Module 2.7.1

Summary of Biopharmaceutic Studies and Associated Analytical Methods

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5. APPENDIX 42

ABBREVIATIONS

APCI	Atmospheric Pressure Chemical Ionization
ARV	Antiretroviral
AUC	Area under concentration-time curve
AUC(0-∞)	AUC from time zero (pre-dose) extrapolated to infinite time
AUC(0-t)	AUC from time zero (pre-dose) to last time of quantifiable concentration
BA	Bioavailability
BCS	Biopharmaceutical Classification System
BST	Bioanalytical Sciences and Toxicokinetics
C24	Drug concentration at 24 hours post-dose
CI	Confidence interval
Cmax	Maximum observed concentration
CV	Coefficient of variance
CVw%	Within-subject coefficients of variation
DCM	Dichloromethane
DCS	Developability Classification System
DMPK	Drug Metabolism and Pharmacokinetics
DTG	Dolutegravir, TIVICAY
DTG/RPV FDC	DTG/RPV 50 mg/25 mg FDC
DTG/RPV Tablets	DTG and RPV Tablets, 50 mg/25 mg
EDTA	Ethylenediaminetetraacetic acid
EFV	Efavirenz
EU	European Union
FaSSIF	Fasted state simulated intestinal fluid
FDC	Fixed-dose combination
GLS	Geometric Least-Squares
GSK	GlaxoSmithKline
h or hr	Hour(s)
HCl	Hydrochloric acid
HIV	Human immunodeficiency virus
HPLC-MS/MS	High-performance liquid chromatography with tandem mass spectrometric detection
INSTI	Integrase strand transfer inhibitor
IV	Intravenous
kg	Kilogram
kp	Kilopascal
λz	Apparent elimination rate constant
LLQ	Lower limit of quantitation
M	Molar
MeOH	Methyl alcohol
mL	Milliliter(s)
MPa	Megapascal
ng	Nanogram(s)

NNRTI	Non-nucleoside HIV-1 reverse transcriptase inhibitor
nm	Nanometer(s)
NVP	Nevirapine
PK	Pharmacokinetic
QC	Quality control
q.s.	As much as suffices
%RSD	Percentage relative standard deviation
RBA	Relative bioavailability
RNA	Ribonucleic acid
RPV	Rilpivirine, EDURANT
RTP	Research Triangle Park
SDS	Sodium dodecyl sulfate
SE	Single entity
SLAD	Solubility limited absorbable dose
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
tlast	Time of last quantifiable concentration
tmax	Time of occurrence of Cmax
µg	Microgram(s)
US	United States

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1. BACKGROUND AND OVERVIEW

Dolutegravir (TIVICAY™, GSK1349572), a HIV INSTI, and RPV (TMC278, EDURANT, GSK3365791), a NNRTI, are currently under clinical development as a FDC tablet. Both DTG and RPV are commercially available products in many markets worldwide. TIVICAY (DTG) Tablets, 50 mg are available in over 85 countries, including the US, EU, and Canada. Dolutegravir was developed by GSK on behalf of ViiV Healthcare. EDURANT (RPV) Tablets, 25 mg have been approved for the treatment of HIV-1 infection in ARV treatment-naïve adult patients in over 85 countries including the US, EU, and Canada. In most countries, the indication is further restricted to patients with plasma viral load ≤100,000 c/mL. RPV was developed by Janssen Sciences Ireland UC. The new formulation being developed is a FDC of DTG/RPV 50 mg/25 mg with a proposed indication for the treatment of HIV-1 infection in virologically-suppressed (HIV-1 RNA <50 c/mL) adults without known or suspected resistance to either ARV component. The proposed recommended oral dose for adults is 1 tablet administered once daily with a meal.

This document summarizes the relevant biopharmaceutical characteristics of the FDC consisting of DTG/RPV 50 mg/25 mg referred to as DTG/RPV FDC and the SEs DTG and RPV.

1.1. Organization of Data

All data pertaining to the DTG/RPV FDC development is considered pivotal and is presented with this application. Where no studies have been performed with DTG and RPV, additional previously submitted studies from DTG or RPV SE development programs support this application and are categorized as “key” studies or “supportive” studies:

Supportive SE Studies: these studies are not essential for the FDC Benefit Risk assessment, but are considered helpful to the reviewer and supportive of the proposed indication. A summary of supportive studies is presented in Table 1, but reports will be made available upon request for the convenience of the reviewer.

Information on the DTG/RPV FDC includes data from the following studies:

- The pivotal bioequivalence Study (201676) completed for the DTG/RPV FDC (Section 2.1);
- The RBA Study (201674) completed for the DTG/RPV FDC (Section 2.3); and
- The impact of food on the systemic exposure of DTG and RPV for DTG/RPV FDC formulations (RBA study 201674 Section 2.4).

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 1 Summary of Completed Biopharmaceutic Studies that were Previously Submitted as Part of the TIVICAY or EDURANT Registration and are "Supportive" to the DTG/RPV FDC Submission

Study	Study Title	Main Conclusions
Bioequivalence and Bioavailability		
ING113674 (DTG) GlaxoSmithKline Document Number: 2010N105142_00 Status: Complete	RBA study of three different tablet formulations of GSK1349572 50 mg and the dose proportionality of and effect of food on the selected formulation in healthy male and female volunteers	Results of the analysis showed that the 2 test tablet formulations (AW and AX) met the criteria for bioequivalence with the reference (Phase IIb) tablet formulation. Plasma DTG AUC(0-∞) increased by 33%, 41%, and 66% when AW tablets were administered with low-fat, moderate-fat, and high-fat food, respectively. Plasma DTG Cmax increased by 46%, 52%, and 67% when the AW tablets were administered with low-fat, moderate-fat, and high-fat food, respectively. Tmax increased with increasing fat content and median values were 2.0, 3.0, 4.0, and 5.0 hours for fasting, low-fat, moderate-fat, and high-fat meals, respectively. The increased exposure with food is not considered clinically significant based on the accumulated safety data in Phase IIb and III studies which permitted DTG dosing without restriction to food or food content.
TMC278-TiDP6-C137 (RPV) Status: Complete	Phase I, randomized, open-label, 4-way crossover, single dose study investigating the effect of different types of meals on the oral BA of RPV after a single dose of 75 mg, formulated as the Phase III tablet	Administration of RPV under fasted conditions decreased RPV AUC(0-∞) by 41% and Cmax by 46%. Administration of RPV after a high-fat breakfast or after a standard breakfast resulted in similar exposures. Administration of RPV with only a protein-rich nutritional drink decreased RPV AUC(0-∞) by 49% and Cmax by 50% compared with a standard meal.

1.2. Main Biopharmaceutical Findings

The conclusions from the DTG/RPV FDC biopharmaceutic evaluations are as follows:

- Bioequivalence was confirmed in terms of systemic exposure of both DTG and RPV for the FDC tablet formulation of DTG/RPV 50 mg/25 mg compared with separate tablet formulations of DTG 50 mg + RPV 25 mg when administered with a moderate-fat meal.
- DTG/RPV FDC should be taken with a meal. Taking DTG/RPV FDC in a fasted condition or with only a protein-rich nutritional drink may result in decreased plasma concentrations of RPV, which could potentially reduce the therapeutic effect of DTG/RPV FDC. This is consistent with the prescribing instructions for RPV to be administered with a meal.
- The bioanalytical methods used to measure concentrations of DTG in human plasma, in the presence of RPV, and RPV in the presence of DTG, were selective, accurate, and reproducible.

1.3. Dolutegravir/Rilpivirine Fixed-dose Combination

1.3.1. Formulation Development

The development of the formulation for DTG and RPV Tablets, 50 mg/25 mg (hereafter referred to as DTG/RPV FDC) was based on [redacted].

[redacted], film coated with a cosmetic pink film coat, were developed for characterization in PK studies.

As stated above, [redacted] for all formulations used in PK studies is the same [redacted]. For the [redacted], several formulations were characterized. Some of the formulations used [redacted] The other formulations used in PK studies used [redacted].

The initial study to characterize the PK for these formulations was Study 201674. A summary of the formulations used in that study is shown in Table 2 and the complete statements of the components and quantitative composition of DTG/RPV FDC are presented in Table 3, Table 4, Table 5, Table 6, and Table 7.

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Table 2 Summary of Formulations Used in Study 201674

	Formulation 1 (AK)	Formulation 2 (AM)	Formulation 4 (AQ)	Formulation 5 (AS)	Formulation 6 (AU)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

Formulations 1, 2, 4, and 5 were used in Part 1 of the study. Formulations 1, 2, and an additional formulation 6 were selected for further characterization in Part 2 of the study (see Section 2.3 for details on the RBA Study 201674).

Table 3 Composition of DTG/RPV FDC, Formulation 1 (Product Code AK)

Component	Quantity (mg/tab)	Function	Reference to Standard
[redacted]			
Dolutegravir Sodium	52.62[a]	Active	[redacted]
D-mannitol	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][c]	[redacted]	[redacted]
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Sodium Stearyl Fumarate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]			
Rilpivirine Hydrochloride	27.50[b]	Active	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Polysorbate 20	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][c]	[redacted]	[redacted]
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted][d]	Film Coat	[redacted]
[redacted]	[redacted][c]	[redacted]	[redacted]
Total Coated Tablet Weight	**515.00**	-	-

a. Equivalent to 50 mg DTG free acid. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
b. Equivalent to 25 mg RPV free base. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
c. [redacted]
d. [redacted]

Table 4 Composition of DTG/RPV FDC, Formulation 2 (Product Code AM)

Component	Quantity (mg/tab)	Function	Reference to Standard
[redacted]			
Dolutegravir Sodium	52.62[a]	Active	[redacted]
D-mannitol	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Sodium Stearyl Fumarate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]			
Rilpivirine Hydrochloride	27.52[c]	Active	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Polysorbate 20	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
D-mannitol	[redacted]	[redacted]	[redacted]
Silicified Microcrystalline cellulose	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted][d]	Film Coat	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
Total Coated Tablet Weight	**515.00**	**-**	**-**

a. Equivalent to 50 mg DTG free acid. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
b. [redacted]
c. Equivalent to 25 mg RPV free base. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
d. [redacted]

Table 5 Composition of DTG/RPV FDC, Formulation 4 (Product Code AQ)

Component	Quantity (mg/tab)	Function	Reference to Standard
[redacted]			
Dolutegravir Sodium	52.62[a]	Active	[redacted]
D-mannitol	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Sodium Stearyl Fumarate	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
Rilpivirine Hydrochloride	27.50[b]	Active	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Polysorbate 20	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][c]		
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted][d]	Film Coat	[redacted]
[redacted]	[redacted][c]	[redacted]	[redacted]
Total Coated Tablet Weight	**422.30**	-	-

a. Equivalent to 50 mg DTG free acid. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
b. Equivalent to 25 mg RPV free base. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
c. [redacted]
d. [redacted]

Table 6 Composition of DTG/RPV FDC, Formulation 5 (Product Code AS)

Component	Quantity (mg/tab)	Function	Reference to Standard
[redacted]			
Dolutegravir Sodium	52.62[a]	Active	[redacted]
D-mannitol	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted][b]	[redacted]	[redacted]
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Sodium Stearyl Fumarate	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]			
Rilpivirine Hydrochloride	27.52[c]	Active	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Polysorbate 20	[redacted][b]	[redacted]	[redacted]
[redacted]			
Silicified Microcrystalline cellulose	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			
[redacted]	[redacted][d] [redacted][b]	Film Coat [redacted]	[redacted]
Total Coated Tablet Weight	**422.30**	**-**	**-**

a. Equivalent to 50 mg DTG free acid. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
b. [redacted]
c. Equivalent to 25 mg RPV free base. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
d. [redacted]

Table 7 Composition of DTG/RPV FDC, Formulation 6 (Product Code AU)

Component	Quantity (mg/tab)	Function	Reference to Standard
[redacted]			
Dolutegravir Sodium	52.62[a]	Active	[redacted]
D-mannitol	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Sodium Stearyl Fumarate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]			
Rilpivirine Hydrochloride	27.50[c]	Active	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Polysorbate 20	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
[redacted]			
Silicified Microcrystalline cellulose	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
[redacted][d]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][e]	Film Coat	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
Total Coated Tablet Weight	**422.30**	**-**	**-**

a. Equivalent to 50 mg DTG free acid. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
b. [redacted]
c. Equivalent to 25 mg RPV free base. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
d. [redacted]
e. [redacted]

The data obtained in Part 1 of Study 201674 (Section 2.3.1.1) showed that in the high-fat fed state, all 4 test formulations (AK, AM, AS, AQ) had similar BA to the reference DTG clinical image Tablets, 50 mg (Note: the DTG clinical image tablets are identical to TIVICAY Tablets, 50 mg except for slight differences in [redacted]) and commercial EDURANT Tablets, 25 mg.

