e., satisfaction with Q4W dosing) was high (approximately 62 out of possible 66 points in the HIVTSQs) and remained high across all time points, without statistically significant differences between Q4W and Q8W dosing (Mod2.7.3/Sec3.4.1.2). For subjects without prior exposure to CAB + RPV, a statistically significant increase from Baseline in treatment satisfaction was observed for both treatment groups at Weeks 24 and 48, favoring the Q8W group compared with the Q4W group (Week 24: p=0.036; Week 48: p=0.004). In the HIVTSQc assessment, subjects with prior CAB + RPV exposure had high scores in both treatment groups at Week 48, with a statistically significant difference favoring the Q8W group (Mod2.7.3/Sec3.4.2.2). Similarly, in subjects without prior exposure to CAB + RPV, both groups had high HIVTSQc scores at Week 48, with a statistically significant difference favoring the Q8W group. These high rates of treatment satisfaction correlate with the low number of discontinuations in both treatment groups at Week 48 (Q8W: 7%; Q4W: 8%).

4.12.2. ACCEPT Scores

In study 201585, the CAB + RPV group demonstrated improvements in treatment acceptance (based on the three-item “General Acceptance” dimension of the Chronic Treatment Acceptance Questionnaire [ACCEPT]), compared with the CAR group from Baseline to Week 44 (Mod2.7.3/Sec3.4.3.1). This difference was statistically significant at all timepoints. The high Baseline values observed in study 201584 limit the opportunity for a significant increase in mean difference between treatment groups from Baseline to Week 44, indicating ceiling effects with this measure. Because subjects in study 201585 had been receiving ART for approximately 5.4 years prior to participating in the study and those in study 201584 were treatment-naïve, subjects from study 201585 were more representative of the demands of HIV treatment over a long period of time.

In study 207966, General Acceptance adjusted mean scores were similar in both treatment groups at Baseline and improved at Weeks 24 and 48, without any statistically significant difference between treatment groups and regardless of prior exposure to CAB + RPV (Mod2.7.3/Sec3.4.3.2).

4.13. Efficacy Conclusions

In summary, the CAB + RPV LA doses explored in the Phase III 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, both IM regimens, enabling 6 to 12 injection visits per year, demonstrated no increased risk of virologic failure (HIV-1 RNA ≥50 c/mL) relative to comparator arms through Week 48.

- 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 every 2 months dosing of CAB + RPV is non-inferior to monthly dosing of CAB + RPV on the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E). The adjusted treatment difference between every 2 months and monthly dosing of CAB + RPV was 0.8% (95% CI: -0.6, 2.2) which met the non-inferiority criterion, set below 4% for the primary endpoint.
- In the pooled Phase III analysis (201584 and 201585; ITT-E population), 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) for this key secondary endpoint with a non-inferiority margin of -10%.
- In study 207966, the key secondary efficacy analyses demonstrated that every 2 months dosing of CAB + RPV is non-inferior to monthly dosing on the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot, ITT-E). The adjusted treatment difference between every 2 months and monthly dosing of CAB + RPV was 0.8% (95% CI: -2.1%, 3.7%) which met the non-inferiority criterion for this secondary endpoint.
- In studies 201584 and 201585, monthly dosing of CAB + RPV effectively maintained virologic suppression, with few CVFs through Week 48. Rates of CVF in both studies and the pooled analysis were <1.5% in the CAB + RPV group and in the CAR group through Week 48 (7/59 [1.2%] in both treatment groups). In study 207966, the rates of CVF were low (8/522 [1.5%] in the Q8W group and 2/523 [0.4%] in the Q4W group) through Week 48.

- The results from studies 201584, 201585, and 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 to replace up to 2 consecutive monthly CAB + RPV injection visits or 1 every 2 months CAB + RPV injection visit.
- The non-inferiority result established in studies 201584 and 201585 demonstrated that the length of HIV-1 RNA virologic suppression prior to initiation of CAB + RPV (ie, <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 and 201585, the pooled analysis, and the Phase IIIb study 207966 no treatment differences were observed within subgroups which is consistent with the results of the overall analysis.
- In the pooled Phase III analysis (201584 and 201585), the CAB + RPV group demonstrated greater improvements from Baseline in treatment satisfaction compared with the CAR group using the HIVTSQs. In study 207966, 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 group, 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 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).
- Results from the post hoc MVA and baseline factors analyses demonstrate that CVF is an infrequent multifactorial event, with a rate of ~1% in the LA arms across the 3 Phase III and IIIb studies (201584, 201585, and 207966) through Week 48. Rilpivirine C_{trough} (4 weeks following initial injection dose [per halving concentration]), archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and higher BMI (≥30 kg/m^2) had a statistically significant association with virologic failure. Regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%), and no baseline factor (archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and higher BMI) when present in isolation was predictive of virologic failure.

5. OVERVIEW OF SAFETY

The safety profile of CAB + RPV in Phase II, III, and IIIb studies supports a favorable benefit-risk assessment for CAB in the indicated HIV-1 infected population.

The open-label, switch design of the studies should be taken into consideration in the review of the safety results. Subjects in the comparator CAR group had been on a stable ART regimen for 52 months on average in study 201585 and on treatment for 5 months in study 201584 prior to the start of the Maintenance Phase. Subjects in the CAB+RPV group had 2 switches in therapy from CAR to oral CAB + oral RPV (OLI) and then to monthly CAB LA + RPV LA.

For a full presentation of safety results, see Mod2.7.4 (Summary of Clinical Safety).

5.1. Population Included in Safety Analyses

The clinical studies used to support the safety of CAB + RPV are the 2 pivotal Phase III studies, 201584 and 201585, and the Phase IIIb study 207966. The safety profiles of CAB and RPV were consistent across studies. All subjects who received at least 1 dose of study drug in these studies were included in the Safety Population or Extension Switch Population.

Additional safety information in HIV-infected subjects, comes from Phase II studies LAI116482 (End of Study) and 200056 (160 weeks).

5.2. Data Cut-off Dates

Pooled Week 48 data from studies 201584 and 201585 that were reported through the last subject last visit (LSLV) cut-off date ([redacted] 20[redacted] and [redacted] 20[redacted], respectively) are presented. Additional safety data from the individual studies through Week 96 LSLV cut-off dates ([redacted] 20[redacted] and [redacted] 20[redacted], respectively) are also provided.

In study 207966, all visits and assessments through Week 48 that occurred up to the LSLV cut-off date of [redacted] 20[redacted] are included in the authorized clinical study database, and results are presented.

For the Phase II studies (LAI116482 and 200056), all visits and assessments through the End of Study ([redacted] 20[redacted]) for study LAI116482 and up to Week 160 ([redacted] 20[redacted]) for study 200056 are included in the authorized clinical study database.

5.3. Exposure in the Clinical Development Program

Overall extent of exposure in the CAB + RPV program is provided in Section 1.2 and Mod2.7.4/Sec1.3.

5.3.1. Phase III Studies

In the pooled Week 48 analysis for studies 201584 and 201585, the median time of exposure of HIV-1 infected subjects to CAB LA + RPV LA was 392 days (approximately 56 weeks); the median time of exposure of HIV-1 infected subjects to oral CAB + RPV during the OLI period of the Maintenance Phase was 5.3 weeks (Mod2.7.4/Sec2.2.2).

At the Week 96 time point, subjects were exposed to CAB LA + RPV LA for at least 737 days (approximately 105 weeks) in study 201584 and at least 911 days (approximately 130 weeks) in study 201585 (Mod2.7.4/Sec2.3.2). Note that in study 201585, 253/308 subjects in the CAB + RPV group and 251/308 subjects in the CAR group transitioned to study 207966 after Week 52, impacting the exposure data.

In the Week 48 analysis for study 207966, the median time of exposure from Baseline to CAB LA + RPV LA was similar between treatment groups (Q8W: 447 days; Q4W: 445 days) (Mod2.7.4/Sec3.3). Subjects were exposed to CAB LA + RPV LA for a maximum of 582 days (approximately 1.5 years).

5.3.2. Phase II Studies

In study 200056, the median number of CAB LA + RPV LA injections was 25 and 46 for Q8W and Q4W treatment groups, respectively. The median number of injections was 11 and 20 for the optimized Q8W IM and optimized Q4W IM groups, respectively, during the Extension Period (Mod 2.7.4/Sec4).

In study LAI116482 through End of Study, median time of exposure to oral RPV was 2,014 days (approximately 5.5 years) and median time of exposure to oral CAB was 2,179 days (almost 6 years) (Mod2.7.4/Sec5.1).

5.4. Nonclinical Data Relevant to Human Safety

CAB and RPV are expected to be well tolerated as a two-drug regimen in patients, given the findings from the comprehensive packages of nonclinical testing of both agents, which suggest no overlapping toxicity. Nonclinical data are discussed in Mod2.7.4/Section 1.2 and a full analysis of the data is presented in Mod2.4/Sec5.

5.5. Safety in Clinical Pharmacology Studies

There were no safety findings in single or multiple dose studies with RPV LA (with or without CAB LA) in healthy volunteers that were different from those identified in studies in HIV-1 infected subjects (Mod2.7.4/Sec5.2).

The safety of RPV LA during 4 Phase I studies and the knowledge of EDURANT support the favorable benefit-risk assessment of RPV LA.

5.6. Adverse Events

Overall, the AE profile of RPV LA is consistent with the established safety profile of oral RPV and expected risks associated with IM injection.

One notable difference in AEs observed with the injectable LA formulations compared with the oral formulations of CAB + RPV is the occurrence of injection site reactions (ISRs), which reflects the method of administration. In all studies, very few ISRs led to withdrawal, and the frequency of ISR reporting decreased over time (Section 5.6.6.1).

In studies 207966 and 200056, 4 subjects were reported to have post-injection reactions; 3 cases apparently were related to injection with RPV (based on PK), which is administered at the same visit as CAB as part of the dosing regimen for HIV-1 treatment. The fourth case was not confirmed because a suitably timed postdose PK sample was not collected (see Section 5.6.8). These events were reported with different preferred terms (see Sections 5.6.4 and 5.6.5). These reactions occurred within minutes of the injection and began to resolve within a few minutes after onset. No such post-injection reactions were reported in studies 201584 and 201585.

An overall trend for greater frequency of drug-related AEs, including ISRs, was observed for CAB + RPV compared with CAR; however, there were few drug-related AEs that were Grade 3 to 5 AEs or SAEs (see Section 5.6.1.1 and Section 5.6.4, respectively). Within study 207966, the proportions of subjects in the overview of AE categories were similar between the Q8W and Q4W groups. A summary of all AEs for studies 201584, 201585, and 207966 (all Week 48 time points) is presented in Table 13 and non-ISR AEs are presented in Table 14. Phase II and long-term Phase III overall AEs were consistent with trends observed in Phase III/IIIb Week 48 results.