Part 2 of the study (Section 2.4.1.1) showed that in the fasted state, the test formulations (AK, AM, AU) had similar BA to the reference TIVICAY Tablets, 50 mg and EDURANT Tablets, 25 mg. Results were similar in a moderate-fat fed state where all formulations showed similar BA to the reference TIVICAY Tablets, 50 mg and EDURANT Tablets, 25 mg.

The results of the RBA Study 201674 did not differentiate any of the 5 DTG/RPV FDC formulations tested. Following a final assessment of the formulation approaches ([redacted]), the decision was taken to maintain similarity with [redacted]. Therefore, [redacted] was selected over the formula and manufacturing process of [redacted]. Furthermore, the formulation [redacted]. Therefore, Formulation 2 (Table 2) was selected for the pivotal bioequivalence study and commercialization.

A very minor adjustment to the master formula (related to the number of decimal places used) was made to the formulation then taken forward. The film coat was also changed to that selected for the commercial product. These changes are reflected in Table 8, which shows the final pivotal/proposed commercial formulation used in the bioequivalence Study 201676. These minor modifications were not expected to change the biopharmaceutical characteristics of the tablet including BA in the presence of food, as demonstrated in Study 201674.

Table 8 Composition of DTG/RPV FDC, (Product Code AW)

Component	Quantity (mg/tab)	Function	Reference to Standard
[redacted]			
Dolutegravir Sodium	52.62[a]	Active	[redacted]
D-mannitol	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
[redacted]			
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Sodium Stearyl Fumarate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]			
Rilpivirine Hydrochloride	27.50[c]	Active	[redacted]
Lactose monohydrate	[redacted]	[redacted]	[redacted]
Croscarmellose sodium	[redacted]	[redacted]	[redacted]
Povidone [redacted]	[redacted]	[redacted]	[redacted]
Polysorbate 20	[redacted]	[redacted]	[redacted]
[redacted]	[redacted][b]	[redacted]	[redacted]
[redacted]			
D-mannitol	[redacted]	[redacted]	[redacted]
Silicified Microcrystalline cellulose	[redacted]	[redacted]	[redacted]
Sodium Starch Glycolate	[redacted]	[redacted]	[redacted]
Magnesium stearate	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]		
[redacted]	[redacted]		
[redacted]	[redacted][d] [redacted][b]	Film Coat [redacted]	[redacted]
Total Coated Tablet Weight	**515.00**	**-**	**-**

a. Equivalent to 50 mg DTG free acid. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
b. [redacted]
c. Equivalent to 25 mg RPV free base. Actual amount may vary based on the purity and water content factor for each batch of drug substance.
d. [redacted]

Study 201676 (Section 2.1.1.1) demonstrated the bioequivalence of formulation AW (possesses minor compositional changes compared with the formulation AM used in Study 201674) to the single agent reference products TIVICAY Tablets, 50 mg and EDURANT Tablets, 25 mg in the presence of a moderate-fat meal. Therefore, this formulation is proposed as the commercial formulation for the DTG/RPV FDC.

1.3.2. In Vitro Dissolution Data

In vitro dissolution testing was performed on all batches of tablets used in the BA Study 201674 and bioequivalence Study 201676. Dissolution results and a summary of the method and conditions used for the DTG/RPV FDC used in the bioequivalence study are presented in this section.

The dissolution conditions used are shown in Table 9.

Table 9 Dissolution Conditions for the Bioequivalence Study

Apparatus	[redacted]
Medium	
Volume	
Paddle Speed	
Temperature	

Dissolution profiles for the batch of the DTG/RPV FDC used in the bioequivalence Study 201676 are shown in Figure 1 for DTG and Figure 2 for RPV. Tabulated results are presented in Table 10.

Figure 1 Dissolution Profile of DTG in DTG/RPV FDC Batch 121363956 (n=12) Used in Bioequivalence Study 201676

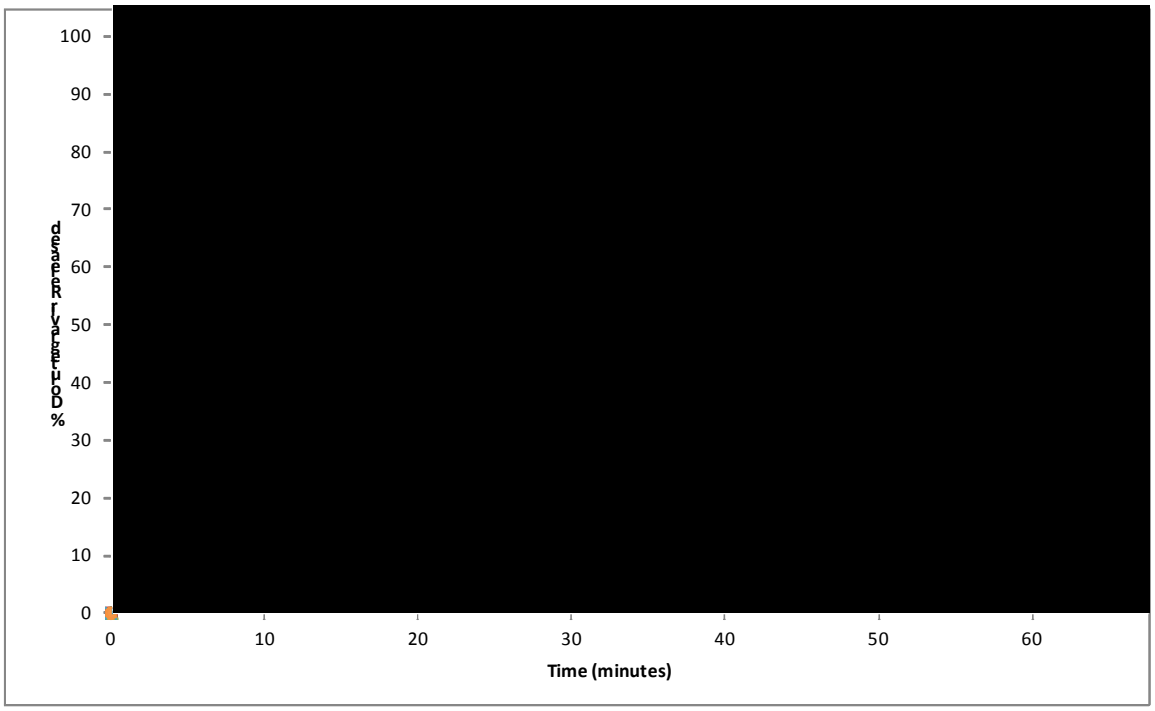


Figure 2 Dissolution Profile of RPV in DTG/RPV FDC Batch 121363956 (n=12) Used in Bioequivalence Study 201676

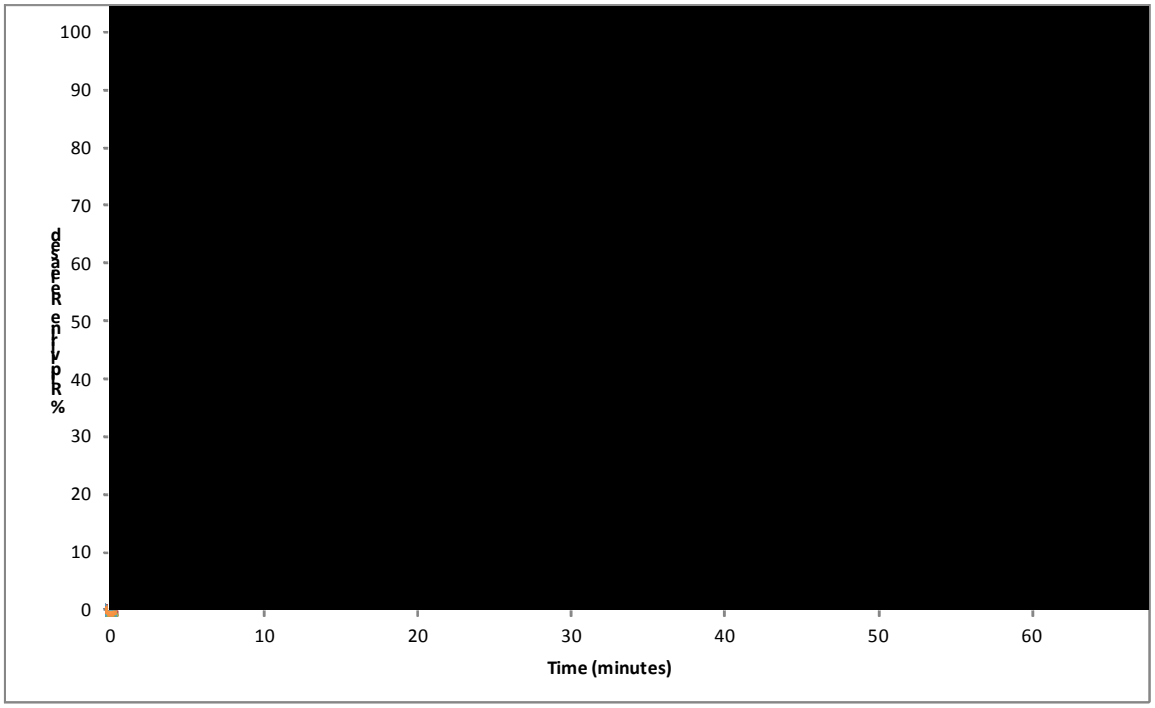


Table 10 Dissolution Results for DTG/RPV FDC Batch 121363956 Used in Bioequivalence Study 201676

Tablet	% Dissolved													
	DTG 50 mg							RPV 25 mg						
	10 min	15 min	25 min	30 min	40 min	45 min	60 min	10 min	15 min	25 min	30 min	40 min	45 min	60 min
1	[redacted]													
2														
3														
4														
5														
6														
7														
8														
9														
10														
11														
12														
Mean														
Min														
Max														
%RSD														

Complete dissolution of the DTG/RPV FDC within the predefined specification by test methods is consistent with the results from the in vivo pivotal bioequivalence Study 201676.

As discussed in Section 1.3.1, Formulation 2 (product code: AM) was selected for progression into the bioequivalence Study 201676. A very minor adjustment to the master formula and the film coat was made (giving product code: AW). These minor modifications were not expected to change the biopharmaceutical characteristics of the tablet including bioavailability in the presence of food and were expected to give comparable release by dissolution with mean profiles presented in Figure 3 and Figure 4 and data presented in Table 11.

Figure 3 Dissolution Profile Showing the Mean Release of Dolutegravir from the Pivotal Bioequivalence Batch (Product Code AW) Against Product Code AM

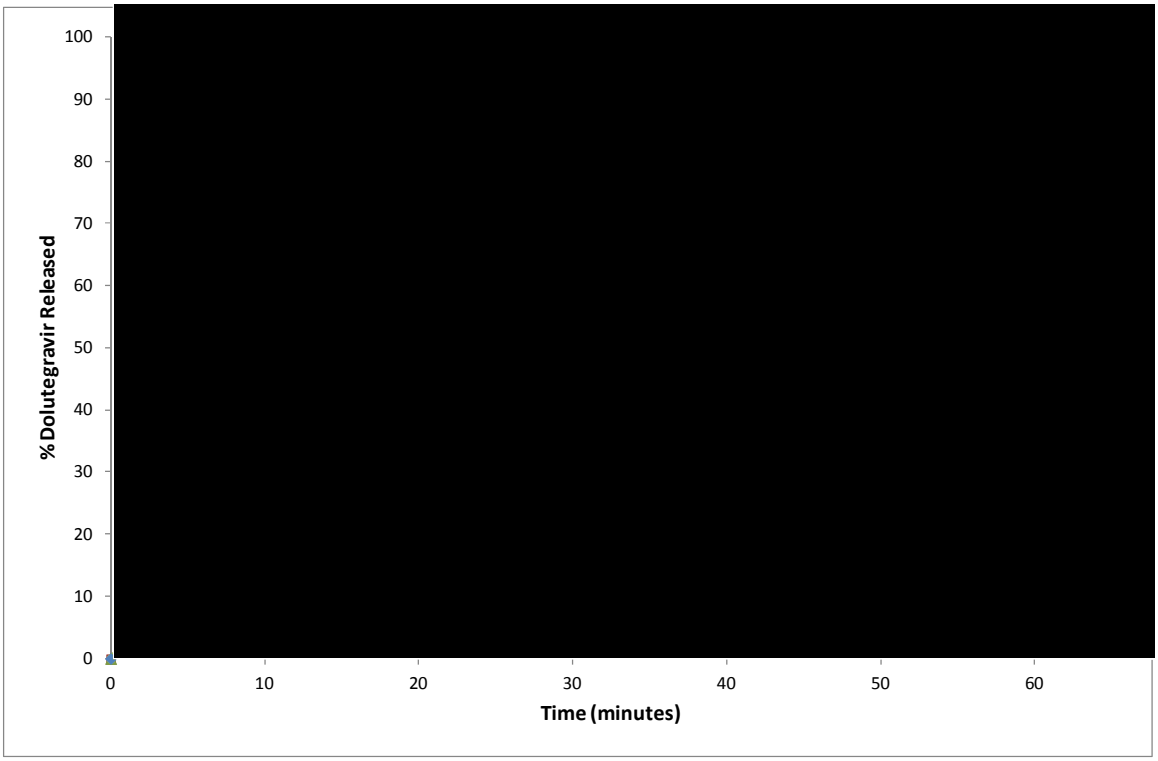


Figure 4 Dissolution Profile Showing the Mean Release of Rilpivirine from the Pivotal Bioequivalence Batch (Product Code AW) Against Product Code AM