Table 13 Overview of All AEs in Studies 201584, 201585, Pooled 201584 + 201585, 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: Mod5.3.5.3/209522 Output Tables & Figures/Tab3.05; Mod5.3.5.3/207966 W48 CSR/Tab25, Tab3.6, Tab3.13, Tab3.16, Tab3.19, Tab3.22, and Tab3.26.
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 14 Overall Summary of Non-ISR AEs in Studies 201584, 201585, Pooled 201584 + 201585, 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: Mod5.3.5.3/209522 Output Tables & Figures/Tab3.07; Mod5.3.5.3/207966 W48 CSR/Tab3.7, Tab3.14, Tab3.19, and ICH Data Listings/Lis15, Lis16, and Lis17.
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.

5.6.1. Common (≥5%) Adverse Events

Across Phase III studies, a higher proportion of subjects who switched to CAB + RPV from SOC reported at least 1 AE.

Through Week 48 in studies 201584 and 201585, the most commonly reported non-ISR AEs (occurring in ≥5% of subjects in either treatment group) were generally similar (nasopharyngitis [18% and 15%] and upper respiratory tract infection [12% and 9%]), and reflect common AEs found in many subjects in studies of 1 year duration (Mod2.7.4/Sec2.2.4.2). Higher rates were reported for CAB + RPV than for CAR for hemorrhoids, pyrexia, dizziness, fatigue, headache, nausea, and back pain (Mod2.7.4/Sec2.2.4.2.2). The majority of events reported had an intensity of Grade 1 or Grade 2. AEs reported through Week 96 in both studies were consistent overall with trends observed at the Week 48 timepoint (Mod2.7.4/Sec2.3.3).

In study 207966, the proportion of subjects reporting at least 1 AE (Q8W: 91%; Q4W: 92%) and the frequency of individual common AEs (≥5% in either treatment 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%) (Mod2.7.4/Sec3.5.2). Non-ISR AEs reported in ≥10% of subjects in either treatment group were nasopharyngitis (14% in both treatment groups) and upper respiratory tract infection (Q8W: 10%; Q4W: 14%).

In Phase II studies, ISRs comprised the most commonly reported AEs (Mod2.7.4/Sec4 and Mod2.7.4/Sec5.1). In study 200056 at Week 160, the most commonly reported non-ISR AEs were nasopharyngitis (38%), diarrhea (22%), and headache (22%) across both randomized IM dosing groups, and nasopharyngitis (14%), back pain (11%), and influenza (11%) across both optimized IM dosing groups. In study LAI116482 at End of Study, the most commonly reported AEs among subjects receiving CAB + RPV were upper respiratory tract infection (36%), diarrhea (29%), nausea (26%), and headache (25%).

5.6.1.1. Drug-Related Adverse Events

In the Phase III studies (201584 and 201584), drug-related AEs (as assessed by the reporting investigator) were more commonly reported for the CAB + RPV group (who switched their regimen at Baseline) compared with subjects who remained on CAR (83% vs 6%), largely driven by the occurrence of ISRs in the CAB + RPV group (Mod2.7.4/Sec2.2.4.4).

Of the reported drug-related AEs across all Phase III/IIIb studies, the greatest proportion comprised ISRs. ISRs are discussed in Section 5.6.6.1. The most common drug-related non-ISR AEs in these studies were headache, pyrexia, nausea, fatigue, asthenia, and body temperature increased (Mod2.7.4/Sec2.3.3.4 and Sec3.5.4). Overall, few drug-related AEs across Phase III/IIIb studies led to treatment interruption or discontinuation.

Across Phase III/IIIb studies, the majority of drug-related AEs were Grade 1 or 2. In the Week 48 analysis of studies 201584 and 201585, a numerically higher proportion of subjects in the CAB + RPV group compared to the CAR group were reported as having Grade 3 to 4 drug-related AEs (5% vs <1%), predominantly attributable to ISRs, acute viral hepatitis, and AEs of laboratory abnormalities (lipase increase; CPK and AST increase) (Mod2.7.4/Sec2.2.4.4). No new Grade 3 or 4 non-ISR drug-related AEs were reported in the Week 96 analysis. In study 207966, the frequency of Grade 3 or 4 drug-related AEs was similar between the Q8W and Q4W groups (3%

and 5%, respectively) (Mod2.7.4/Sec3.5.4). No Grade 5 drug-related AEs occurred in the Phase III/IIIb studies.

In the Phase II studies, ISRs were the most commonly reported drug-related AEs (Mod2.7.4/Sec4 and Sec5.1). In study 200056 at Week 160, 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 randomized IM dosing groups. In study LAI116482 through End of Study, non-ISR drug-related AEs reported by ≥10% of subjects were nausea (17%), headache (15%), and diarrhea (10%).

Refer to Section 5.6.6.1 for details on ISRs and Section 5.6.4 for details on drug-related SAEs.

5.6.2. Deaths

A total of 11 deaths (10 in the Safety Population) have been reported on CAB + RPV or CAR in studies 201584, 201585, 207966, LAI116482, and 200056 (Mod2.7.4/Sec2.2.4.5, Sec3.5.5, Sec4, Sec5.1, and Sec7). All cases were considered by the investigators to be unrelated to study drug with the exception of a case of fatal myocardial infarction (study 200056) where the investigator could not rule out the possibility of relationship to study drug. No deaths were reported in studies 201584 and 201585 between the Week 48 and Week 96 analyses.

The following deaths were reported during the Phase III/IIIb studies:

- 1 subject in study 201584, a 30 to 40-year-old male in the CAR group, died due to a reported homicide during the Induction Phase. The event was reported as a [redacted] and not considered related to study drug.
- 1 subject in study 201585, a 40 to 50-year old female in the CAR group, died due to a methamphetamine overdose during the Maintenance Phase. This event was not considered related to study drug by the investigator.
- 1 subject in study 207966, 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 LA + RPV LA for 17 months prior to presenting 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 98 days after the last dose of study drug. 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 AR. 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 drug being causative in this instance.
- 1 subject in study 207966, a 30- to 40-year-old male, 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.

The following deaths were reported during the Phase II studies:

Note: the number of subjects in the oral CAB group of study 200056 was limited to 56 vs 230 for CAB + RPV. The number of subjects in the control (efavirenz) group of study LAI116482 was limited to 62 vs 181 for CAB + RPV.

- 1 subject in Phase II study 200056, a 30 to 40-year-old subject in the oral CAB group, died due to a road traffic accident that occurred during the Induction Phase of the study. The event was not considered related to study drug.
- 1 subject in Phase II study 200056, a 40 to 50-year-old male in the CAB + RPV group, died due to myocardial infarction after approximately 3 years of CAB + RPV exposure. 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 and adipositas (obesity) and hypertension. An autopsy was performed but the results have not been made available to the study. Despite potential confounders, the investigator could not exclude that this may have been caused by study drug.
- 1 subject in Phase II study 200056, a 30 to 40-year-old male in the CAB + RPV group, died due to acute onset refractory epilepsy. 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 suggest recreational drug use. The subject had no known prior history of seizure disorder. The event was not considered related to study drug.
- 1 subject in Phase II study LAI116482, a 50 to 60-year old male in the CAB + RPV group, died due gastrointestinal hemorrhage. The event was not considered related to study drug.
- 1 subject in Phase II study LAI116482, a 40 to 50-year old male in the CAB + RPV group, died after a cardiac arrest while undergoing elective shoulder repair. The event was not considered related to study drug.

The following deaths were reported after the data lock point of the individual studies:

- 1 subject in Phase IIIb study 207966, a 60 to 70-year-old male subject died by a self-inflicted gunshot wound. The reported cause of death was suicide. The subject had been on CAB + RPV (Q4W) for almost 3 years, receiving his first IM CAB + RPV dose on 25 January 2017 in study 201585. The subject had a longstanding history of depression and anxiety, although he did not report suicidal thoughts or behavior. At his last study visit he reported feelings of depression and anxiety and attributed this to social stressors and was isolating himself from his family and friends. He denied suicidal ideation or intent and there were no eC-SSRS alerts or possible suicidality-related AEs (PSRAEs) throughout his study participation. Other AEs and SAEs were not of a neuropsychiatric nature. An autopsy was performed but the results are not known so far. The investigator considered that there was no possible reason to suspect the suicide to be related to CAB + RPV. The Sponsor does not consider the fatal event to be related to treatment with CAB + RPV due to the long latency period before the event and the subject's risk factors.

- 1 subject in Phase II study 200056, a 50- to 60-year-old female, 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 and was not considered related to study drug.

5.6.3. Other Serious Adverse Events

For studies 201584 and 201585 (Week 48 analysis), the proportions of subjects developing at least 1 SAE were low and similar between treatment groups in the Maintenance Phase (5% on CAB + RPV; 4% on CAR). The most frequently reported SAEs were Hepatitis A (4 subjects on CAB + RPV and 2 subjects on CAR), colitis (1 subject on CAB + RPV and 2 subjects on CAR), anal abscess (reported in 0 subjects in the CAB + RPV Q4W group and 2 subjects in the CAR group), and anogenital warts (1 subject on CAB + RPV and 2 subjects on CAR). All other SAEs were reported in ≤1 subject per treatment group. Two subjects had a drug-related SAE during the Maintenance Phase of the pooled Phase III studies: 1 subject with right knee mono-arthritis in the CAB + RPV group and 1 subject with suicidal ideation in the CAR group (Mod2.7.4/Sec2.2.4.6).

At Week 96 in both studies 201584 and 201585, the frequency of SAEs was similar to that observed during the Maintenance Phase for each study. None of the SAEs reported between Week 48 and Week 96 in either study was fatal or drug-related. No patterns of clinical concern for SAEs were noted as individual SAEs were reported across diverse system organ classes and preferred terms for both treatment groups in each study (Mod2.7.4/Sec2.3.3.5).

In study 207966, the frequency of subjects reporting at least 1 SAE was similar in the 2 treatment groups (Q8W: 5%; Q4W: 4%) (Mod2.7.4/Sec3.5.6). 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). Otherwise, all SAEs were reported for single subjects in 1 or both treatment groups (ie, ≤2 subjects overall). Two subjects had SAEs related to post-injection reactions after RPV administration (see Section 5.6.8).

In the Phase II studies, no trends of concern were observed (Mod2.7.4/Sec4 and Sec5.1). In study 200056 through 160 weeks of treatment, 38 (17%) CAB + RPV subjects reported an SAE. In study LAI116482 through End of Study, 36 (20%) CAB + RPV subjects reported an SAE. The majority of SAEs in both studies were single occurrences with no demonstrated trends per treatment group.

5.6.4. Drug-Related Serious Adverse Events

In the pooled Week 48 analysis of studies 201584 and 201585, 1 subject in each treatment group had a drug-related SAE during the Maintenance Phase (Mod2.7.4/Sec2.2.4.6). In study 201584, a subject in the CAB + RPV group had a drug-related SAE of right knee monoarthritis. In study 201585, a subject in the CAR group had a drug-related SAE of suicidal ideation, and the subject was withdrawn from the study. Between Week 48 and Week 96, no drug-related SAEs were reported in either study.

In study 207966, SAEs were considered drug-related by the investigator in 3 subjects in the Q8W group and in 1 subject in the Q4W group.