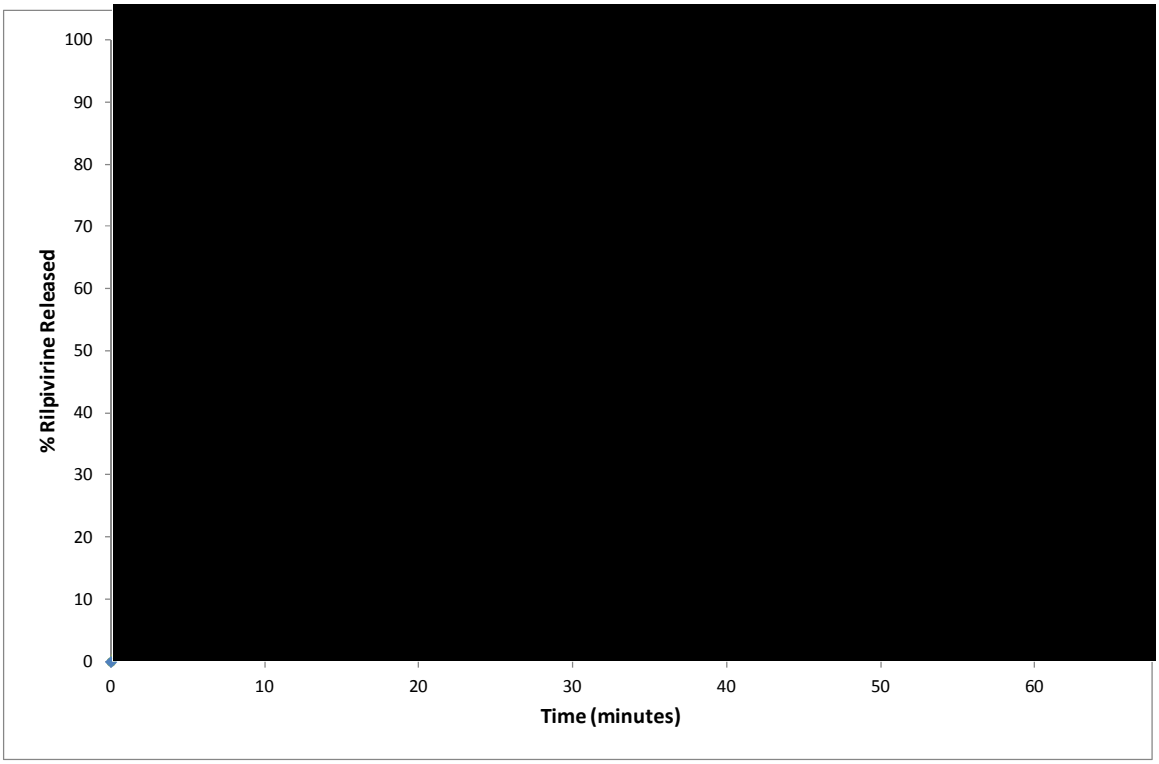


Table 11 Dissolution Results for DTG/RPV Tablet Pivotal Bioequivalence Batch (Product code AW) against Product Code AM

Batch		% Dissolved															
		DTG 50 mg								RPV 25 mg							
		5 min	10 min	15 min	25 min	30 min	40 min	45 min	60 min	5 min	10 min	15 min	25 min	30 min	40 min	45 min	60 min
R759861	Mean	[redacted]															
	Min																
	Max																
	%RSD																
R705839	Mean																
	Min																
	Max																
	%RSD																

1.3.3. Tablet Shape Modification from Pivotal Bioequivalence to Commercial Image

A slight change to the tablet shape was made between the product used in the Study 201676 and that proposed for the final commercial image. This change was [redacted]. The length and width of the tablet (14.1 mm × 7.05 mm) and the debossing (SV 3JT) were unchanged between the product used in the Study 201676 and that proposed for the final commercial image. This slight change in tablet [redacted] is not expected to have any impact on in vivo performance as supported by the dissolution data shown in Figure 5 (DTG), Figure 6 (RPV), and Table 12. These graphs compare the dissolution profiles (method conditions as shown in Table 9) for the pivotal bioequivalence/primary stability batch and 2 other primary stability batches with a representative batch made using the commercial image. In all cases, the data shown are for the uncoated tablet cores (to show the effect at compression without any film coat present) made at the target hardness [redacted] kp). As can be seen, the change in tablet [redacted] has not impacted the dissolution profiles for either DTG or RPV.

Figure 5 Dissolution Profile Showing the Mean Release of Dolutegravir from the Primary Stability/Pivotal Bioequivalence Batches and Batch R786987 (Commercial Image) at Target Tensile Strength

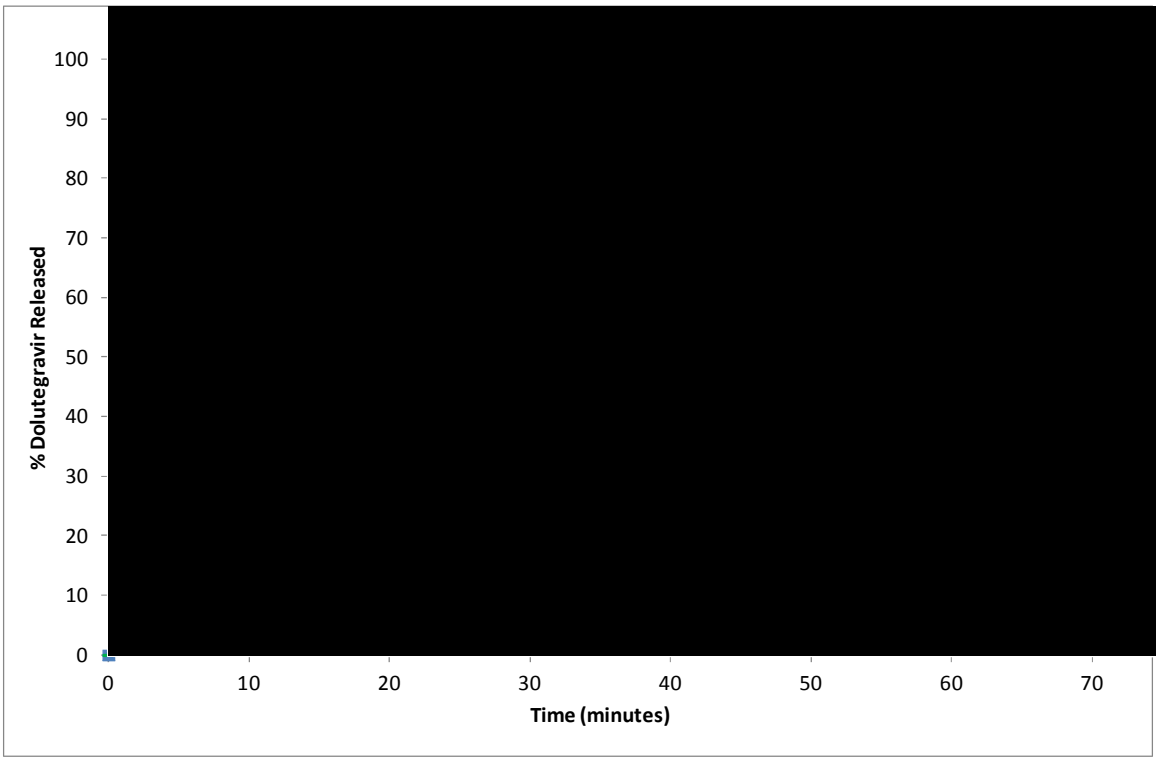


Figure 6 Dissolution Profile Showing the Mean Release of Rilpivirine from the Primary Stability/Pivotal Bioequivalence Batches and Batch R786987 (Commercial Image) at Target Tensile Strength

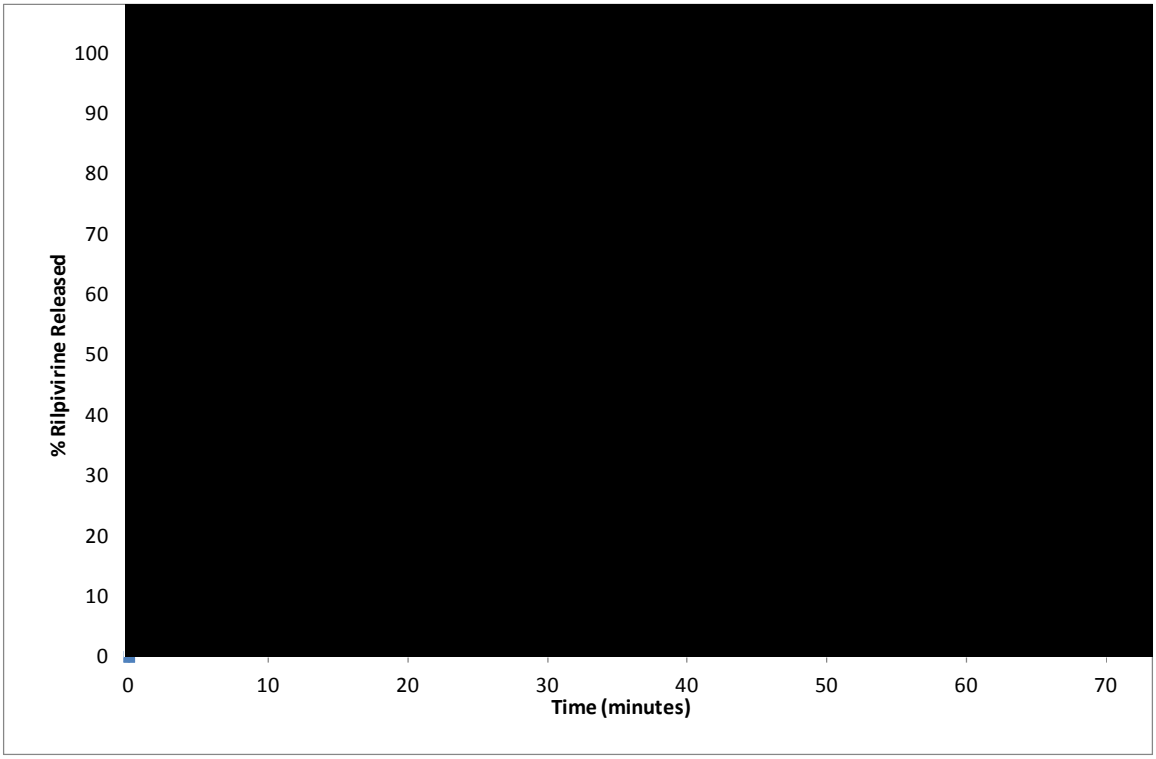


Table 12 Dissolution Results for DTG/RPV Tablet Primary Stability/Pivotal Bioequivalence Batches and Batch R786987 (Commercial Image) at Target Tensile Strength

Batch		% Dissolved													
		DTG 50 mg							RPV 25 mg						
		10 min	15 min	25 min	30 min	40 min	45 min	60 min	10 min	15 min	25 min	30 min	40 min	45 min	60 min
R758571	Mean	[redacted]													
	Min														
	Max														
	%RSD														
R758569	Mean														
	Min														
	Max														
	%RSD														
R757877	Mean														
	Min														
	Max														
	%RSD														
R786987	Mean														
	Min														
	Max														
	%RSD														

1.3.4. Analytical Methods

1.3.4.1. Validation

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

Dolutegravir

The bioanalytical method for the measurement of DTG concentrations in plasma in the presence of RPV was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([$^{2}H_{7}$ ^{15}N]-DTG) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. Following completion of the validation [GlaxoSmithKline Document Number 2012N147635_00], additional precision, accuracy, and stability assessments in the presence of RPV were performed [GlaxoSmithKline Document Number 2015N231443_00] over the concentration range of 20 to 20,000 ng/mL by [redacted]. The DTG method in the presence of RPV was followed to provide analysis of DTG concentrations in plasma samples from studies 201674, 201676, 201636, and 201637.