- Injection site abscess (Q8W), see Mod2.7.4/Sec3.5.6.
- Presyncope (Q8W) as suspected post-injection reaction; see Section 5.6.8.
- Acute pancreatitis (Q8W); this subject died due to sepsis, see Section 5.6.2.
- Hypersensitivity (Q4W) as suspected post-injection reaction; see Section 5.6.8.

In Phase II studies, there were few drug-related SAEs (Mod2.7.4/Sec4 and Sec5.1). In study 200056, 1 fatal SAE of myocardial infarction was reported; the investigator could not rule out relatedness to study drug (see Section 5.6.2). In study LAI116482, 3 drug-related SAEs were reported in 2 subjects in the CAB + RPV group: suicidal ideation and depression (CAB 30 mg; both in same subject) and seizure (CAB 60 mg) (Mod5.3.4.2/LAI116482 EOS CSR/Sec7.4.3).

5.6.5. Other Significant Adverse Events

In the pooled Week 48 analysis of studies 201584 and 201585, the rate of discontinuation was low. Overall, 22 (4%) subjects in the CAB + RPV group and 9 (2%) subjects in the CAR group had AEs leading to withdrawal/permanent discontinuation of study drug during the Maintenance Phase (Mod2.7.4/Sec2.2.4.7.1). Additionally, 1 subject in the CAB + RPV group (study 201585) had acute hepatitis C and was discontinued due to meeting the protocol-defined liver stopping criteria (LSC), which was not captured as an AE leading to withdrawal prior to the data cut-off date. With the exception of acute viral hepatitis (1.7% [10/591]), all non-ISR AEs leading to withdrawal had an incidence of <1%.

For ISRs leading to withdrawal, see Section 5.6.6.1.

Table 15 Summary of AEs Leading to Withdrawal/Permanent Discontinuation of Study Drug During the Maintenance Phase in Study 201584, Study 201585, and Pooled – Week 48 Analysis (Safety Population)

	201584		201585		POOLED (201584+201585)	
System Organ Class Preferred Term	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
Number of Subjects with any event, n (%)	9 (3)	4 (1)	13 (4)	5 (2)	22 (4)	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)

System Organ Class Preferred Term	201584		201585		POOLED (201584+201585)	
	CAB + RPV (N=283)	CAR (N=283)	CAB + RPV (N=308)	CAR (N=308)	CAB + RPV (N=591)	CAR (N=591)
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: Mod2.7.4/Tab17.

Note: In the Data Source tables, the CAB + RPV group is listed as Q4W IM. For study 201584, CAR = ABC/DTG/3TC.

a. For details of subjects who withdrew due to acute viral hepatitis, see Mod2.7.4/Tab84

Between Week 48 and Week 96 in both studies (201584 and 201585), AEs leading to withdrawal were consistent with those observed during the Maintenance Phase (Mod2.7.4/Sec2.3.3.6). In study 201584, 5 subjects in the CAB + RPV group withdrew since the Week 48 analysis. Reasons for withdrawal were Hepatitis A, Hepatitis C, injection site pain, and depression. The AEs of injection site pain and depression were considered study drug-related by the investigator (Mod5.3.5.1/201584 W96 CSR). In study 201585, during the Extension Phase, 2 subjects in the CAB + RPV group had AEs leading to withdrawal of study drug (AEs of Hepatitis B [serious, Grade 3, not related to study drug] and fear [non-serious, Grade 1, related to study drug]) (Mod5.3.5.1/201585 W96 CSR). In the Extension Switch to CAB + RPV group, 1 subject had an AE (injection site pain) that led to withdrawal from study drug.

In study 207966, 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 (Mod2.7.4/Sec3.5.7.1). Except for fatigue, abnormal dreams, and hyperhidrosis, all in the Q4W group, no individual non-ISR AE term resulted in withdrawal/permanent discontinuation of study drug in >1 subject per treatment group. Ten

subjects had non-ISR, Grade 3 or 4 AEs that led to withdrawal of study drug, and 13 subjects had non-ISR, drug-related AEs that led to withdrawal. Six subjects had Grade 3 or 4, drug-related AEs that led to withdrawal and are listed below. ISR AEs leading to withdrawal are detailed in Section 5.6.6.1.

- Pyrexia (Q8W) – see case narrative in Mod5.3.5.3/207966 W48 CSR.
- Presyncope (Q8W) as suspected post-injection reaction; see mini narrative in Mod2.7.4/Sec3.5.6.
- Acute pancreatitis (Q8W) – see mini narrative in Section 5.6.2.
- Hypersensitivity (Q4W) as suspected post-injection reaction; see mini narrative in Mod2.7.4/Sec3.5.6.
- Transaminases increased (Q4W) – see case narrative in Mod5.3.5.3/207966 W48 CSR.
- Depression and fatigue (Q4W) – Subject had a medical history of depression. AEs were reported during OLI and led to withdrawal. See case narrative in Mod5.3.5.3/207966 W48 CSR.

In Phase II studies, the frequency of AEs leading to withdrawal was consistent with those observed in the Phase III/IIIb studies (Mod2.7.4/Sec4 and Mod2.7.4/Sec5.1). In study 200056 through Week 160, 15 (7%) subjects experienced AEs leading to withdrawal/permanent discontinuation of study drug. In LAI116482 through the End of Study, 12 (7%) subjects in the CAB + RPV group and 9 (15%) subjects in the EFV group experienced AEs leading to withdrawal/permanent discontinuation of study drug.

5.6.6. 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, or known association for approved INSTIs or NNRTIs, and/or regulatory authority requirements. Further details about AEs of special interest, as well supportive data from Phase II studies, are provided in Mod2.7.4/Sec6.

There were no expected or observed additive or synergistic effects on AEs of special interest in subjects taking CAB + RPV beyond those effects associated with the individual components.

AEs of special interest for RPV LA included local ISRs (Section 5.6.6.1), rash (Section 5.6.6.2), QT interval prolongation (Section 5.6.6.3), and neuropsychiatric events (Section 5.6.6.4). Some of the AEs of special interest identified for monitoring in the Phase II/III studies of CAB + RPV were specific for CAB, ie, hepatotoxicity, hypersensitivity reactions, seizures and seizure-like events, rhabdomyolysis, pancreatitis, weight gain, and impact on creatinine. Review of the results for hypersensitivity reactions, seizures and seizure-like events, rhabdomyolysis, pancreatitis, and AEs indicating a potential impact on creatinine showed that these were not associated with CAB + RPV treatment. Given the inclusion of LSC in the Phase III/IIIb and II studies, data related to hepatic safety are discussed in detail in Section 5.6.6.5. In addition, since a trend towards higher weight gain in the CAB + RPV group compared to the CAR group was observed in the Phase III studies, weight gain is described in more detail in Section 5.6.6.6 for completeness.

Information on AEs of special interest is supplemented by data from laboratory assessments and ECGs as appropriate. Relevant safety information on AEs of special interest from the supporting Phase II studies LAI116482 and 200056 is also presented in this section.

5.6.6.1. Injection Site Reactions

ISRs were recorded from study drug (CAB + RPV) injections only and are expected with IM injections. Throughout the CAB + RPV program, injections were well tolerated and ISRs were mostly mild to moderate in severity and resolved after a short duration. The overall frequency, intensity, and rates of withdrawal for study drug ISRs were generally similar between the Q8W and Q4W treatment groups. When analyzed by each injection drug, no notable differences in ISR characteristics between CAB and RPV were observed (Mod2.7.4/Sec6.1).

In the pooled Phase III studies 201584 and 201585, ISRs were very commonly reported (84% in the CAB + RPV group) (Mod2.7.4/Sec6.1). Most subjects in the CAB + RPV group experienced ISRs related to pain (77%), and fewer experienced AEs of nodule (14%), induration (12%), swelling (8%), erythema (4%), and pruritus (4%). Other ISRs occurred less commonly (affecting ≤3% of subjects). Incidence and severity of ISRs decreased over the course of the studies (Mod2.7.4/Fig8). Most subjects had ISRs that were Grade 1 (75%) or Grade 2 (36%), and 4% of subjects had Grade 3 ISRs. None of the ISRs were considered serious. Few subjects (1%) discontinued treatment as a result of an ISR. The low rate of discontinuation indicates that while ISRs occurred commonly, these were generally tolerable and resolved in most subjects (94%) within 14 days, with a median duration overall of 3 days.

At Week 96, the ISRs reported in studies 201584 and 201585 were consistent with those observed during the first 48 weeks (Mod2.7.4/Sec6.1). In both studies, no ISRs reported as SAEs occurred since the Week 48 analysis. In study 201584, at the end of the Maintenance Phase, a total of 3 subjects had ISR AEs leading to withdrawal: 2 subjects had Grade 3 AEs of injection site pain that led to discontinuation of study drug, and 1 subject withdrew consent from the study due to intolerability of injections. In study 201585 during the Extension Phase, only 1 subject (Extension Switch Population) had 2 AEs of injection site pain that led to withdrawal from study drug. Frequency of ISRs continued to decrease after Week 48 in the CAB + RPV groups of both studies, mostly due to a reduction in reports of injection site pain (Mod2.7.4/Fig8 and Mod5.3.5.1/201585 W96 CSR/Tab14).

In study 207966, overall ISR profiles were similar between treatment groups. The most commonly reported ISR was injection site pain (Q8W: 371 [72%] subjects; Q4W: 363 [70%] subjects) (Mod2.7.4/Sec6.1). Other common ISRs (≥5% of subjects in either treatment group) were injection site nodules (Q8W: 10%; Q4W: 17%), induration (Q8W: 8%; Q4W: 7%), discomfort (Q8W: 7%; Q4W: 8%), swelling (Q8W: 6%; Q4W: 5%), and pruritus (5% in both groups). Relative risk of common ISRs (≥5% of subjects in either treatment group) was similar between treatment groups with the exception of nodules at the injection site, which were reported less frequently in the Q8W group (Mod2.7.4/Fig14). One ISR SAE was reported in the Q8W group (Grade 3 injection site abscess) (see mini narrative in Mod2.7.4/Sec3.5.6).

The 2 treatment groups were similar with regards to severity and duration of ISRs (Mod2.7.4/Sec6.1). Most ISRs were Grade 1 or Grade 2, and 3% and 4% of subjects in the Q8W and Q4W groups, respectively, had Grade 3 ISRs. There were no Grade 4 or 5 ISRs. For both groups, the majority of ISRs (86% in both groups) resolved within 7 days and the median duration

was 3 days. ISRs lasting more than 14 days occurred in 10% of subjects in the Q8W group and 15% of subjects in the Q4W group.

Five (<1%) subjects in each treatment group had ISRs that led to withdrawal/permanent discontinuation of study drug (Mod2.7.4/Sec6.1). Additionally, 1 subject in the Q8W group and 4 subjects in the Q4W group withdrew consent from the study in the absence of AEs, but subjects' stated reasons were injection intolerability. Overall, 1% of subjects in the Q8W group and 2% of subjects in the Q4W group withdrew from the study due to intolerability of the injections.

In the Phase III studies, the Perception of Injection (PIN) instrument was used to collect information on how the injections were perceived by the subject. Based on pooled safety data from studies 201584 and 201585, the median acceptance of ISRs domain score of the PIN instrument at Week 5 was 2.00 ("very acceptable") on a 5-point scale (1=totally acceptable" and 5="not at all acceptable"). At Week 48 the median score improved to 1.5, ie, between 1.00 ("totally acceptable") and 2.00 ("very acceptable"). The change in overall acceptance of ISRs from Week 5 to Week 48 was statistically significant; p <0.001; missing data imputed using LOCF (Mod2.7.4/Sec6.1).

Consistent results were reported for remaining dimensions and individual items of the PIN, although statistical analysis was not performed.

In study 207966, the median Acceptance of ISRs domain score was 2.00 ("very acceptable") for both treatment groups at the first assessment (Week 8) (Mod2.7.4/Sec6.1). 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. These results are supportive of the observation that acceptability of injections improves over duration of treatment irrespective of differences in injection volumes such as between initiation dose and continuation doses (injection volume decreases compared with initiation dose in the Q4W group but remains constant for the Q8W group) and are also consistent with reduction in reporting incidence of ISRs that notably reduces over time through Week 48 for both treatment groups. The sponsor proposes labeling that will manage the risk for ISRs and has added the event to the list of ARs for CAB+ RPV (see Section 5.8).

5.6.6.2. Rash

In the pooled Phase III studies 201584 and 201585 (through Week 96) and the Phase IIIb study 207966 (through Week 48), there were no reports in the database for severe rash with terms that included Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, or other severe cutaneous reactions. Grade 1 and Grade 2 rashes were reported with CAB + RPV treatment (Mod2.7.4/Sec2.1.6.4). Serious AEs or Grade 3 or Grade 4 rashes have not been reported with CAB + RPV. Most events did not lead to withdrawal. In studies 201584 and 201585, the incidence of rash in the CAB + RPV groups was comparable to CAR (Mod2.7.4/Sec6.2).

The observations in the clinical studies of CAB LA + RPV LA are in line with what could be expected from the known safety profile of oral RPV. Rash is an AR for EDURANT.

5.6.6.3. QT Interval Prolongation

Treatment with CAB + RPV did not have clinically relevant effects on the QT interval (Mod2.7.4/Sec6.3).

In the pooled Phase III studies 201584 and 201585 through Week 48, no SAEs potentially associated with QT prolongation were reported. Grade 1 and 2 AEs have been reported with CAB + RPV treatment; few were considered related to study drug or led to treatment withdrawal. No AEs of QT prolongation were reported between Week 48 and Week 96 in either study (Mod2.7.4/Sec6.3).

In study 207966 through Week 48, ECG results were similar between treatment groups (Mod2.7.4/Sec6.3). Overall, treatment with CAB and RPV did not have any clinically relevant effect on the QTc of the ECG. No AEs potentially related to QT prolongation have been reported.

EDURANT at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc (Mod2.7.4/Sec6.3). The RPV plasma concentrations with CAB LA + RPV LA Q4W or Q8W are in line with those observed with oral RPV 25 mg once daily. At supratherapeutic doses (75 and 300 mg once daily), oral RPV has been associated with prolongation of the QTc of the ECG (refer to the EDURANT Product Information and Mod2.7.2/Sec2.5.4). Steady-state administration of RPV 75 mg once daily and 300 mg once daily resulted in a mean steady-state C_{max} approximately 4.4-fold and 11.6-fold, respectively, higher than the mean steady-state C_{max} for the recommended 600 mg monthly dose of RPV LA. Steady-state administration of oral RPV 75 mg once daily and 300 mg once daily resulted in a mean C_{max} approximately 4.1-fold and 10.7-fold, respectively, higher than the mean steady-state C_{max} observed with the recommended 900 mg every 2 months dose of RPV LA.

5.6.6.4. Neuropsychiatric Events

Observations from clinical studies are in line with what can be expected based on the known background rate of depression and suicidal ideation/behavior and mood and sleep disorders (including irritability, insomnia, and abnormal dreams) in the HIV-infected population compared to the general population and the known safety profile of EDURANT and dolutegravir (DTG, an INSTI compound related to CAB).

Insomnia, depression, depressed mood, abnormal dreams, sleep disorders and somnolence are ARs of EDURANT. In addition, DTG is associated with reports of depression, suicidal ideation and behavior (particularly in patients with a pre-existing history of depression or psychiatric illness), and mood (anxiety) and sleep disorders (abnormal dreams and insomnia) in HIV-infected patients [Tivicay SmPC].

Neuropsychiatric AEs of special interest occurring in >1% of subjects in all treatment groups in Phase III/IIIb studies 201584, 201585, and 207966 were those potentially related to depression, anxiety, or sleep disorders (Table 16). All other neuropsychiatric AEs of special interest occurred in ≤1% of subjects in all treatment groups. AEs of bipolar disorder and psychosis were infrequently reported during the Phase III/IIIb studies.

Table 16 Summary of Neuropsychiatric AEs of Special Interest in Studies 201584, 201585, 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: Mod2.7.4/Tab78.

In the Phase III/IIIb studies 201584, 201585, and 207966 (through Week 48), subjects with a past history of psychiatric illness and specifically in the categories of depression, anxiety, and suicidal ideation had a higher incidence of these events reported during the studies (Mod2.7.4/Sec6.4).

Suicidal Ideation/Behavior

Suicidality assessments were collected prospectively during Phase III/IIIb studies (Mod2.7.4/Sec6.4.1). A summary of cases of validated possible suicidality related AEs is provided in the PSRAE (and AE or SAE) forms (PSRAE listings are available in Mod5.3.5.1/201584 W48 CSR/ICH Data Listings/Lis26; Mod5.3.5.1/201585 W48 CSR/ICH Data Listings/Lis24). Serious events potentially related to suicidal ideation or behavior were reported at low incidence with CAB + RPV treatment.

Incidence of suicidal ideation and behavior was low (<1%) across the Phase III/IIIb studies. Suicidal ideation and behavior are not considered attributable to treatment with CAB + RPV.

In the pooled Phase III studies 201584 and 201585, no completed suicides occurred. Validated true positive alerts for suicidality assessments occurred at 1% in the CAB + RPV group and 2% in the CAR group (Week 48 analysis). Four (<1%) subjects in the CAB + RPV group and 5 (<1%) subjects in the CAR group had AEs of suicidal ideation or behavior (Mod2.7.4/Sec6.4.1).

No SAEs of suicidal ideation or suicidal attempts were reported in subjects receiving CAB + RPV in studies 201584 and 201585 at Week 48. In study 201584, 2 subjects in the CAR group had neuropsychiatric Grade 3 SAEs (suicidal ideation 1 subject, suicide attempt 1 subject) and were withdrawn from the study. The SAE of suicidal ideation was considered related to study drug.

In most cases, treatment with CAB + RPV was continued without interruption. One subject in the CAB + RPV group of study 201585 was withdrawn from the study due to an AE of depression suicidal on Day 4 of the OLI phase.

In studies 201584 and 201585 between the Week 48 and Week 96 analyses, there were no AEs reported that were potentially related to suicidal ideation or behavior in either the Safety or Extension Switch Populations (Mod2.7.4/Sec6.4.1).

No completed suicides occurred in study 207966 through Week 48 (Mod2.7.4/Sec6.4.1). No AEs of suicide or suicide attempts were reported. Twelve (2%) subjects in the Q8W group and 21 (4%) subjects in the Q4W group reported suicidal ideation or behavior during the Maintenance Phase. PSRAE data showed 5 (<1%) subjects in each treatment group with suicidal ideation or behavior alerts. Of these, 2 subjects (1 Q8W; 1 Q4W) had positive PSRAEs.

Depression

Incidence of depression was low (≤3%) in subjects treated with CAB + RPV across the Phase III/IIIb studies. Depression is an AR for treatment with CAB + RPV.

In the pooled Phase III studies (through Week 48), 16 (3%) subjects in the CAB + RPV group and 14 (2%) subjects in the CAR group reported AEs of depression. There were no SAEs or Grade 3 or 4 AEs of depression with CAB + RPV. One 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 withdrawal from the study (Mod2.7.4/Sec6.4.2).

In the Week 96 analysis of study 201584, there were 2 new AEs of depression, both considered related to study drug, which resulted in withdrawal from the study. At Week 96 in study 201585, there were no new SAEs or AEs leading to withdrawal that were potentially related to depression in either the Safety or Extension Switch Populations.

In study 207966 through Week 48, a similar proportion of subjects in each treatment group reported at least 1 AE potentially related to depression (12 [2%] subjects in the Q8W group and 14 [3%] subjects in the Q4W group) (Mod2.7.4/Sec6.4.2). One subject in the Q8W group had an SAE of major depression that was considered not related to study drug and did not lead to withdrawal. The same subject had a concurrent SAE of substance-induced psychotic disorder. One subject in the Q4W group had an AE of depression considered related to study drug that led to withdrawal.

Anxiety

Anxiety has been reported at a low incidence (≤5% in any treatment group) with CAB + RPV across Phase III/IIIb studies. Anxiety is an AR for CAB+RPV.

In the pooled Phase III studies at Week 48, 27 (5%) subjects in the CAB + RPV group and 20 (3%) subjects in the CAR group had AEs related to anxiety. Most of these were reported as 'anxiety' (21 [4%] and 13 [2%], respectively) (Mod5.3.5.3/209522 Output Tables & Figures/Tab3.11). Drug-related AEs of anxiety were reported at a higher incidence in the CAB + RPV group (8 [1%] subjects) compared with CAR (2 [<1%] subjects). No SAEs of anxiety were reported. One subject in each treatment group had AEs related to anxiety that led to withdrawal (Mod2.7.4/Sec6.4.3).

In the Week 96 analysis of study 201584, no new AEs potentially related to anxiety were reported (Mod2.7.4/Sec6.4.3). At Week 96 in study 201585, there were no SAEs that were potentially related to anxiety in either the Safety or Extension Switch Populations (Mod2.7.4/Sec6.4.3). In the Safety Population, 1 subject had an AE of fear (considered related to study drug) that led to withdrawal.

In study 207966, through Week 48, 22 (4%) subjects in the Q8W group and 14 (3%) subjects in the Q4W group were reported with at least 1 AE potentially related to anxiety. None of the anxiety-related AEs were serious and none led to discontinuation of study drug (Mod2.7.4/Sec6.4.3).

Mood Disorders

Mood disorders included affect lability, affective disorder, irritability, mood altered, mood swings, lethargy) (Mod2.7.4/Sec6.4.4). Events of mood disorders were reported at a low incidence (≤1%) with CAB + RPV treatment across the Phase III/IIIb studies.