Rilpivirine

The bioanalytical method [GlaxoSmithKline Document Number 2015N232840_00] for the measurement of RPV concentrations in plasma from Study 201674 was based on liquid/liquid extraction using methanol:dimethylformamide (80:20) containing an isotopically labeled internal standard ([$^{2}H_{6}$]-RPV) followed by HPLC-MS/MS detection using positive ion APCI and multiple reaction monitoring. The method was validated over a range of 0.5 to 250 ng/mL and assessed in the presence of DTG. Since it was noted that RPV converts to its [redacted] under ambient light, additional bioanalytical method testing was performed [GlaxoSmithKline Document Number 2016N270364_00]. It was determined that the separation of RPV from its [redacted] was not achieved by the current method, and although all other checks met the predetermined acceptance criteria, the low QC (1.2 ng/mL) standards stored for at least 24 hours in ambient light failed (at 16.3%) to meet the acceptance criteria of ±15% of theoretical concentration. As a result, it was decided this method [GlaxoSmithKline Document Number 2015N232840_00] would be discontinued and a different method validated using yellow light conditions and monitoring for the RPV [redacted] would be used for Study 201676 (new method discussed below).

The bioanalytical method [GlaxoSmithKline Document Number 2012N144315_00] for the measurement of RPV concentrations in plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ^{13}C d4-TMC278 followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The method was validated over a range of 1 to 2000 ng/mL under yellow light. Further validation (BA10991) was conducted at [redacted] ([redacted], The Netherlands), including testing of

the possible influence of DTG on the RPV analytical method [GlaxoSmithKline Document Number 2017N319704_00]. These experiments showed there was no influence of DTG on the RPV analytical method under yellow light. This method was used in studies 201676, 201636, and 201637.

Efavirenz and Nevirapine

The bioanalytical method for the measurement of EFV and NVP [GlaxoSmithKline Document Number 2016N269537_00] concentrations in plasma was based on supported liquid extraction. EFV and NVP and their internal standards, efavirenz-$^{13}C_6$ and nevirapine-d4, were isolated through supported liquid extraction using a Biotage, Isolute 200-mg SLE+ plate. The final extract was analyzed via HPLC with MS/MS detection using positive ion electrospray. Following completion of the validation, additional analyte stability in frozen matrix and stability of standards in solution data were generated [GlaxoSmithKline Document Number 2017N321175_00]. The EFV and NVP method was followed to provide analysis of EFV and NVP concentrations in plasma samples from studies 201636 and 201637.

1.3.4.2. Summary of within study quality control sample analysis for dolutegravir/rilpivirine fixed-dose combination studies

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

The overall precision (%CV) and accuracy (%Bias) of the DTG assays for Study 201674 and Study 201676 are shown in Appendix Table 4. The between-run precision for DTG in Study 201674 and Study 201676 ranged from 6.19% to 9.35% and 3.21% to 7.61% with a bias that ranged from 0.0969% to 1.32% and -3.59% to 0.870% for each study, respectively. The overall precision and accuracy of the RPV assays for Study 201674 and 201676 are shown in Appendix Table 5. The between-run precision for RPV in Study 201674 and Study 201676 ranged from 3.21% to 7.46% and 2.6% to 6.0% with a bias that ranged from 0.786% to 1.17% and -1.3% to 0.0% for each study, respectively.

For Study 201636 and Study 201637, the overall precision and accuracy are presented in Appendix Table 4 for DTG assays, Appendix Table 5 for RPV assays, Appendix Table 6 for EFV assays, and Appendix Table 7 for NVP assays.

1.4. Dolutegravir Analytical Methods

This section summarizes the validation and assay performance data for the development of DTG as a SE product.

1.4.1. Validation

The bioanalytical method for the measurement of DTG concentrations in plasma was based on extraction by protein precipitation using acetonitrile containing an isotopically labeled internal standard ([$^{2}H_{7}$ ^{15}N]-DTG) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The method was first validated over a range of 5 to 5000 ng/mL and then was validated at a range of 20 to 20,000 ng/mL to accommodate the higher concentrations of DTG being seen at the clinical dose of 50 mg [GlaxoSmithKline Document Number RD2010/00175/00]. These validations were conducted by the BST Section of Platform Technology and Science DMPK (PTS DMPK), GSK, RTP, North Carolina. The assay was transferred to [redacted], [redacted] and [redacted] and independently validated over the concentration range of 20 to 20,000 ng/mL by [redacted], and [redacted] to provide continuing support.

A summary of the validation data that supported application of the bioanalytical method used for Study ING113674 is presented in Appendix Table 3.

1.4.2. Summary of Within Study Quality Control Sample Analysis for Dolutegravir Studies

Quality control samples were analyzed with each batch of study samples. Performance results of the bioanalytical methods used for each study were generated from bioanalytical runs meeting the same run acceptance criteria based upon the predefined requirements for QC performance that no more than one-third of the QC results and 50% from each QC concentration were to deviate from the nominal concentration by more than 15%. The overall precision (%CV) and accuracy (%Bias) of the DTG assays for ING113674 are shown in Appendix Table 4. The between-run precision for DTG ranged from 3.5% to 4.4% with a bias that ranged from 0.2% to 3.9%

1.5. Rilpivirine Analytical Methods

This section summarizes the validation and assay performance data for the development of RPV as a SE product.

1.5.1. Validation

The bioanalytical method (BA1674) for the measurement of RPV concentrations in plasma was based on extraction by protein precipitation using acetonitrile, with an isotopically-labeled internal standard (TMC278-d4-13C) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and multiple reaction monitoring. The method was validated at [redacted] over a range of 1 to 2000 ng/mL, and additionally, a 100-fold dilution was validated.

For Study TMC278-TiDP6-C137, a method (BA218) was validated at [redacted] over a range of 1 to 2000 ng/mL, and additionally, a 100-fold dilution was validated [GlaxoSmithKline Document Number 2017N323743_00]. It was based on extraction by protein precipitation using acetonitrile, with an isotopically-labeled internal standard (RPV-d4-^{13}C) followed by HPLC-MS/MS analysis with a TurboIonSpray interface and

multiple reaction monitoring. The overall precision and accuracy of the RPV assays for TMC278-TiDP6-C137 are shown in Appendix Table 5. The between-run precision for RPV in Study TMC278-TiDP6-C137 ranged from 5.0% to 7.0% with a bias that ranged from 2.6% to 7.6%.

When RPV is exposed to light, the drug is transformed to another [redacted] ([redacted]), which could have an impact on the data obtained. Therefore, all PK samples in each of the trials were protected from light during processing and storage.

A summary of the validation data that supported application of the bioanalytical methods to each PK study applicable for this submission is summarized in Appendix Table 3. The methods were validated to perform to the same predefined acceptance criteria for precision and accuracy.

1.5.2. Summary of Within Study Quality Control Sample Analysis for Rilpivirine Studies

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

The overall precision (%CV) and accuracy (%Bias) of the RPV assay for Study TMC278-TiDP6-C137 is shown in Appendix Table 5. The between-run precision for RPV in TMC278-TiDP6-C137 ranged from 5.0% to 7.0% with a bias that ranged from 2.6% to 7.6%.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

A tabular summary of the study design, objectives, and treatment arms in each of the biopharmaceutical studies conducted with DTG/RPV FDC, DTG, and RPV formulations are provided in Appendix Table 8, and a tabular summary of the PK data is provided in Appendix Table 9.

2.1. Pivotal Bioequivalence

2.1.1. Dolutegravir/Rilpivirine Fixed-dose Combination

2.1.1.1. Study 201676: Pivotal Bioequivalence Study

Study title: An Open-label, Randomized, Two-Way Crossover, Single Dose, Pivotal Bioequivalence Study of a Fixed-Dose Combination of Dolutegravir and Rilpivirine in Healthy Volunteers

Location of Report: m5.3.1.2

Formulations Used

- DTG/RPV FDC: Formulation AW
- DTG (TIVICAY), RPV (EDURANT) (refer to Section 1.3.3)

Methods: This was a single-center, randomized, open-label, 2-period, single-dose, crossover study in healthy adult subjects. The study was designed to evaluate the pivotal bioequivalence of an oral DTG/RPV 50 mg/25 mg FDC tablet formulation proposed for commercial use compared with co-administration of the separate tablet formulations of DTG 50 mg (clinical trial material image) and EDURANT (RPV 25 mg) with each treatment administered under moderate-fat fed conditions (m2.7.1 from the original TIVICAY submission). The planned sample size was to randomize 86 subjects (to complete 82) based on 28% CVw% of RPV to assess bioequivalence with 90% power. Due to a high CVw% of RPV, a safeguard of sample size re-estimation was installed. During the study, a blinded (i.e., the sequence of dosing for each subject was unknown) sample size re-estimation was performed by an independent party, as a safeguard to evaluate the appropriateness of the assumed PK parameter variability and associated sample size, based on the CVw% of DTG and RPV Cmax actually observed within the study [Golkowski, 2014]. At the time of this re-estimation, 56 subjects had been enrolled, and the actual CVw% estimates for DTG and RPV Cmax were 14.8% and 32.9%, respectively. Based on the higher RPV CVw%, a total of 110 evaluable subjects (i.e., 28 subjects in addition to original 82) would be needed to maintain 90% power. As a result, 32 additional subjects were randomized to account for dropouts and thus 118 subjects in total were enrolled in the study. As the sample size re-estimation estimation was blinded and no formal hypothesis testing was carried out, there were no adjustments for multiplicity or introduction of bias. Each subject received a single dose of study drug in each of 2 treatment periods. There was a washout period of 21 days prior to dosing and between treatments. The follow-up visit occurred 12 to 17 days after the last dose of study drug.

Results: For all four DTG PK parameters derived using actual sampling times, the 90% CIs of the ratios were all contained within (0.80, 1.25) bioequivalence limits (Table 13).

Table 13 Summary of the Statistical Analysis of Log-transformed DTG PK Parameters Based on Actual Sampling Times

PK Parameter	Test vs. Reference[a]	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
C_{max} (μg/mL)	A vs B	113	3.646	113	3.474	1.050	(1.022, 1.078)
AUC(0-t) (μg.h/mL)	A vs B	113	63.583	113	61.265	1.038	(1.011, 1.066)
AUC(0-∞) (μg.h/mL)	A vs B	113	64.968	113	62.655	1.037	(1.010, 1.064)
C24 (μg/mL)[a]	A vs B	112	1.001	112	0.958	1.044	(1.012, 1.077)
	A vs B[a]	113	1.003	112	0.960	1.045	(1.012, 1.078)

Data Source: 201676 In-text Table 9

a. For C24, 1 subject was excluded due to no result for Period 2; in a separate supportive analysis this subject's Period 1 C24 was included.

A = Tablet formulation of DTG/RPV 50 mg/25 mg FDC

B = DTG 50 mg + RPV 25 mg

For all 4 RPV PK parameters derived using actual sampling times, the 90% CIs of the ratios were all contained within (0.80, 1.25) bioequivalence limits (Table 14).

Table 14 Summary of the Statistical Analysis of Log-transformed RPV PK Parameters Based on Actual Sampling Times

PK Parameter	Test vs. Reference[a]	Adjusted Geometric Means				Ratio	90% CI of the Ratio
		n	Test	n	Reference		
C_{max} (µg/mL)	A vs B	113	0.093	113	0.083	1.124	(1.047, 1.207)
AUC(0-t) (µg.h/mL)	A vs B	113	3.062	113	2.767	1.107	(1.042, 1.176)
AUC(0-∞) (µg.h/mL)[a]	A vs B	112	3.248	112	2.933	1.108	(1.045, 1.174)
	A vs B[a]	113	3.254	112	2.936	1.108	(1.046, 1.175)
C24 (µg/mL)	A vs B	113	0.031	113	0.028	1.101	(1.034, 1.173)

Data Source: 201676 In-text Table 11

a. For AUC(0-∞), 1 subject was excluded due to a result "not determined" in Period 1 because AUCextrap>20%, R^2<0.85 in estimation of terminal phase rate constant, and range of time over which t½ calculated was <2 x t½; in a separate supportive analysis this subject's Period 1 AUC(0-∞) was included.

A = DTG/RPV 50 mg/25 mg FDC
B = DTG 50 mg + RPV 25 mg

A post-hoc sensitivity analysis also confirmed the primary analysis results (DTG/RPV FDC is bioequivalent to individual SE tablets, Data Source: 201676, Section 6.4).

Conclusions: Bioequivalence was confirmed in terms of both DTG and RPV for the FDC tablet formulation of DTG/RPV 50 mg/25 mg compared with separate tablet formulations of DTG 50 mg + RPV 25 mg when administered after a moderate-fat meal.

These data provide a PK bridge to the DTG 50 mg + RPV 25 mg regimen used in the Phase III trials, 201636 and 201637, which were conducted with the separate DTG and RPV tablet formulations; the recommended intake in the Phase III studies was with a meal.