In the pooled Phase III studies at Week 48, AEs related to mood disorders were reported in 7 (1%) subjects in the CAB + RPV group and in 1 (<1%) subject in the CAR group. Drug-related events were reported in 3 subjects (<1%) in the CAB + RPV group and 1 subject (<1%) in the CAR group. There were no SAEs or Grade 3 or 4 AEs of mood disorders in the CAB + RPV group during Phase III and II studies. Mood disorder events did not lead to withdrawal (Mod2.7.4/Sec6.4.4). Although there was a higher incidence of mood disorders with CAB + RPV, review of the individual cases did not suggest a compelling association between mood disorders and treatment with CAB + RPV.

At Week 96 in studies 201584 and 201585, there were no SAEs or AEs leading to withdrawal that were potentially related to mood disorders in either the Safety or Extension Switch Populations (Mod2.7.4/Sec6.4.4).

In study 207966 through Week 48, 4 (<1%) subjects in the Q8W group and 2 (<1%) subjects in the Q4W group were reported with at least 1 AE potentially related to mood disorders (Mod2.7.4/Sec6.4.4). There were no SAEs or AEs leading to withdrawal potentially related to mood disorders reported in either treatment group.

Mood disorders are not considered attributable to treatment with CAB + RPV.

Bipolar Disorders

No AEs related to bipolar disorders were reported in the pooled Phase III studies through Week 96.

In study 207966, 1 subject in the Q8W group had an SAE of bipolar disorder which was considered not related to study drug and did not lead to withdrawal. No AEs potentially related to bipolar disorder were reported in the Q4W group (Mod2.7.4/Sec6.4.5).

Psychosis

Two events potentially related to psychosis were reported with CAB + RPV in the Phase III/IIIb studies (Week 48 analyses): 1 non-serious AE which was considered related to study drug and 1 SAE considered not related to study drug; neither led to withdrawal (Mod2.7.4/Sec6.4.6).

Sleep Disorders

Events of sleep disorders were reported with CAB + RPV treatment. The incidence of sleep disorders was ≤7% in any treatment group across the Phase III/IIIb studies. Insomnia and abnormal dreams are ARs for treatment with CAB + RPV. Insomnia, abnormal dreams, sleep disorders, and somnolence are ARs of EDURANT.

In the pooled Phase III studies at Week 48, the incidence of AEs of sleep disorders (38 [6%] vs 21 [4%] subjects), including drug-related events (15 vs 4 subjects), particularly insomnia (22 [4%] vs 8 [1%] subjects), was higher in the CAB + RPV group compared with CAR. There were no SAEs of sleep disorders with CAB + RPV during Phase II and Phase III studies. Severity was generally Grade 1 or Grade 2. Sleep disorder AEs did not lead to withdrawal. Sleep disorders, including abnormal dreams and insomnia, are considered associated with CAB + RPV treatment.

At Week 96, there were no new SAEs or AEs leading to withdrawal that were potentially related to sleep disorders in either the Safety or Extension Switch Populations in studies 201584 and 201585 (Mod2.7.4/Sec6.4.7).

In study 207966 through Week 48, 22 (4%) subjects in the Q8W group and 36 (7%) subjects in the Q4W group reported at least 1 AE potentially related to sleep disorders. One subject had a sleep disorder-related SAE and 2 subjects had sleep disorder-related AEs that led to withdrawal (Mod2.7.4/Sec6.4.7).

- 1 subject in the Q4W group had an SAE (sleep apnea) that was not related to study drug and no change was made to study drug.
- 1 subject in the Q4W group had 2 AEs (abnormal dreams, sleep disorder) simultaneously that were both considered to be related to study drug and led to withdrawal of study drug.
- 1 subject in the Q4W group had 2 AEs (abnormal dreams, insomnia) simultaneously that were considered to be related to study drug and led to withdrawal of study drug.

Refer to Mod2.7.4/Sec6.4.7 for more details.

The sponsor has included depression, anxiety, abnormal dreams, somnolence, and insomnia to the list of ARs for CAB+ RPV.

5.6.6.5. Hepatotoxicity

The hepatic safety data for CAB + RPV supports administration in HIV-infected patients.

No cases of drug-induced liver injury (DILI) in subjects meeting LSC and receiving RPV LA have been identified in the pooled Phase III studies (201584 and 201585), Phase IIIb study 207966, and supporting Phase II studies (200056 and LAI16482). In study 207966, there was 1 report of possible DILI that was considered related to oral CAB + RPV that occurred during the OLI part of the Maintenance Phase. Four cases of suspected DILI were identified during the Phase II studies, all on oral CAB.

Isolated ALT elevations have been observed with exposure to CAB + RPV during the development program. These elevations were primarily attributed to the occurrence of acute viral hepatitis. Aminotransaminase elevations in these subjects have been transient and reversible.

In the pooled Phase III studies, 11 subjects met LSC in the CAB + RPV group, 10 of whom had acute viral hepatitis (6 subjects in study 201584 and 4 subjects in study 201585); 1 subject met LSC due to chronic HCV infection, illicit drug use, and inorganic solvent abuse. One subject met liver monitoring criteria, but never reached LSC. Three subjects met LSC in the CAR group, all of whom had acute viral hepatitis (2 subjects in study 201584 and 1 subject in study 201585) (Mod2.7.4/Sec6.5).

In the pooled Phase III studies, 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 Grade 2 (57/59 on CAB + RPV; 28/31 on CAR). No Grade 3 bilirubin elevations occurred. Five Grade 4 elevations occurred (2 on CAB + RPV; 3 on CAR) (Mod2.7.4/Sec6.5).

Between Week 48 and Week 96, few additional liver stopping events were reported (Mod2.7.4/Sec6.5). In study 201584, 2 additional subjects (hepatitis A and hepatitis C) in the CAB + RPV group and 1 additional subject (transaminitis) in the CAR group met LSC. In study 201585, 2 additional subjects (acute hepatitis E and acute hepatitis B) in the CAB + RPV group met LSC.

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 (Mod2.7.4/Sec6.5). Overall, 5 subjects (2 on Q8W and 3 on Q4W) met LSC during the Maintenance Phase of study 207966, and 3 additional subjects warranted monitoring based on liver chemistries. Six of these 8 subjects had acute viral hepatitis. Of the 2 subjects who did not, 1 subject had possible DILI that was considered to be related to oral CAB + RPV that was identified during OLI, and 1 subject had liver biochemistry elevations that resolved after discontinuation of a concomitant medication (Melanotan II), which was presumed the 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.

Hepatotoxicity has been observed with oral CAB treatment and with other INSTIs. In addition, the observations in the clinical studies of CAB LA + RPV LA are in line with what could be expected from the known safety profile of EDURANT. Increased transaminases is an AR to EDURANT. HBV/HCV co-infection is considered a risk factor for increased hepatic parameters during EDURANT treatment (refer to Section 5.10.2).

5.6.6.6. Weight Gain

Weight gain has been reported with treatment with INSTIs such as DTG but not with RPV or other NNRTIs.

In the pooled Phase III studies (201584 and 201585) at Week 48, subjects in the CAB + RPV group gained a median of 1.5 kg in weight and those in the CAR group gained a median of 1.0 kg (Mod2.7.4/Sec6.6). In the individual studies at Week 96, median weight gain from Baseline in study 201584 was 2.00 kg in both treatment groups, and in study 201585 was 2.1 kg in the CAB + RPV group and 1.1 kg in the Extension Switch to CAB + RPV group (Mod2.7.4/Sec6.6).

In study 207966 through Week 48, median weight gain from Baseline was 1.0 kg in both treatment groups.

5.6.6.7. Safety of CAB + RPV in Pregnancy

The safety of CAB + RPV during human pregnancy has not been established (Section 5.11).

For a summary of nonclinical results relating to pregnancy, see Mod2.4/Sec4.

During the Phase III studies 201584 and 201585 through Week 48, 7 pregnancies were reported, 4 of which occurred in subjects exposed to CAB + RPV (Mod2.7.4/Sec2.2.10). Pregnancy-related AEs included abortion missed (nonviable pregnancy was terminated) (n=1, CAB + RPV group) and abortion spontaneous (n=1, CAR group).

Between Week 48 and Week 96, 5 new pregnancies were reported in study 201584: 3 in the CAB + RPV Q4W group and 1 in the Extension switch to CAB + RPV population. In addition, 1 pregnancy was reported in a subject who became pregnant after study withdrawal, the subject previously received CAB+RPV Q4W. No AEs related to ongoing pregnancies were reported. In study 201585, no additional pregnancies were reported between Week 48 and Week 96 (Mod2.7.4/Sec2.3.7).

In study 207966 through Week 48, 4 pregnancies were reported. One subject (<1%) in the Q4W group reported at least 1 pregnancy-related SAE (spontaneous abortion) considered unrelated to study drug (Mod2.7.4/Sec3.8).

5.6.7. Adverse Events Reported During Oral Lead-in

An OLI of CAB + RPV was included in the Phase III/IIIb studies to evaluate the tolerability to the individual components prior to starting LA dosing. Total exposure numbers in the clinical program can be found in Section 1.2. In pooled Phase III studies 201584 and 201585 through Week 48, 590 subjects received OLI. In study 207966, 655 subjects received OLI. In studies LAI116482 and 200056, there was no OLI period.

During the OLI period in studies 201584 and 201585, 6 subjects (1%) (3 subjects in each study) experienced AEs leading to withdrawal/permanent discontinuation of study drug (Mod2.7.4/Sec2.2.11). In study 201584 these AEs were acute hepatitis C (Grade 2), hepatitis A (Grade 4), and transaminases increased (Grade 3, due to solvent abuse). None of these AEs were considered to be related to study drug. AEs leading to withdrawal in study 201585 were asthenia (Grade 1), myalgia (Grade 1), headache (Grade 3), and depression suicidal (Grade 2), all considered to be related to study drug. There were no reports of HSR or DILI, and no withdrawals due to AEs during that period that could have represented early HSR or DILI.

In study 207966 during OLI, 1 subject had a Grade 3 AE of increased transaminases and the case was adjudicated as possible DILI (Section 5.6.6.5), and the subject was withdrawn from the study. No subjects had AEs consistent with hypersensitivity that led to withdrawal.

To date, all studies (with the exception of study LAI114433) conducted with CAB LA + RPV LA included a period of oral dosing with CAB + RPV (induction/OLI) prior to IM dosing in order to evaluate individual subject tolerability.

5.6.8. Post-injection Reactions

Inadvertent partial IV injections have been identified infrequently during the CAB + RPV clinical development program.

Ad hoc analysis of CAB and RPV plasma concentrations measured 2 hours postdose at several visits during the Phase III studies 201584 and 201585, and Phase IIb study 200056 suggest that inadvertent (partial) IV injections occurred infrequently (~0.8% of the ~4,996 2-hour post injection

CAB and RPV concentrations measured) and in most cases, without AEs or impact on virologic expression (Mod2.7.4/Sec8.4.1).

Across the CAB + RPV development program, 4 subjects were reported to have post-injection reactions; 3 were apparently associated with inadvertent IV injection of RPV (based on PK) (Mod2.7.4/Sec8.4.1). The fourth case was not confirmed as due to inadvertent IV administration because a suitably timed postdose PK sample was not collected. The cases were reported in study 207966 (n=3) and in study 200056 (n=1). These reactions occurred within minutes of the injection and began to resolve within a few minutes after onset.

As over 39,626 injections with RPV LA and CAB LA have been administered in the CAB + RPV development program, these events appear to be very rare. While the mechanism for these events is currently not known, the reported events have been characterized by rapid improvement of associated signs and symptoms. In each case, the treating physicians and study sites had been participating in the CAB + RPV studies for several years and were experienced with administering injections.

5.7. Clinical Laboratory Evaluations

5.7.1. Clinical Chemistry

Results of the clinical laboratory findings demonstrate that there are no laboratory signals of concern in subjects switching from CAR to receiving CAB + RPV treatment (Mod2.7.4/Sec2.2.5, Sec2.3.4 and Sec3.6). In studies 201584 and 201585 through Week 48, the majority (75% on CAB + RPV, 80% on CAR) of the post-Baseline emergent clinical chemistry toxicities were Grade 1 or Grade 2 in intensity. No clinically relevant differences were observed overall in subjects with at least 1 Grade 3 or 4 post-Baseline emergent toxicity between the CAB + RPV and CAR groups. At Week 96, trends in clinical laboratory parameters were consistent with those observed at Week 48 for both studies. 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, and no new safety concerns were identified in clinical chemistry parameters.

5.7.1.1. Liver Chemistry Results

Details about AEs related to livery chemistry and liver chemistry laboratory abnormalities in the CAB + RPV development program are presented as part of the hepatotoxicity AEs of Interest in Section 5.6.6.5.

5.7.1.2. Creatinine

Creatinine elevation without evidence of worsening renal function is associated with DTG, a closely related INSTI.

In the pooled Phase III studies, a non-clinically significant median decrease of 3.5 µm/L in serum creatinine from Baseline was observed at Week 48 with CAB + RPV treatment (Mod2.7.4/Sec2.2.5.1.2). No clinically significant changes were observed in the CAR group (median increase from baseline at Week 48 of 0.9 µmol/L). There were no cases of creatinine-related AEs considered related to treatment with CAB +RPV during the pooled Phase III studies through Week 96.

In study 207966 there were no clinically relevant differences between treatment groups for creatinine (Mod2.7.4/Sec3.6.1). There was 1 subject with a creatinine-related AE considered related to treatment with CAB + RPV (renal impairment, non-serious and not leading to discontinuation).

5.7.1.3. Creatine Kinase

During the Maintenance Phase of the pooled Phase III studies up to Week 48, 122 subjects in the CAB + RPV group and 94 subjects in the CAR group had post-Baseline-emergent elevated creatine kinase (CK) levels. Grade 3 or Grade 4 elevations of CK were observed in 47 (8%) subjects in the CAB + RPV group and 26 (4%) subjects in the CAR group. CK elevations were considered exercise-related (Mod2.7.4/Sec2.2.5.1.6). At Week 96 in study 201584, there were 11 new Grade 3 or 4 cases of post-Baseline-emergent elevated CK levels (10 in the CAB + RPV group and 1 in the Extension Switch to CAB + RPV group) (Mod5.3.5.1/201584 W96 CSR). At Week 96 in study 201585, there were 4 new Grade 3 or 4 cases of post-Baseline-emergent elevated CK levels (3 in the CAB + RPV group and 1 in the Extension Switch to CAB + RPV group) (Mod2.7.4/Sec2.3.4.1).

In study 207966, there were no clinically relevant differences between treatment groups (79 [15%] subjects in Q8W and 74 [14%] subjects in Q4W) and no change from Baseline for CK results (Mod2.7.4/Sec3.6.1).

5.7.1.4. Lipase

In the pooled Phase III studies at Week 48, post-Baseline emergent lipase elevations were observed in both treatment groups. No AEs of pancreatitis considered related to study drug were reported (Mod2.7.4/Sec2.2.5.1.7). The majority of these changes were Grade 1 (50 [8%] on CAB + RPV and 49 [8%] on CAR) or Grade 2 (46 [8%] and 43 [7%]) and were asymptomatic. Grade 3 abnormalities occurred in 23 (4%) and 10 (2%) subjects in the CAB + RPV and CAR group and Grade 4 abnormalities in 10 (2%) and 6 (1%) subjects, respectively. At Week 96 in study 201584, there were 7 additional Grade 3 or 4 post-Baseline emergent lipase elevations (2 in the CAB + RPV group and 5 in the CAR group). At Week 96 in study 201585, there were 5 additional Grade 3 or 4 post-Baseline emergent lipase elevations (all occurred in the Extension Switch to CAB + RPV group) (Mod2.7.4/Sec2.3.4.1).

In study 207966, there were no clinically relevant differences between treatment groups or changes from Baseline for lipase (Mod2.7.4/Sec3.6.1).

5.7.1.5. Lipid Parameters

In the pooled Phase III studies, most of the treatment-emergent cholesterol and triglycerides abnormalities were Grade 1 or 2 (Mod2.7.4/Sec2.2.5.1). The differences between the treatment groups in the change from Baseline in lipid profile through Week 48 were not clinically significant. There were no cases of lipid-related AEs attributed to treatment with CAB + RPV in the pooled Phase III studies. In the Week 96 analysis, no clinically relevant patterns in changes in NCEP fasting lipids from Baseline were observed in either study (Mod2.7.4/Sec2.3.4.1).

In study 207966, minimal increases from Baseline in median total cholesterol (1.10%), LDL cholesterol (2.80%), and cholesterol/HDL ratio (1.27%) were noted for the Q4W group at Week 48

(Mod2.7.4/Sec3.6.1). The changes were 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 in either treatment group.

5.7.2. Hematology

In the pooled Phase III studies, the changes from Baseline to Week 48 in hematology values were not clinically relevant; most hematology abnormalities were Grade 1 or 2 (Mod2.7.4/Sec2.2.5.2). Eleven subjects (4 on CAB + RPV; 7 on CAR) had Grade 3 or 4 post-Baseline emergent hematology abnormalities at Week 48. These included abnormalities in hemoglobin (n=5), neutrophils (n=4), and platelets (n=2). In the Week 96 analysis, 6 additional subjects (1 on CAB + RPV; 5 on CAR) had Grade 3 or 4 post-Baseline emergent hematology abnormalities (all occurred in study 201584) (Mod2.7.4/Sec2.3.4.2). These included abnormalities in hemoglobin (n=3), platelets (n=2), and neutrophils (n=1). Overall, hematology laboratory values did not significantly change over time or between treatment groups and no trends were observed.

In study 207966, there were no clinically relevant differences between treatment groups for hematology parameters (Mod2.7.4/Sec3.6.2).

5.8. Adverse Reactions for CAB + RPV

The safety assessment (and AR identification) was performed for the CAB + RPV regimen as these agents were administered together in the clinical studies. The assessment was based on the analysis of pooled data from the pivotal Phase III studies 201584 and 201585 at Week 48 and data from the Phase IIIb study 207966 at Week 48 (Mod2.7.4/Sec11).

CAB + RPV was administered as a combination regimen (monthly and every 2 months dosing) and associated ARs are listed in Table 17 by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 and <1/10), and uncommon (≥1/1,000 and <1/100). ARs listed include those attributable to both the oral and injectable formulations of CAB + RPV.

The most frequently reported ARs from monthly dosing studies were ISRs (up to 84%), headache (up to 12%) and pyrexia (10%).

The most frequently reported ARs from study 207966 every 2 months dosing were ISRs (76%), headache (7%) and pyrexia (7%).

Table 17 Adverse Reactions for CAB + RPV

MedDRA System Organ Class	Frequency Category	ARs for CAB+RPV Regimen
Psychiatric disorders	Common	depression, anxiety, abnormal dreams, insomnia
Nervous system disorders	Very common	headache
	Common	dizziness
	Uncommon	somnolence, vasovagal reactions (in response to injections)
Gastrointestinal disorders	Common	nausea, vomiting, abdominal pain[1], flatulence, diarrhea
Hepatobiliary Disorders	Uncommon	hepatotoxicity
Skin and subcutaneous tissue disorders	Common	rash[2]
Musculoskeletal and connective tissue disorders	Common	myalgia
General disorders and administrative site conditions	Very common	injection site reactions[4] (pain and discomfort, site nodule, induration), pyrexia[3]
	Common	injection site reactions[4] (swelling, erythema, pruritis, bruising, warmth, haematoma), fatigue, asthenia, malaise
	Uncommon	injection site reactions[4] (cellulitis, abscess, anaesthesia, haemorrhage, discolouration)
Investigations	Common	weight increased
	Uncommon	transaminase increased

[1] Abdominal pain includes the following grouped MedDRA preferred terms: abdominal pain, upper abdominal pain.
[2] Rash includes the following grouped MedDRA preferred terms: rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash papular, rash pruritic.
[3] Pyrexia includes the following grouped MedDRA preferred terms: feeling hot, body temperature increased, pyrexia.
[4] Injection site reactions listed in the table have been reported in 2 subjects or more.

Note that certain ARs (eg, anxiety, diarrhea, flatulence, weight increased) have not been identified as RPV-associated ARs in previous clinical experience with oral RPV but have been associated with the use of INSTIs.

Additionally, ARs identified for EDURANT that are not listed in Table 17 may occur with RPV LA treatment. For an overview of these ARs, refer to the local Prescribing Information of EDURANT.

5.9. Pharmacokinetic – Pharmacodynamic Relationship: Safety

Differences in RPV PK exposure following Q4W dosing and Q8W dosing are not considered clinically relevant in terms of safety, as PK/PD analyses following RPV LA administration did not identify an association between plasma exposure and safety parameters (Mod2.7.2/Sec2.1.3).

No clinically relevant relationships between plasma RPV concentrations and safety parameters of interest, including changes in QTc, ALT, and total bilirubin, were identified in the Phase III/IIIb studies 201584, 201585, and 207966 (Mod2.7.2/Sec2.1.3).

5.10. Special Patient Populations

5.10.1. Sex, Age, and Race

The pooled Phase III analysis (201584 and 201585) at Week 48 does not suggest any effect of sex, age, or race on the safety profile of CAB + RPV (Mod2.7.4/Sec8.1.1).

Across the Phase III/IIIb studies, no clinically significant differences in the PK of RPV were observed based on age, sex, or race.

5.10.2. Hepatitis B and/or C Virus Co-infection

No conclusions can be made about the safety of CAB + RPV in HBV co-infected patients as HIV-infected subjects with evidence of HBV co-infection were excluded from the RPV LA clinical program. The use of CAB LA and RPV LA has not been studied in these patients. In studies 201584 and 201585, subjects who developed isolated ALT elevations and were identified to have acquired acute infectious hepatitis B had CAB + RPV dosing withheld. Resumption of dosing with acute HBV infection was not studied (Mod2.7.4/Sec8.1.2). It is not recommended to initiate treatment with CAB + RPV in HBV co-infected patients. HIV treatment guidelines recommend NRTI-containing regimens with activity against HBV [DHHS, 2019; EACS, 2019; IAS, 2016]. In study 207966 at Baseline, 2 (<1%) subjects in the Q8W group and 1 (<1%) subject in the Q4W group tested positive for hepatitis B antibody (Mod5.3.5.3/207966 W48 CSR). Based upon additional testing in which all 3 subjects had HBV DNA <lower limit of quantification, these subjects were not considered to have active HBV infection and were allowed to participate in the study.