2.2. Absolute Bioavailability

2.2.1. Dolutegravir/Rilpivirine Fixed-dose Combination

No absolute (IV/oral) BA studies have been carried out with the DTG/RPV FDC formulation or the SEs due to a lack of IV formulation associated with low solubility of both DTG and RPV.

2.3. Relative Bioavailability

2.3.1. Dolutegravir/Rilpivirine Fixed-dose Combination

2.3.1.1. Study 201674: Relative Bioavailability of Fixed-dose Combinations of Dolutegravir and Rilpivirine

Study Title: A Phase I, 2-Part Relative Oral Bioavailability Study of Different Fixed Dose Combinations of Dolutegravir and Rilpivirine in Fasted and Fed Healthy Subjects

Location of Report: m5.3.1.2

Formulations Used:

- DTG/RPV FDC:
  - Formulations Part 1: AS, AM, AQ, AK
  - Formulations Part 2: AK, AM, AU Part 2 (AS and AU are the same except for the manufacturing site)
- DTG (TIVICAY), RPV (EDURANT) (refer to Section 1.3.3)

Methods: Part 1 of the study was conducted to evaluate the RBA in the fed state of a single dose of DTG 50 mg and RPV 25 mg when administered together in a DTG/RPV FDC compared with the co-administration of a single dose of the SE DTG and RPV products. The study was conducted as a randomized, open-label, 3-way, crossover, incomplete-block, and Youden square design with 6 treatment sequences in a single cohort of 24 subjects. In this design, each of the 4 test formulations was administered with equal frequency across the 3 periods. Each subject received the reference treatment A, 1 dose of DTG 50 mg (clinical image) and RPV 25 mg co-administered as SE tablets, and was randomized to receive single doses of 2 of the 4 (FDC Product Codes: AM, AQ, AK, AS) experimental DTG/RPV FDC over 3 treatment periods (m2.7.1 from the original TIVICAY submission). The reference and test formulations were administered to subjects with a high-fat meal (~900 total calories: 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat).

Part 2 of the study was conducted to evaluate the RBA in the fasted state of a single dose of DTG 50 mg and RPV 25 mg when administered together in a DTG/RPV FDC compared with the co-administration of a single dose of the SE DTG and RPV products. Part 2 was a randomized, open-label, 3-way crossover design in 3 distinct cohorts each with 12 subjects (maximum n=36). Up to 2 formulations from Part 1 and a previously untested 5th formulation were evaluated in Part 2. Subjects in a given cohort were randomized to a specific treatment sequence and received single doses of a given test formulation – 1 dose administered under fasted conditions (10 hours pre-dose to 4 hours post-dose) and 1 dose within 30 minutes of a moderate-fat meal (~625 total calories: 125 calories from protein, 300 calories from carbohydrate, and 200 calories from fat). Each subject also received the reference treatment from Part 1 (a single dose of DTG 50 mg and RPV 25 mg SE tablets) administered under fasted conditions. The food effect results are summarized in Section 2.4.1.1.

Results:

In Part 1, systemic exposure of DTG and RPV following all FDC formulations (AS, AM, AQ, AK) were comparable to exposures following the SE tablets under fed conditions (high-fat meal). The AUC(0-∞), AUC(0-t), and Cmax of DTG following administration of various DTG/RPV FDC formulations ranged from 2% lower to 9% higher (depending on the DTG/RPV FDC formulation) than those of the reference DTG single agent co-administered with RPV (Table 15). The AUC(0-∞) and Cmax of RPV following administration of various DTG/RPV FDC formulations were comparable to or ranged

from 8% lower to 10% higher (depending on the DTG/RPV FDC formulation) than those of the reference RPV single agent co-administered with DTG (Table 16).

The proposed final formulation (AW) for commercial marketing possesses minor compositional changes compared with the formulation AM. The main change was the use of a different but compositionally very similar film coat to achieve the target shade of pink desired for the commercial product. This minor modification is not expected to change biopharmaceutical characteristics of the tablet including BA (see Section 1.3.1).

Table 15 Summary of Plasma Dolutegravir Pharmacokinetic Parameters and Treatment Comparisons to Assess Relative Bioavailability (Fed – High Fat) (Part 1)

Parameter	Comparison Test vs. Reference	Geometric LS Mean		GLS Means Ratio (90% CI)	%CVw
		Test (n=12 or 13)[a]	Reference (n=25)		
AUC(0-t)[b] (μg.h/mL)	AS (Fed) vs. A (Fed)	60.991	60.439	1.009 (0.946, 1.076)	10.3
	AM (Fed) vs. A (Fed)	64.032	60.439	1.059 (0.993, 1.130)	
	AQ (Fed) vs. A (Fed)	61.631	60.439	1.020 (0.956, 1.087)	
	AK (Fed) vs. A (Fed)	65.697	60.439	1.087 (1.019, 1.160)	
AUC(0-∞) (μg.h/mL)	AS (Fed) vs. A (Fed)	62.599	61.895	1.011 (0.949, 1.077)	10.1
	AM (Fed) vs. A (Fed)	65.427	61.895	1.057 (0.992, 1.126)	
	AQ (Fed) vs. A (Fed)	62.883	61.895	1.016 (0.954, 1.082)	
	AK (Fed) vs. A (Fed)	67.032	61.895	1.083 (1.016, 1.154)	
Cmax (μg/mL)	AS (Fed) vs. A (Fed)	3.496	3.439	1.016 (0.948, 1.090)	11.2
	AM (Fed) vs. A (Fed)	3.382	3.439	0.983 (0.917, 1.055)	
	AQ (Fed) vs. A (Fed)	3.591	3.439	1.044 (0.974, 1.119)	
	AK (Fed) vs. A (Fed)	3.360	3.439	0.977 (0.911, 1.048)	

Data Source: 201674, In-text Table 22

a. AS; n = 13; AM, n = 12; AQ, n = 13; AK, n = 12

b. t = tlast. Median tlast ~72h for A (Fed), AS (Fed); ~73h AM (Fed); ~74h for AQ (Fed); ~120h for AK (Fed)

Treatment A: DTG 50 mg tablet (clinical image) plus a single RPV 25 mg tablet (EDURANT).

Treatments AS, AM, AQ, AK: DTG/RPV 50 mg/25 mg FDC tablet product codes

Table 16 Summary of Plasma Rilpivirine Pharmacokinetic Parameters and Treatment Comparisons to Assess Relative Bioavailability (Fed – High Fat[a]) (Part 1)

Parameter	Comparison Test vs. Reference	Geometric LS Mean		GLS Means Ratio (90% CI)	%CVw
		Test (n=12 or 13)[b]	Reference (n=25)		
AUC(0-t)[c] (ng.h/mL)	AS (Fed) vs. A (Fed)	2967	3093	0.959 (0.869, 1.059)	16.1
	AM (Fed) vs. A (Fed)	3493	3093	1.129 (1.021, 1.249)	
	AQ (Fed) vs. A (Fed)	3258	3093	1.053 (0.954, 1.163)	
	AK (Fed) vs. A (Fed)	3484	3093	1.126 (1.019, 1.245)	
AUC(0-∞) (ng.h/mL)[d, e]	AS (Fed) vs. A (Fed)	3624	3635	0.997 (0.911, 1.091)	14.4
	AM (Fed) vs. A (Fed)	3834	3635	1.055 (0.960, 1.160)	
	AQ (Fed) vs. A (Fed)	3830	3635	1.054 (0.963, 1.153)	
	AK (Fed) vs. A (Fed)	3984	3635	1.096 (0.997, 1.205)	
Cmax (ng/mL)	AS (Fed) vs. A (Fed)	93.42	101.6	0.920 (0.789, 1.072)	25.8
	AM (Fed) vs. A (Fed)	112.1	101.6	1.104 (0.944, 1.290)	
	AQ (Fed) vs. A (Fed)	111.4	101.6	1.096 (0.941, 1.277)	
	AK (Fed) vs. A (Fed)	107.0	101.6	1.053 (0.901, 1.231)	

Data Source: 201674 In-text Table 23

a. High-fat breakfast contained ~900 total calories: 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat.
b. AS; n = 13; AM, n = 12; AQ, n = 13; AK, n = 12
c. t = tlast. Median tlast ≈ 168h for all treatments
d. 2 subjects (fed) were excluded from the statistical analysis AUC(0-∞), because >40% of AUC(0-∞) extrapolated and λz time duration <2x calculated t½.
e. Interpret with caution as ~20% of profiles across study have AUC(0-∞) with % extrapolated >20% or poorly estimated t½

Treatment A: DTG 50 mg tablet (clinical image) plus a single RPV 25 mg tablet (EDURANT).
Treatments AS, AM, AQ, AK: DTG/RPV 50 mg/25 mg FDC tablet product codes

In Part 2, systemic exposure of DTG following all DTG/RPV FDC formulations was lower than exposure following co-administration of the SE tablets under fasted conditions. The AUC(0-∞), AUC(0-t), and Cmax following administration of various DTG/RPV FDC formulations ranged from 19% lower to 5% lower (depending on the DTG/RPV FDC tablet) than those of the reference DTG single agent co-administered with RPV (Table 17). The AUC(0-∞), AUC(0-t), and Cmax of RPV from the various DTG/RPV FDC tablets were comparable to or ranged from 1% lower to 10% higher (depending on the DTG/RPV FDC tablet) than those of the reference RPV single agent co-administered with DTG (Table 18).

Table 17 Summary of Dolutegravir Pharmacokinetic Parameter Treatment Comparisons for Relative Bioavailability under Fasted Conditions (Part 2)

Parameter	Geometric LS Mean		GLS Means Ratio (90% CI)	%CVw
	Test	Reference		
Cohort 2 (N=12)	**AK (Fasted)**	**A (Fasted)**		
AUC(0-t) (μg.h/mL)[a]	34.65	36.62	0.946 (0.761, 1.177)	31.8
AUC(0-∞) (μg.h/mL)	35.64	37.77	0.944 (0.761, 1.170)	31.3
Cmax (μg/mL)	1.946	2.229	0.873 (0.697, 1.092)	32.7
Cohort 3 (N=12)	**AM (Fasted)**	**A (Fasted)**		
AUC(0-t) (μg.h/mL)[a]	33.56	38.69	0.868 (0.715, 1.052)	27.9
AUC(0-∞) (μg.h/mL)	34.64	39.75	0.871 (0.720, 1.054)	27.6
Cmax (μg/mL)	1.941	2.197	0.883 (0.708, 1.102)	32.1
Cohort 4 (N=12)	**AU (Fasted)**	**A (Fasted)**		
AUC(0-t) (μg.h/mL)[a]	35.78	41.15	0.870 (0.739, 1.023)	23.3
AUC(0-∞) (μg.h/mL)	37.26	42.33	0.880 (0.752, 1.031)	22.7
Cmax (μg/mL)	1.917	2.378	0.806 (0.720, 0.902)	16.1

Data Source: 201674 In-text Table 24

a. t = tlast. Median tlast ~72h for all treatments

Treatment A: DTG 50 mg tablet (clinical image) plus a single RPV 25 mg tablet (EDURANT).

Treatment AK, AM, AU: DTG/RPV 50 mg/25 mg FDC tablet product codes

Table 18 Summary of Rilpivirine Pharmacokinetic Parameter Treatment Comparisons for Relative Bioavailability under Fasted Conditions (Part 2)

Parameter	Geometric LS Mean		GLS Means Ratio (90% CI)	%CVw
	Test	Reference		
Cohort 2 (N=12)	**AK (Fasted)**	**A (Fasted)**		
AUC(0-t) (ng.h/mL)[a]	2148	2027	1.060 (0.930, 1.208)	18.8
AUC(0-∞) (ng.h/mL)[b,c]	2427	2278	1.065 (0.929, 1.222)	19.0
Cmax (ng/mL)	61.71	56.25	1.097 (0.912, 1.320)	26.7
Cohort 3 (N=12)	**AM (Fasted)**	**A (Fasted)**		
AUC(0-t) (ng.h/mL)[a]	1843	1809	1.019 (0.802, 1.295)	35.1
AUC(0-∞) (ng.h/mL)[b,c]	2236	2149	1.040 (0.818, 1.323)	33.8
Cmax (ng/mL)	50.29	49.30	1.020 (0.723, 1.440)	52.1
Cohort 4 (N=12)	**AU (Fasted)**	**A (Fasted)**		
AUC(0-t) (ng.h/mL)[a]	1886	1877	1.005 (0.809, 1.248)	31.4
AUC(0-∞) (ng.h/mL)[b,c]	2062	2094	0.985 (0.784, 1.238)	33.3
Cmax (ng/mL)	54.69	54.06	1.012 (0.776, 1.319)	39.0

Data Source: 201674 In-text Table 25

a. t = tlast. Median tlast ~72h for all treatments

b. 2 subjects (fasted) were excluded from the statistical analysis of AUC(0-∞) because >40% of AUC(0-∞) was extrapolated and λz time duration <2x calculated t½.

c. Interpret with caution as ~20% of profiles (across study) have AUC(0-∞) with % extrapolated >20% or poorly estimated t½.