Asymptomatic subjects with stable HCV were allowed to enroll in the Phase III/IIIb and Phase II studies for CAB + RPV provided that certain criteria were met. In the pooled Phase III analysis of studies 201584 and 201585, 7% of subjects were co-infected with HCV at Baseline, based on HCV serology testing alone. The subjects in the CAB + RPV group did not develop signs or symptoms of DILI during their study participation, suggesting that the risk of DILI is not higher in HIV/HCV co-infected subjects although limited conclusions can be drawn about this small sub-population (Mod2.7.4/Sec8.1.2). In study 207966 at Baseline, 5 (<1%) subjects in the Q8W group and 6 (1%) subjects in the Q4W group tested positive for HCV (Mod5.3.5.3/207966 W48 CSR). One subject with HCV in the Q4W group had LSC and then restarted study drug.

5.10.3. Hepatic Impairment

No dose adjustment for RPV (oral or LA) is required for patients with mild or moderate hepatic impairment (see Section 3.3.1). No data are available for RPV (oral or LA) in severe hepatic impairment (Mod2.7.4/Sec8.1.3).

5.10.4. Renal Impairment

No dose adjustment of RPV LA is required for patients with mild or moderate renal impairment (creatinine clearance ≤30 mL/min and not on dialysis) (see Section 3.3.2). No data are available for RPV (oral or LA) in subjects with end stage renal disease or severe renal impairment (Mod2.7.4/Sec8.1.4).

5.11. Pregnancy and Lactation

The safety of CAB + RPV during human pregnancy and breastfeeding has not been established.

No studies have been conducted with RPV LA in pregnant women. Subjects who became pregnant during CAB + RPV treatment were discontinued from CAB + RPV treatment. Data from the use of oral RPV in pregnant women are limited; lower exposures of RPV were observed during pregnancy. Viral load should be closely monitored during pregnancy. Pregnancy data are discussed in Mod2.7.4/Sec8.3.1.

RPV has not been studied in mothers breastfeeding infants. Women who were breastfeeding infants were excluded from study participation.

Based on animal data, it is expected that RPV will be secreted into human milk, although this has not been confirmed in humans. RPV may be present in human milk for up to 12 months or longer after the last RPV injection. Because of both the potential for HIV transmission and the potential for AEs in nursing infants, mothers should be instructed not to breastfeed if they are receiving RPV LA (Mod2.7.4/Sec8.3.2).

5.12. Medication Errors

Over 39,626 injections have been administered in the CAB + RPV clinical program (studies 201584, 201585, 207966, 200056 up to the cut-off date of the individual studies). Medication errors can occur based on the IM method of administration for both the CAB and RPV injections. No AEs or evidence of lack of efficacy were identified in the Phase III/IIIb studies as a result of medication errors. There have been no reports of attempts to combine CAB + RPV into a single syringe. In addition, device malfunctions were reported infrequently.

In studies 201584 and 201585 up to Week 48, medication errors not associated with device malfunction were formally reported in 15 subjects out of the total of 14,682 injections and included both overdosing (6 subjects) and underdosing (8 subjects), and in 1 subject this involved receiving the right dose and drug but from the wrong study (Mod2.7.4/Sec8.4).

In study 207966, there were few reports of dosing errors or device malfunctions (Mod2.7.4/Sec8.4).

- 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.
- Device malfunctions were reported for 4 subjects in the Q8W group and for 3 subjects in the Q4W group.

Inadvertent partial IV injections are discussed in Section 5.6.8. Medication errors resulting in the delivery of more than the intended dose are discussed in Section 5.14. Given the volume fill of the vials, the risk of overdose is very limited (refer to Mod3.2.P.2.2.1).

5.13. Injection Site Selection

Due to the injection volume required for RPV LA dosing (3 mL or 2 mL), the gluteal muscle was selected early in clinical development. During clinical studies involving RPV LA, both the

dorsogluteal and ventrogluteal injection sites have been used. The ventrogluteal approach is favored by current guidance for administering injections as it avoids proximity to the neurovascular bundle in the gluteal region. Therefore, this injection site will be recommended as preferred.

5.14. Withdrawal Effects, Abuse Potential, and Overdose

Due to the lack of psychoactive effects, there is no risk for withdrawal effects or abuse potential for RPV LA. Withdrawal effects with RPV LA have not been observed during the 1-year follow-up after treatment discontinuation. No propensity for abuse potential was observed during the CAB + RPV development program.

The highest dose of RPV LA studied in the CAB + RPV development program to date is 1200 mg of RPV LA.

Medication errors could lead to a potential overdose and are discussed in Section 5.12. No AEs have been reported in association with the medication errors in studies 201584 and 201585. In study 207966, 2 subjects had an SAE with acute symptoms believed to be secondary to high exposure to RPV, believed to be related to inadvertent (partial) IV injection (see Section 5.6.8).

Management of any occurrence of overexposure should be as clinically indicated by the presenting toxicity, such as monitoring of vital signs and ECG (QT interval). RPV is known to be highly protein bound in plasma, therefore dialysis is unlikely to be helpful in removal of the drug from the body.

Refer to Mod2.7.4/Sec8.5, Sec8.6, and Sec8.7 for more details.

5.15. Post-Marketing

The safety profile observed in clinical studies with RPV during the CAB + RPV development program is consistent with post-marketing reports of oral RPV.

At the time of finalization of this Clinical Overview, no post-marketing data on RPV LA were available.

5.16. Safety Conclusions

- The integrated analysis of safety across the Phase III clinical studies (201584 and 201585) in combination with Phase IIIb data (study 207966) and Phase II data (studies 200056 and LAI116482) supports a favorable safety profile of CAB + RPV in a monthly or every 2 months dosing regimen.
- 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 non-ISR AEs.
- In the pivotal Phase III studies, the overall safety profile observed with oral CAB + RPV was similar to that observed overall with the CAB + RPV treatment regimen (with the exception of ISRs). There were few safety events observed with oral treatment (OLI).

- There were no changes to the overall safety profile during long-term treatment. Few additional subjects, if any, had AEs of special interest, and at Week 96 no additional SAEs assessed as drug-related were reported since the Week 48 analysis in studies 201584 and 201585.
- No relationships between plasma RPV concentrations and safety parameters of interest were identified in the CAB + RPV Phase III/IIIb studies.
- Review of safety data of ongoing studies 201584, 201585, 207966, and 200056 from the time of the cut-off of the analyses presented in this Clinical Overview up to 31 January 2020 did not show any trends in the occurrence of SAEs.
- Results from the CAB + RPV development program support the use of RPV LA in combination with CAB LA in virologically suppressed HIV-1 infected patients. In the Week 48 pooled Phase III analysis, a higher incidence of AEs leading to withdrawal/permanent discontinuation (4% vs 2%) and Grade 3 and 4 AEs (11% vs 6%) was reported in the CAB + RPV group. Overall, CAB + RPV appeared to be generally safe and well tolerated. Although ISRs occurred frequently, few were treatment limiting, ISRs were generally mild to moderate in severity and decreasing and stabilizing over time.

6. BENEFITS AND RISKS CONCLUSIONS

RPV, when used in combination with CAB, is an effective, and well tolerated regimen for the maintenance of HIV-1 suppression, based on the Week 48 and Week 96 data from the 2 pivotal Phase III studies with CAB + RPV (studies 201584 and 201585) and the Week 48 data from the Phase IIIb study with CAB + RPV (study 207966). CAB + RPV is a 2-drug, NRTI-sparing injectable regimen intended for the long-term treatment of HIV-1 infection. The benefit/risk profile of the CAB + RPV 2-drug regimen was defined through evaluation of the efficacy, safety, and tolerability of the individual components as well as the combination through the Phase III/IIIb studies. The Phase III studies showed that CAB + RPV is non-inferior to daily oral CAR in maintaining virologic suppression in HIV-1 infected subjects. The Phase IIIb study 207966 showed that the CAB + RPV every 2 months dosing regimen is non-inferior to the CAB + RPV monthly dosing regimen in maintaining virologic suppression in HIV-1 infected subjects. Rates of CVF were low in CAB + RPV treatment groups. The overall safety profile was similar for both dosing regimens. The most frequently reported AE in both treatment groups was ISR, which were generally mild, self-limited, and led to a very low rate of treatment discontinuations.

6.1. Therapeutic Context

Upon approval, this will be the first 2-drug LA injectable regimen for the treatment of HIV-1 infection. IM administration of a 2-drug combination therapy with CAB + RPV may be a convenient therapeutic option offering opportunities for improved treatment satisfaction and adherence to treatment in HIV-1 infected patients due to factors such as less frequent dosing (with options for monthly or every 2 months dosing injections) and the treatment administration being directly observed. HIV-infected patients may also potentially avoid stigma associated with pill-taking and fewer reminders of disease status than daily oral treatments. This regimen may also be an important option for patients who are unable to take or absorb oral medications.

Authorization Applications for the combination regimen of CAB LA + RPV LA have been submitted in several countries, including the US and EU, and the regimen was approved as a co-packaged product in Canada on 18 March 2020 (Cabenuva, ViiV Healthcare).

6.1.1. HIV-1 Infection

In 2018, an estimated 37.9 million people worldwide were living with HIV/AIDS and 1.7 million people were newly infected with HIV [UNAIDS, 2019]. In 2018, 770,000 people died from AIDS-related illness. Of the people living with HIV in 2018, 23.3 million were on ART [UNAIDS, 2019]. Increasing access to treatment is contributing to a reduction in AIDS-related deaths among adults and children, and efforts to strengthen HIV prevention and treatment programs are reducing the transmission rate of HIV. Recent trial results have confirmed that people living with an undetectable viral load do not transmit virus to uninfected contacts [Cohen, 2016].

6.1.2. Current Therapies and Unmet Medical Need

Current treatment of HIV infection involves life-long, daily, oral therapy most commonly with 3 or 4 drugs, including N(t)RTIs, NNRTIs, PIs, PK boosters, INSTIs, or fusion inhibitors. Over the last 3 decades, there have been substantial improvements in the durability, safety and tolerability, and convenience of all ARV classes. FDCs have greatly advanced HIV treatment by allowing simplification of dosing and reduction of pill burden. However, close adherence to daily prescribed treatment is essential to achieve and maintain viral suppression and prevent emergence of viral resistance mutations [Orrell, 2017].

Although combination ART has significantly reduced AIDS-related morbidity and mortality, treatment failure and drug resistance continue to impact treated HIV-infected people. Factors contributing to these less optimal outcomes include inadequate adherence to life-long daily therapy, pre-existing or acquired drug resistance, DDIs leading to sub-therapeutic concentration of ARV medication, and drug toxicities, both short and long-term. Among regimens of comparable efficacy, physicians and HIV-1-infected patients who receive ART, rate total pill burden, dosing frequency, and safety concerns among the greatest obstacles to achieving full adherence.