Treatment A: DTG 50 mg tablet (clinical image) plus a single RPV 25 mg tablet (EDURANT).

Treatment AK, AM, AU: DTG/RPV 50 mg/25 mg FDC tablet product codes

2.4. Effect of Food on Bioavailability

2.4.1. Dolutegravir/Rilpivirine Fixed-dose Combination

2.4.1.1. Study 201674: Effect of Food on Different Fixed-dose Combinations of Dolutegravir and Rilpivirine

Study title: A Phase I, 2-part Relative Oral Bioavailability Study of Different Fixed Dose Combinations of Dolutegravir and Rilpivirine in Fasted and Fed Healthy Subjects

Location of Report: m5.3.1.2

Formulations Used:

- DTG/RPV FDC:
  - Formulations Part 1: AS, AM, AQ, AK
  - Formulations Part 2: AK, AM, AU Part 2 (AS and AU are the same except for the manufacturing site)
- DTG (TIVICAY), RPV (EDURANT) (refer to Section 1.3.3)

Methods: The methods are described in the RBA section of the study (Section 2.3.1.1).

The RBA results of different FDCs of DTG/RPV are summarized in Section 2.3.1.1.

Results: The statistical comparisons results for Part 2 showed that a moderate-fat meal increased the exposure of both DTG and RPV following administration of the DTG/RPV FDC formulations (AK, AM, AU) (Table 19, Table 20). Likewise, cross-cohort comparisons between fed (High Fat Part 1) and fasted (Part 2) showed that a high-fat meal increased DTG and RPV systemic exposure following administration of three FDC formulations (AK, AM and AS/AU) and as co-administration as the SEs DTG or RPV.

In Part 2, co-administration of various DTG/RPV FDC formulations with a moderate-fat meal increased DTG AUC(0-∞) by 74 to 87% and Cmax by 75 to 88%. RPV AUC(0-∞) was increased by 38 to 57% and Cmax by 74 to 94%.

The cross-cohort comparison (Part 1 High Fat fed vs. Part 2 Fasted) showed that co-administration of the various DTG/RPV FDC formulations with a high-fat meal increased DTG AUC(0-∞) by 71 to 87% and Cmax by 71 to 85%. RPV AUC(0-∞) was increased 68 to 72% and Cmax by 73 to 117%. Co-administration of the SE reference formulations with a high-fat meal showed 51 to 55% higher DTG exposures and 63% and 91% higher RPV AUC(0-t) and Cmax, respectively.

The proposed final formulation (AW) for commercial marketing possesses minor compositional changes compared with the formulation AM. The main change was the use of a different but compositionally very similar film coat to achieve the target shade of pink desired for the commercial product. This minor modification is not expected to change biopharmaceutical characteristics of the tablet including BA in presence of food (see Section 1.3.1).

Table 19 Summary of Selected Dolutegravir Pharmacokinetic Parameters Following a High-fat Meal[a] (Part 1) or a Moderate-fat Meal[b] (Part 2) and Fasted (Part 2)

Parameter	Geometric LS Mean		GLS Means Ratio (90% CI)	%CVw
	Test	Reference		
Formulation A: High Fat	**A (Fed) Part 1 (N=25)**	**A (Fasted) Part 2 (N=36)**		
AUC(0-t) (μg.h/mL)[c]	60.22	38.78	1.553 (1.340, 1.800)	22.1
AUC(0-∞) (μg.h/mL)	61.67	39.91	1.545 (1.337, 1.786)	21.7
Cmax (μg/mL)	3.429	2.267	1.513 (1.313, 1.743)	21.5
Formulation AK: High Fat	**AK (Fed) Part 1 (N=12)**	**AK (Fasted) Part 2 (N=12)**		
AUC(0-t) (μg.h/mL)[c]	65.76	35.85	1.835 (1.496, 2.250)	22.1
AUC(0-∞) (μg.h/mL)	67.12	36.83	1.823 (1.492, 2.227)	21.7
Cmax (μg/mL)	3.367	1.965	1.714 (1.407, 2.087)	21.5
Formulation AK: Moderate Fat	**AK (Fed) Part 2 (N=12)**	**AK (Fasted) Part 2 (N=12)**		
AUC(0-t) (μg.h/mL)[c]	60.19	34.65	1.737 (1.396, 2.161)	31.8
AUC(0-∞) (μg.h/mL)	62.10	35.64	1.742 (1.405, 2.161)	31.3
Cmax (μg/mL)	3.615	1.946	1.858 (1.485, 2.325)	32.7
Formulation AM: High Fat	**AM (Fed) Part 1 (N=12)**	**AM (Fasted) Part 2 (N=12)**		
AUC(0-t) (μg.h/mL)[c]	63.68	33.61	1.895 (1.545, 2.324)	22.1
AUC(0-∞) (μg.h/mL)	65.03	34.72	1.873 (1.533, 2.289)	21.7
Cmax (μg/mL)	3.397	1.977	1.718 (1.411, 2.092)	21.5
Formulation AM: Moderate Fat	**AM (Fed) Part 2 (N=12)**	**AM (Fasted) Part 2 (N=12)**		
AUC(0-t) (μg.h/mL)[c]	62.94	33.56	1.875 (1.547, 2.274)	27.9
AUC(0-∞) (μg.h/mL)	64.62	34.64	1.865 (1.542, 2.257)	27.6
Cmax (μg/mL)	3.395	1.941	1.749 (1.403, 2.181)	32.1
Formulation AS[d]: High Fat	**AS[d] (Fed) Part 1 (N=13)**	**AU[d] (Fasted) Part 2 (N=12)**		
AUC(0-t) (μg.h/mL)[c]	59.89	34.54	1.734 (1.418, 2.122)	22.1
AUC(0-∞) (μg.h/mL)	61.48	35.98	1.709 (1.402, 2.083)	21.7
Cmax (μg/mL)	3.444	1.864	1.848 (1.521, 2.244)	21.5
Formulation AU[d]: Moderate Fat	**AU (Fed) Part 2 (N=11)**	**AU (Fasted) Part 2 (N=12)**		
AUC(0-t) (μg.h/mL)[c]	64.96	35.78	1.815 (1.535, 2.148)	23.3
AUC(0-∞) (μg.h/mL)	66.83	37.26	1.793 (1.523, 2.112)	22.7
Cmax (μg/mL)	3.605	1.917	1.881 (1.673, 2.114)	16.1

Data Source: 201674 In-text Table 26

a. High-fat breakfast contained ~900 total calories: 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat.

b. Moderate-fat meal contained ~625 total calories: 125 calories from protein, 300 calories from carbohydrate, and 200 calories from fat.

c. t = tlast. Median tlast ~72h for all treatments

d. Formulation AS and AU are identical ([redacted]) except for the site of manufacture of [redacted] . Note: there is a slight difference in the unit formulae presented in Table 7 and Table 8 due to a very minor adjustment to the master formula for AU (related to the number of decimal places used)

Treatment A: DTG 50 mg tablet (clinical image) plus a single RPV 25 mg tablet (EDURANT).

Treatment AK, AM, AU: DTG/RPV 50 mg/25 mg FDC tablet product codes

Table 20 Summary of Selected Rilpivirine Pharmacokinetic Parameters Following a High-fat Meal[a] (Part 1) or a Moderate-fat Meal[b] (Part 2) and Fasted (Part 2)

Parameter	Geometric LS Mean		GLS Means Ratio (90% CI)	%CVw
	Test	Reference		
Formulation A: High Fat	**A (Fed) Part 1 (N=25)**	**A (Fasted) Part 2 (N=36)**		
AUC(0-t) (ng.h/mL)[c]	3090	1902	1.625 (1.364, 1.934)	21.7
AUC(0-∞) (ng.h/mL)[d, e]	3643	2168	1.680 (1.400, 2.016)	20.7
Cmax (ng/mL)	101.3	53.12	1.907 (1.541, 2.360)	31.4
Formulation AK: High Fat	**AK (Fed) Part 1 (N=12)**	**AK (Fasted) Part 2 (N=12)**		
AUC(0-t) (ng.h/mL)[c]	3466	2052	1.689 (1.349, 2.116)	21.7
AUC(0-∞) (ng.h/mL)[d, e]	3924	2332	1.683 (1.334, 2.122)	20.7
Cmax (ng/mL)	106.3	59.57	1.785 (1.333, 2.389)	31.4
Formulation AK: Moderate Fat	**AK (Fed) Part 2 (N=12)**	**AK (Fasted) Part 2 (N=12)**		
AUC(0-t) (ng.h/mL)[c]	3153	2148	1.468 (1.288, 1.674)	18.8
AUC(0-∞) (ng.h/mL)[e]	3498	2427	1.442 (1.262, 1.646)	19.0
Cmax (ng/mL)	119.6	61.71	1.939 (1.611, 2.333)	26.7
Formulation AM: High Fat	**AM (Fed) Part 1 (N=12)**	**AM (Fasted) Part 2 (N=12)**		
AUC(0-t) (ng.h/mL)[c]	3542	1911	1.853 (1.480, 2.321)	21.7
AUC(0-∞) (ng.h/mL)[d, e]	3886	2265	1.716 (1.360, 2.164)	20.7
Cmax (ng/mL)	114.2	52.66	2.168 (1.619, 2.902)	31.4
Formulation AM: Moderate Fat	**AM (Fed) Part 2 (N=12)**	**AM (Fasted) Part 2 (N=12)**		
AUC(0-t) (ng.h/mL)[c]	2907	1843	1.577 (1.241, 2.004)	35.1
AUC(0-∞) (ng.h/mL)[e]	3508	2236	1.569 (1.244, 1.980)	33.8
Cmax (ng/mL)	95.08	50.29	1.891 (1.339, 2.669)	52.1
Formulation AS[f]: High Fat	**AS[f] (Fed) Part 1 (N=13)**	**AU[f] (Fasted) Part 2 (N=12)**		
AUC(0-t) (ng.h/mL)[c]	2943	1904	1.546 (1.237, 1.931)	21.7
AUC(0-∞) (ng.h/mL)[e]	3604	2118	1.702 (1.357, 2.134)	20.7
Cmax (ng/mL)	93.32	54.10	1.725 (1.293, 2.301)	31.4
Formulation AU[f]: Moderate Fat	**AU (Fed) Part 2 (N=11)**	**AU (Fasted) Part 2 (N=12)**		
AUC(0-t) (ng.h/mL)[c]	2606	1886	1.381 (1.104, 1.728)	31.4
AUC(0-∞) (ng.h/mL)[e]	2836	2062	1.375 (1.086, 1.742)	33.3
Cmax (ng/mL)	95.28	54.69	1.742 (1.324, 2.292)	39.0

Data Source: 201674 In-text Table 27

a. High-fat breakfast contained ~900 total calories: 150 calories from protein, 250 calories from carbohydrate, and 500 calories from fat.
b. Moderate-fat meal contained ~625 total calories: 125 calories from protein, 300 calories from carbohydrate, and 200 calories from fat.
c. t = tlast. Median tlast ~168h for all treatments
d. 4 subjects (2 fed, 2 fasted) were excluded from the statistical analysis of AUC(0-∞) because >40% of AUC(0-∞) extrapolated and λz time duration <2x calculated t½
e. Interpret with caution as large number of profiles (~20% across study) have AUC(0-∞) with % extrapolated >20% or poorly estimated t½

f. Formulation AS and AU are identical ([redacted]) except for the site of manufacture of [redacted]. Note: there is a slight difference in the unit formulae presented Table 7 and Table 8 due to a very minor adjustment to the master formula for AU (related to the number of decimal places used

Treatment A: DTG 50 mg tablet (clinical image) plus a single RPV 25 mg tablet (EDURANT).
Treatment AK, AM, AU: DTG/RPV 50 mg/25 mg FDC tablet product codes

2.4.2. Dolutegravir

Study ING113674 was designed to assess the RBA of three different tablet formulations of DTG 50 mg and the effect of food (low-, moderate-, high-fat meals) on the BA of the DTG formulation selected for Phase III studies and commercialization. This study is supportive to the DTG/RPV FDC submission; the study design and conclusions are summarized in Table 1. In summary, food increased systemic exposure of DTG by 33% to 66%.

2.4.3. Rilpivirine

Study TMC278-TiDP6-C137 was designed to investigate the effect of different types of meals (moderate-fat meals, high-fat meals, protein-rich drink) on the oral BA of RPV after a single dose of 75 mg formulated as the Phase III tablet. This study is supportive to the DTG/RPV FDC submission; the study design and conclusions are summarized in Table 1. In summary, the exposure to RPV was approximately 40% lower when EDURANT was taken in a fasted condition as compared with a standard (533 kcal) or high-fat high breakfast (928 kcal). When EDURANT was taken with only a protein-rich nutritional drink, exposures were 50% lower than when taken with a standard meal.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. In Vitro Dissolution and In Vivo Bioavailability

Dolutegravir sodium is considered a poorly soluble compound, demonstrating low solubility over the physiological pH range (pH 1 to 7.4). Dolutegravir was determined to have high passive membrane permeability (333 nm/s at pH 7.4). The absorptive membrane permeabilities were also high in the presence of FaSSIF at pH 7.4 and pH 5.5 (P7.4[abs] value of 253 nm/s and a P5.5[abs] value of 265 nm/s, respectively). Based on solubility and permeability determinations, DTG sodium is classified as a BCS Class 2. The SLAD concept has been introduced recently [Butler, 2010], and represents the region between Class IIa and IIb for high permeability drugs. The DCS proposed by Butler et al, assigns DTG sodium (up to a dose of 50 mg) in DCS Class I, indicating that the absorption is not expected to be limited by dissolution and/or solubility at that dose level [Butler, 2010].

Rilpivirine hydrochloride is considered a poorly soluble compound demonstrating low solubility over the physiological pH range (pH 1 to 7.4). In vitro evaluation indicated that RPV had intermediate permeability and overall, RPV permeation is thought to occur predominantly via a passive transcellular diffusion mechanism.

The discriminating dissolution test, discussed in m3.2.P.2.2, is therefore, expected to be more of a QC test than an indicator of biopharmaceutical performance.

3.2. Dosing Relative to Food

The proposed final formulation (AW) for commercial marketing possesses minor compositional changes compared with the formulation AM. The main change was the use of a different but compositionally very similar film coat to achieve the target shade of pink desired for the commercial product. This minor modification is not expected to change biopharmaceutical characteristics of the tablet including BA in presence of food (see Section 1.3.1). Co-administration of DTG/RPV FDC formulation AM with a moderate-fat meal increased the DTG AUC(0-∞) by 87% and Cmax by 75%, and RPV AUC(0-∞) was increased by 57% and Cmax by 89%. A cross cohort comparison showed that co-administration of the DTG/RPV FDC formulation AM with a high-fat meal increased DTG AUC(0-∞) by 87% and Cmax by 72%, and RPV AUC(0-∞) was increased by 72% and Cmax by 117%. Co-administration of the SE reference formulations with a high-fat meal showed 51 to 55% higher DTG exposures and 63% and 91% higher RPV AUC(0-t) and Cmax, respectively, compared with the fasted state. The increases in DTG and RPV systemic exposures with food observed following DTG/RPV FDC formulation AM were consistent with those observed for the reference treatment in Study 201674 and in previous food effect studies of the single agents (ING113674, TMC278-TiDP6-C137).

These data support the recommendation that the DTG/RPV FDC should be administered with a meal. This is consistent with the prescribing information for RPV.

4. MAIN BIOPHARMACEUTICAL FINDINGS

The conclusions from the biopharmaceutic evaluations are as follows:

- Bioequivalence was confirmed in terms of systemic exposure of both DTG and RPV for the DTG/RPV FDC tablet formulation of DTG/RPV 50 mg/25 mg compared with separate tablet formulations of DTG 50 mg + RPV 25 mg when administered with a moderate-fat meal.
- DTG/RPV FDC should be taken with a meal. Taking DTG/RPV FDC in a fasted condition or with only a protein-rich nutritional drink may result in decreased plasma concentrations of RPV, which could potentially reduce the therapeutic effect of DTG/RPV FDC. This is consistent with the prescribing instructions for RPV to be administered with a meal.
- The bioanalytical methods used to measure concentrations of DTG in human plasma, in the presence of RPV, and RPV in the presence of DTG, were selective, accurate and reproducible.

5. APPENDIX

Appendix Table 1 Summary of Drug Substance and Drug Product

Study Ref. No.	Formula Code	Drug Product Batch No.	Dosage Form	Input Drug Substance Batch		Study Report Location
				Dolutegravir Sodium	Rilpivirine Hydrochloride	
201674	AK	152387925 (R705828)	50 mg / 25 mg Tablet	142385303 (108006C)	142385272 (A14EC1616)	m5.3.1.2
	AM	152387926 (R705839)	50 mg / 25 mg Tablet	142385303 (108006C)	A14EC1615	
	AQ	152387928 (R705842)	50 mg / 25 mg Tablet	142385303 (108006C)	142385272 (A14EC1616)	
	AS	152387927 (R705841)	50 mg / 25 mg Tablet	142385303 (108006C)	A14EC1615	
	AU	152390609 (R727308)	50 mg / 25 mg Tablet	152389502 (149017)	142385272 (A14EC1616)	
	BC	132373670 (R634503)	Dolutegravir Tablet, 50 mg	108004A	N/A	
	N/A	152387796 (EKL1C00)	Edurant Tablet, 25 mg	N/A	525239	
201676	AW	162395454 (R759861)	50 mg / 25 mg Tablet	157035	152393115 (A15HC2209)	m5.3.1.2
	BC	132373670 (R634503)	Dolutegravir Tablet, 50 mg	108004A	N/A	
	N/A	162396354 (GAL7E00)	Edurant Tablet, 25 mg	N/A	525239	

Appendix Table 2 Summary of In vitro Dissolution Studies

Study Ref. No.	Product Code/ Packaged Batch No.	Dosage Form	Conditions: USP Apparatus 2 (Media, Volume, Paddle Speed)	No. of Dosage Units	Component	Collection times (min) Mean % Dissolved (range)									Study Report Location
						5	10	15	20	25	30	40	45	60	
201676	AW R759861 (162395454)	DTG/RPV Tablets, 50/25 mg	Media A [redacted] mL [redacted] rpm	12	DTG	[redacted]									m5.3.1.2
					RPV										
201674	AK 152387925	DTG/RPV Tablets, 50/25 mg	Media A [redacted] mL [redacted] rpm	6	DTG										m5.3.1.2
					RPV										
	AM 152387926	DTG/RPV Tablets, 50 /25 mg	Media A [redacted] mL [redacted] rpm	6	DTG										m5.3.1.2
					RPV										
	AS 152387927	DTG/RPV Tablets, 50/25 mg	Media A [redacted] mL [redacted] rpm	6	DTG										m5.3.1.2
					RPV										
	AQ 152387928	DTG/RPV Tablets, 50/25 mg	Media A [redacted] mL [redacted] rpm	6	DTG										m5.3.1.2
					RPV										
	AR 152387929	DTG/RPV Tablets, 50/25 mg	Media A [redacted] mL [redacted] rpm	6	DTG										m5.3.1.2
					RPV										
201676 201674	BC 132373670	DTG Tablets, 50 mg	Media B [redacted] mL [redacted] rpm	6	DTG										m5.3.1.2
201676	GAL7E	RPV Tablets 25 mg	Media C, [redacted] mL, [redacted] rpm	6	RPV										m5.3.1.2
201674	EKL1C00	RPV Tablets 25 mg	Media C, [redacted] mL, [redacted] rpm	6	RPV										m5.3.1.2

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Media A: [redacted]
Media B: [redacted]
Media C: [redacted]

Appendix Table 3 Bioanalytical Methods Summary

Validation Report	Clinical Studies Supported	Method Description and Performance	
Dolutegravir **Human Plasma (EDTA)** GlaxoSmithKline, Five Moore Drive Research Triangle Park, NC 27709 **Title:** The Validation of a Method for the Determination of GSK1349572 (range 20 to 20000 ng/mL) in Human Plasma using HPC-MS/MS GlaxoSmithKline Document Number: RD2010/00175 **Supplemental Reports (Incorporation of long term stability and interference checks)** GlaxoSmithKline Document Number: 2011N112542	ING113674	Dolutegravir is extracted from 25 μL human plasma by protein precipitation using acetonitrile containing [$^{2}H_{7}{}^{15}N$]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	20.0 ng/mL
		Validated Range	20.0 to 20000 ng/mL
		Within-run Precision (%CV)	≤4.5%
		Between-run Precision (%CV)	≤2.7%
		Accuracy (%Bias)	-0.3% ≤ bias ≤ 9.6%
		Stability in Human Plasma	3 freeze-thaw cycles at approximately -20°C at least 24 hours at ambient temperature at least 265 days at approximately -20°C
Dolutegravir **Human Plasma (EDTA)** [redacted] **Title:**	201674 201676 201636 201637	Dolutegravir is extracted from 25 μL human plasma by protein precipitation using acetonitrile containing [$^{2}H_{7}{}^{15}N$]-dolutegravir as an internal standard. Extracts are analyzed by HPLC-MS/MS using a Turbo IonSpray interface and multiple reaction monitoring.	
		LLQ	20.0 ng/mL
		Validated Range	20.0 to 20000 ng/mL

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
Quantification of GSK1349572 in Human Plasma via UPLC with MS/MS detection (range 20 to 20000 ng/mL) GlaxoSmithKline Document Number: 2015N231443_00 (in presence of RPV) **Supplemental Reports (Incorporation of long term stability and interference checks)** GlaxoSmithKline Document Number: 2012N147635_00 2012N151911_00 2013N161036_00 2013N173708_00 2014N188856_00 2014N202882_00 2015N264419_00 2016N309796_00		Within-run Precision (%CV)	≤10.4%
		Between-run Precision (%CV)	≤-7.37%
		Accuracy (%Bias)	-7.33% ≤ bias ≤ 11.1%
		Stability in Human Plasma (in presence of RPV)	6 freeze-thaw cycles at approximately -20°C and -70°C at least 25 hours at ambient temperature at least 498 days at approximately -20°C and -70°C
		Processed Extract Stability (in presence of RPV)	at least 69 hours at 2 to 8°C
Rilpivirine **Human Plasma (sodium heparin)** [redacted] Title: Quantification of Rilpivirine in Human Plasma via HPLC with MS/MS Detection	201674	Rilpivirine is extracted from 50 μL human plasma by liquid/liquid extraction using MeOH:DCM (80:20) containing [$^2H_6$]-rilpivirine as an internal standard. Extracts are analyzed by HPLC-MS/MS using positive ion APCI and multiple reaction monitoring	
		LLQ	0.500 ng/mL
		Validated Range	0.500 to 250 ng/mL

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
GlaxoSmithKline Document Number: 2015N232840_00 2015N264415_00 2016N270364_00		Within-run Precision (%CV)	≤12.7%
		Between-run Precision (%CV)	≤7.30%
		Accuracy (%Bias)	-10.5% ≤ bias ≤8.82%
		Stability in Human Plasma	5 freeze-thaw cycles at -20°C and -70°C at least 30 hours at ambient temperature at least 155 days at approximately -20°C and -70°C
		Processed Extract Stability	at least 169 hours at 2 to 8°C
Rilpivirine **Human Plasma (heparin)** [redacted], The Netherlands Title: Validation of a Method for the Determination of JNJ-16150108 (TMC278) in Human Plasma Samples GlaxoSmithKline Document Number: 2012N144315_00 Original method	201676 201636 201637	RPV is extracted from 100 μL human plasma by protein precipitation using acetonitrile with [^{13}C d4]-RPV as an internal standard. Extracts are analyzed by HPLC-MS/MS using TurboIonSpray and multiple reaction monitoring.	
		LLQ	1 ng/mL
		Validated Range	1 to 2000 ng/mL
		Within-run Precision (%CV)	≤5.4%
		Between-run Precision (%CV)	≤4.7%
		Accuracy (%Bias)	96.7% ≤ bias ≤114.1%
		Stability in Human Plasma	Freeze-thaw not performed (supplied by sponsor) Bench top not performed (supplied by sponsor) 828 days long-term stability
		Processed Extract Stability	At least 119 hours at ambient temperature

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
Rilpivirine **Human Plasma (heparin)** [redacted], The Netherlands Title: Validation of a Method for the Determination of JNJ-16150108 (TMC278) in Human Plasma Samples GlaxoSmithKline Document Number: 2017N319704_00 Revalidation for combination with DTG	201676 201636 201637	RPV is extracted from 100 μL human plasma by protein precipitation using acetonitrile with [^{13}C-d4]-RPV as an internal standard. Extracts are analyzed by HPLC-MS/MS using TurboIonSpray and multiple reaction monitoring.	
		LLQ	1 ng/mL
		Validated Range	1 to 2000 ng/mL
		Between-run Precision (%CV)	≤6.2%
		Accuracy (%Bias)	-12.5% ≤ bias ≤11.2%
		Stability in Human Plasma	5 freeze-thaw cycles at -20°C and -70°C at least 24 hours at ambient temperature long term stability in presence of DTG currently ongoing
		Processed Extract Stability	at least 120 hours at ambient temperature
Rilpivirine **Human Plasma (sodium heparin)** [redacted], Belgium Title: Quantification of Rilpivirine in Human Plasma via HPLC with MS/MS Detection BA218 GlaxoSmithKline Document Number: 2017N323743_00	TMC278-TiDP6-C137	RPV is extracted from 50 μL human plasma by protein precipitation using acetonitrile with [^{13}C-d4]-RPV as an internal standard. Extracts are analyzed by HPLC-MS/MS using positive ion TurboIonSpray interface and multiple reaction monitoring	
		LLQ	1.00 ng/mL
		Validated Range	1.00 to 2000 ng/mL
		Between-run Precision (%CV)	≤ 15.6%
		Accuracy (%Bias)	-1.8% ≤ bias ≤ 6.6%