Furthermore, patients in their adolescence and patients with mental illness, homelessness, drug abuse or major life events face substantial adherence challenges. Even with convenient oral single tablet regimens, patients remain burdened by daily reminders of their HIV infection. Additionally, for some patients, pill packs within the patient's home and personal environment may be associated with stigma. More discreet treatment options may avoid stigma associated with daily oral therapy. Consequently, there continues to be a medical need for the development of novel ARV agents and new approaches to improve therapy compliance.

An injectable, long-acting, 2-drug regimen for the treatment of HIV-1 addresses some of the treatment issues patients infected with HIV are currently facing. The option for monthly or every 2 months dosing with the CAB + RPV injectable regimen provides a durable therapy that is expected to improve adherence and treatment satisfaction.

6.2. Benefits of CAB + RPV in the Treatment of HIV-1 Infection

New therapeutic options that combine potency, tolerability and ease of use are needed for all sectors of the HIV population. There is substantial evidence in the literature that supports the benefit of streamlined treatment regimens. Further, data indicate that patients prefer less frequent dosing; adherence benefits are important given that HIV is a life-long, incurable infection.

RPV, when used with CAB in a 2-drug, NRTI-sparing regimen, is intended for the long-term treatment of HIV-1 infection. RPV is an NNRTI, currently already marketed as an oral formulation

with a proven efficacy and well-established safety profile. Based on the Week 48 data from the 2 large pivotal Phase III clinical studies (201584 and 201585) and the Phase IIIb study 207966, CAB + RPV is an effective maintenance regimen for the treatment of HIV-1 infection. Once-monthly CAB + RPV is non-inferior to daily oral SOC (CAR) therapy in maintaining virologic suppression in HIV-1 infected subjects. The CAB + RPV every 2 months dosing regimen was demonstrated to be non-inferior to the CAB + RPV monthly dosing regimen in study 207966 (Week 48). Across the Phase III/IIIb studies, few cases of CVF were observed and the few discontinuations prior to Week 48 show that the regimen is well tolerated.

RPV, when used in combination with CAB as a 2-drug injectable treatment regimen, has distinct benefits for virologically suppressed HIV-1 infected patients:

- Subjects on the every 2 months dosing regimen maintained HIV-1 suppression comparable to those on the monthly dosing regimen. Subjects on the monthly dosing regimen maintained HIV-1 suppression comparable to those on their SOC regimen.
- CAB + RPV targets HIV replication at both the early and the late stage of the virus lifecycle resulting in durable maintenance of viral suppression with a low risk of HIV-1 RNA ≥50 c/mL.
- CAB + RPV can be administered on an infrequent basis (eg. monthly or every 2 months), may improve adherence to therapy, and may extend opportunities for therapeutic intervention to underserved patient populations. Since CAB + RPV is administered as a directly observed therapy, there is an increased possibility that patients will be fully compliant with the regimen. Infrequent discreet dosing provides relief for patients from the daily reminders of their HIV infection, thereby helping to avoid stigma.
- After the OLI, monthly injections eliminate the need for daily oral dosing. Therefore, the CAB + RPV regimen offers far fewer reminders of disease status; maintenance therapy may entail 6 or 12 dosing visits per year compared with daily dosing with oral SOC.
- RPV has limited DDI liabilities, enabling co-dosing with many commonly used medications. Only potent CYP3A4 enzyme activity inducers will be contraindicated for dosing concurrently with RPV LA.
- Compliance with the scheduled visit windows was high in all Phase III/IIIb studies. Dosing flexibility is inherent to the dosing schedule, with allowable windows of ±7 days from the target injection date. Under exceptional circumstances, oral once daily treatment with CAB + RPV can be used as oral therapy for short periods of time to cover planned pauses in IM dosing (eg, due to travel). Oral therapy can be used in place of 1 every 2 months injection visit or 2 monthly injection visits, and the overall time since the last dose will determine how LA dosing should be resumed, which should be done as soon as possible and as recommended.
- CAB + RPV is as effective in subjects who have just recently achieved a suppressed viral load (median 16 weeks suppressed in study 201584) as it is in subjects whose viral suppression is much longer (median 4.3 years on therapy in study 201585). Rates of HIV-1 RNA ≥50 c/mL at Week 48 per the Snapshot algorithm were similar between study 201584 (2.1% on CAB + RPV and 2.5% on CAR) and study 201585 (1.6% and 1.0%), suggesting that the duration of SOC ART prior to the initiation of monthly CAB + RPV does not impact virologic non-response rates overall.

- Low risk of CVF (n=7) with the use of this novel LA 2-drug regimen was identified in studies 201584 and 201585. Low rates of phenotypic drug resistance were observed: RPV (5/591 [0.8%]), CAB (4/591 [0.7%]), and 2-drug resistance (3/591 [0.5%]) among CVFs. In study 207966, protocol-defined CVF occurred in <1% of subjects overall (8 subjects [1.5%] in Q8W and 2 subjects [0.4%] in Q4W) through Week 48 (including subjects with dosing beyond Week 48). In vitro phenotypic RPV resistance was present in 9 subjects and 4 subjects had CAB resistance. Based on results from these studies, multi-class treatment options exist for subjects who fail with ART resistance. Results from post hoc multivariable and baseline factors analyses demonstrate that CVF is an infrequent multifactorial event, with a rate of ~1% in the LA arms across the 3 Phase III and IIIb studies (201584, 201585, and 207966) through Week 48. Rilpivirine C_{trough} (4 weeks following initial injection dose [per halving concentration]), archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and higher BMI ($\geq$30 kg/m^2) had a statistically significant association with virologic failure. Regardless of the presence of these factors, a high proportion of subjects continued to maintain viral suppression (94%), and no baseline factor (archived RPV RAMs at Baseline, HIV-1 Subtype A6/A1, and higher BMI) when present in isolation was predictive of virologic failure.
- Overall, the Phase III/IIIb studies included a high percentage of female subjects (approximately 27% of subjects across studies). Results in women and men were consistent, suggesting that the CAB + RPV regimen is suitable for both females and males.
- Results from the Phase III/IIIb studies suggest CAB + RPV is an effective and well tolerated regimen in individuals >50 years of age (ie, no evidence of poorer tolerability or reduced efficacy in older compared with younger adults). CAB + RPV is an NRTI-sparing regimen that has a number of features that could be considered to favor use in older individuals with medical co-morbidities or who may be receiving multiple other medications, which include reduced oral pill burden and food requirements, limited DDI, favorable safety profile, and enhanced ART dosing compliance.
- Given the high treatment satisfaction with and preference for the CAB + RPV regimen in Phase III/IIIb studies, continued treatment adherence and durable viral suppression can be anticipated beyond the trial context. Subjects on the every 2 months dosing regimen expressed a high rate of preference for this regimen compared with subjects on the monthly dosing regimen.

6.3. Risks of CAB + RPV in the Treatment of HIV-1 Infection

Clinical studies have shown that there are no clinically significant interactions between CAB and RPV. There are no shared metabolism pathways between CAB and RPV, and no common target organs were identified in respective nonclinical studies. As such, there are no pharmacologic data that would predict increased safety risk for the combination of CAB + RPV beyond those effects associated with the individual components.

Overall, 2,141 subjects were exposed to CAB + RPV (oral and/or LA) during ViiV sponsored HIV treatment clinical studies in Phase II and Phase III/IIIb (LA116482, 200056, 201584, 201585, 207966) as of [redacted] 20[redacted].

The main risks for considerations when prescribing RPV, when used in combination with CAB, are:

- ISRs were very common (84%) with the first dose of IM RPV and decreased in frequency with continued dosing. The majority of ISRs consisted of mild to moderate pain/discomfort localized to the injection site and were short lived. Significant episodes of pain were uncommon (no Grade 4). Discontinuations due to ISRs were infrequent (1%). The use of acetaminophen or NSAIDs may be beneficial in ameliorating symptoms occurring post injection.
- Plasma concentrations of RPV may persist for longer than 1 year in some patients after administration of the last IM dose. Following discontinuation of RPV for any reason, patients should be initiated on active SOC to minimize the risk of emergent viral resistance to RPV.
- Post-injection reactions were reported with RPV injections in 4 subjects in studies 207966 and 200056. Three of these events appear to have been associated with inadvertent (partial) IV injection. All events began to improve within minutes after the injection and resolved without sequelae. These types of events were not observed in any of the other clinical studies and the Sponsor expects these to be very rare occurrences.
- Neuropsychiatric events, including anxiety, depression, sleep disorders, mood disorders, and suicidal ideation and behavior, have been observed with CAB + RPV treatment. The highest incidence of events observed were in the categories of depression, anxiety, and sleep disorders.

6.4. Benefit-risk Assessment

The efficacy and safety data presented in this application for RPV LA support a favorable benefit-risk profile when used monthly or every 2 months as part of a 2-drug regimen in combination with CAB in the proposed indication.

CAB + RPV dosed monthly was non-inferior to guideline recommended SOC (CAR) in maintaining HIV-1 suppression through Week 48 in the pooled analysis and in each of the pivotal Phase III studies (201584 and 201585). Study 207966 demonstrated that every 2 months dosing is non-inferior to monthly dosing.

CAB + RPV was not found to increase risk of plasma HIV-1 RNA ≥50 c/mL in studies 201584 and 201585 compared with CAR. Every 2 months dosing was comparable to monthly dosing with respect to the primary efficacy endpoint of plasma HIV-1 RNA ≥50 c/mL in study 207966. The number of subjects on CAB + RPV with CVF and resistance was low in all Phase III/IIIb studies.

There are no expected additive or synergistic effects on the safety profile in patients taking CAB + RPV beyond those effects associated with the individual components.

The CAB + RPV monthly or every 2 months dosing regimen provides an acceptable safety profile and efficacious treatment option for patients living with HIV-1. The majority of ARs have not been treatment limiting and injection tolerability has overall been acceptable, with few discontinuations.

The safety profile of RPV LA in studies 201584, 201585, and 207966 is consistent with the established safety profile for EDURANT as evaluated in its clinical program and during the post-marketing period, with the exception of ISRs associated with the injectable formulation.

The CAB + RPV monthly or every 2 months dosing regimen is expected to provide greater treatment satisfaction and improved adherence to treatment in virologically suppressed patients due to less frequent dosing. Improved overall satisfaction with the regimen may result in increased patient compliance, especially in patients who have challenges with daily oral dosing, and as a more convenient alternative to oral therapy. Overall, the anticipated risks are considered manageable and therefore supportive of a positive benefit/risk balance. The data presented in this application support a favorable risk-benefit profile for the 2-drug CAB + RPV monthly or every 2 months dosing regimen in the indicated HIV-1 infected population.

Based on totality of clinical data to date, the anticipated risks are considered manageable and therefore supportive of an overall positive benefit-risk balance for RPV LA.

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