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Validation Report	Clinical Studies Supported	Method Description and Performance	
		Stability in Human Plasma	3 freeze-thaw cycles at -20°C 72 hours at ambient temperature 296 days long term stability at -20°C
		Processed Extract Stability	144 days at room temperature
Efavirenz and Nevirapine Human Plasma (EDTA) [redacted] Title: Method Validation Report Quantitation of Efavirenz and Nevirapine in Human Plasma via UHPLC with MS/MS Detection GlaxoSmithKline Document Number: 2016N269537_00 **Supplemental Report (Incorporation of long term stability and analyte stability in solution)** GlaxoSmithKline Document Number: 2017N321175_00	201636 201637	Efavirenz and nevirapine are extracted from 50 µL human plasma by supported liquid extraction using a Biotage, Isolute 200-mg SLE + plate with efavirenz-$^{13}C_6$ / nevirapine-d_4 as an internal standard. Final extracts are analyzed via HPLC and MS/MS detection using positive ion electrospray.	
		LLQ	4 ng/mL
		Validated Range	4 to 2000 ng/mL
		Between-run Precision (%CV)	≤6.14% Efavirenz ≤4.46% Nevirapine
		Accuracy (%Bias)	-2.22% ≤ bias ≤7.04% Efavirenz -5.49% ≤ bias ≤3.79% Nevirapine
		Stability in Human Plasma	5 freeze-thaw cycles at -20°C and -70°C at least 24 hours at ambient temperature 22 and 273 days at -20°C and -70°C
		Processed Extract Stability	135.15 hours at 2 to 8 °C

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

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
201674 (2015N237780_00)		**60**	**160**	**640**	**2400**	**15200**
	Overall Mean (ng/mL)	60.8	160	648	2410	15400
	S.D. (within-run means)	4.51	11.0	60.6	215	952
	Precision (%CV)	7.43	6.90	9.35	8.91	6.19
	Average Bias (%)	1.31	0.0969	1.32	0.496	1.16
	n=	78	78	78	78	78
201676 (2016N292177_00)	Overall Mean (ng/mL)	60.5	161	638	2410	14700
	S.D. (within-run means)	2.47	6.69	20.5	91.1	1120
	Precision (%CV)	4.08	4.16	3.21	3.78	7.61
	Average Bias (%)	0.870	0.390	-0.376	0.436	-3.59
	n=	92	92	92	92	92
ING113674 (RD2010/00558/00)		**60**	**1600**	**16000**		
	Overall Mean (ng/mL)	61.3	1662.6	16024.6		
	S.D. (within-run means)	2.1	67.7	707.1		
	Precision (%CV)	3.5	4.1	4.4		
	Average Bias (%)	2.1	3.9	0.2		
	n=	44	44	44		
201636 (2015N257512_00)		**60**	**160**	**640**	**2400**	**15200**
	Overall Mean (ng/mL)	60.7	163	639	2420	15300
	S.D. (within-run means)	3.47	8.58	35.2	172	724
	Precision (%CV)	5.72	5.25	5.51	7.11	4.73
	Average Bias (%)	1.20	2.14	-0.162	0.922	0.824
	n=	32	32	32	32	32
201637 (2015N257514_00)		**60**	**160**	**640**	**2400**	**15200**
	Overall Mean (ng/mL)	60.3	163	642	2470	15200
	S.D. (within-run means)	3.00	6.33	35.4	135	950

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
	Precision (%CV)	4.98	3.88	5.51	5.48	6.26
	Average Bias (%)	0.521	1.95	0.363	2.85	-0.123
	n=	28	28	28	28	28

Appendix Table 5 Between-run Accuracy and Precision of Quality Control (QC) Samples for Rilpivirine

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
201674 (2015N237781_00)		**1.20**	**3.00**	**12.0**	**40.0**	**200**
	Overall Mean (ng/mL)	1.21	3.02	12.1	40.3	202
	S.D. (within-run means)	0.0904	0.119	0.390	1.61	8.02
	Precision (%CV)	7.46	3.92	3.21	3.99	3.98
	Average Bias (%)	1.04	0.786	1.17	0.829	0.868
	n=	72	72	72	72	72
201676 (2017N318483_00)		**3.0**		**50.0**		**1600**
	Overall Mean (ng/mL)	2.96		49.6		1600
	Precision (%CV)	6.0		2.8		2.6
	Average Bias (%)	-1.3		-0.8		0.0
	n=	122		122		122
TMC278-TiDP6-C137		**2.77**		**59.0**		**1550**
	Overall Mean (ng/mL)	2.98		62.3		1590
	S.D. (within-run means)	0.154		3.10		111
	Precision (%CV)	5.2		5.0		7.0
	Average Bias (%)	7.6		5.6		2.6
	n=	40		40		40
201636 (2017N326555_00)		**3.0**		**50.0**		**1600**
	Overall Mean (ng/mL)	3.04		50.2		1610
	Precision (%CV)	6.7		2.2		2.9
	Average Bias (%)	1.3		0.4		0.6
	n=	22		22		22
201637 (2017N326557_00)		**3.0**		**50.0**		**1600**
	Overall Mean (ng/mL)	3.10		49.6		1620
	Precision (%CV)	6.0		3.6		3.3
	Average Bias (%)	3.3		-0.8		1.3

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Study (GlaxoSmithKline Document Number)		**Nominal Concentration (ng/mL)**		
	n=	22	22	22

Appendix Table 6 Between-run Accuracy and Precision of Quality Control (QC) Samples for Efavirenz

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
201636(2016N273207_00)		**12**	**24**	**90**	**300**	**1500**
	Overall Mean (ng/mL)	12.7	25.5	95.8	317	1590
	S.D. (within-run means)	0.530	0.216	1.15	6.20	55.7
	Precision (%CV)	4.18	0.849	1.20	1.96	3.51
	Average Bias (%)	5.70	6.16	6.45	5.62	5.76
	n=	4	4	4	4	4
201637(2016N273208_00)		**12**	**24**	**90**	**300**	**1500**
	Overall Mean (ng/mL)	12.6	25.0	95.3	310	1550
	S.D. (within-run means)	0.164	0.325	3.38	2.72	12.0
	Precision (%CV)	1.29	1.30	3.55	0.878	0.773
	Average Bias (%)	5.40	4.14	5.88	3.29	3.08
	n=	4	4	4	4	4

Appendix Table 7 Between-run Accuracy and Precision of Quality Control (QC) Samples for Nevirapine

Study (GlaxoSmithKline Document Number)		Nominal Concentration (ng/mL)				
201636(2016N273207_00)		**12**	**24**	**90**	**300**	**1500**
	Overall Mean (ng/mL)	12.3	24.4	92.5	305	1510
	S.D. (within-run means)	0.304	0.522	1.72	1.71	32.6
	Precision (%CV)	2.47	2.13	1.86	0.562	2.16
	Average Bias (%)	2.32	1.87	2.80	1.51	0.830
	n=	4	4	4	4	4
201637(2016N273208_00)		**12**	**24**	**90**	**300**	**1500**
	Overall Mean (ng/mL)	12.2	24.2	91.8	297	1490
	S.D. (within-run means)	0.313	0.351	4.07	8.44	13.7
	Precision (%CV)	2.57	1.45	4.43	2.85	0.917
	Average Bias (%)	1.25	0.819	2.02	-1.15	-0.578
	n=	4	4	4	4	4

Appendix Table 8 Tabular Listing of all Biopharmaceutic Studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
Dolutegravir/Rilpivirine FDC								
201674	PK Relative bioavailability	To evaluate the relative bioavailability in the fed (Part 1) or fasted state (Part 2) of a single dose of DTG 50 mg and RPV 25 mg when administered together in a FDC tablet compared with the co-administration of a single dose of the single-entity DTG and RPV products	O, R, XO	Healthy subjects	Part 1: 27: 20/7: 40 yrs (20-61) Part 2: 36: 28/8: 40.6 (21-63)	Part 1: Treatment A = DTG 50 mg tablet (clinical image) plus a single EDURANT™ 25 mg tablet Treatment B = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AS Treatment C = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AM Treatment D = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AQ Treatment E = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AK Part 2:	Complete; Full	m5.3.1.2

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
						Treatment A Treatment F = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AK Treatment G = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AM Treatment H = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AU		
201676	PK Bioequivalence	To evaluate the bioequivalence between an FDC tablet formulation of DTG 50 mg and RPV 25 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus EDURANT (RPV 25 mg), in the fed state.	O, R, XO	Healthy subjects	118: 82/36: 30.7 yrs (18-56)	Treatment A; Test Formulation: DTG/RPV 50 mg/25 mg FDC oral Tablet (Product Code AW) Treatment B; Reference Formulation: DTG 50 mg (TIVICAY clinical image) and RPV 25 mg (EDURANT) oral Tablets	Complete; Full	m5.3.1.2

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
Dolutegravir								
ING113674	PK Relative bioavailability Food effect	To evaluate the relative bioavailability of three different tablet formulations of DTG 50 mg and effect of food on the selected formulation	R, O, XO	Healthy subjects	24: 10/14: 38.6 yrs (20-61)	Part A (fasted) DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AP DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AW DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AX Part B DTG/ 50 mg/ tablet/ oral/ single dose DTG/ 50 mg/ tablet/ oral/ single dose, low fat DTG/ 50 mg/ tablet/ oral/ single dose, high fat DTG/ 50 mg/ tablet/ oral/ single dose, mod fat	Complete; Full	

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/Dose/Form/ Route/Frequency/ Duration)	Study Status; Type of Report	Location of Study Report
Rilpivirine								
TMC278-TiDP6-C137	PK Food effect on bioavailability	Determine the effect of different types of meals on the oral bioavailability of RPV after a single dose, formulated as the Phase III tablet	R, O, XO	Healthy subjects	20: 18/2: 36.7 yrs (21-55)	Treatment A: single dose RPV 75 mg; normal-fat breakfast, oral Treatment B: single dose RPV 75 mg; fasted oral. Treatment C: single dose RPV 75 mg; high-fat breakfast, oral. Treatment D: single dose RPV 75 mg; protein-rich nutritional drink, oral.	Complete; Full	

Degree of Blinding
O = Open

Degree of Control

Treatment Assignment
R = Random

Treatment Sequence
XO = Crossover

M - Male
F - Female

Legend to Table 9 Summary Results of All Biopharmaceutic Studies

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

Appendix Table 9 Summary Results of all Biopharmaceutic Studies

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
Dolutegravir/Rilpivirine FDC								
					Dolutegravir PK Parameters			
201674	To evaluate the relative bioavailability in the fed (Part 1) and fasted (Part 2) state of a single dose of DTG 50 mg and RPV 25 mg when administered together in a FDC tablet compared with the co administration of a single dose of the single-entity DTG and RPV products, the effect of food on the bioavailability of selected FDC formulation(s) of DTG and RPV (Part 2)	R, OL, XO,	Part 1: 27: (20/7): 37.0 (20-61) Healthy subjects Part 2: 36: (28/8): 43.0 (21-63) Healthy subjects	**Part 1:** Fed (high fat) Treatment A = DTG 50 mg tablet (clinical image) plus a single EDURANT 25 mg tablet	3.43 (19.3)	3.01 (1.0 - 5.0)	61.89 (22.7)	15.33 (17.4)
				Treatment B = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AS	3.31 (17.0)	4.00 (1.0 - 7.0)	60.48 (19.6)	16.52 (21.1)
				Treatment C = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AM	3.36 (18.6)	4.00 (2.0 - 6.0)	60.75 (25.6)	15.67 (21.1)
				Treatment D = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AQ	3.56 (20.0)	3.00 (1.5 - 6.0)	65.15 (29.9)	15.12 (18.5)
				Treatment E = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AK	3.55 (20.1)	5.00 (3.0 - 9.0)	70.65 (25.9)	16.47 (21.4)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (ng/mL)	tmax (h) Median (Range)	AUC(0-∞) (ng.h/mL)	t1/2 (h)
					Rilpivirine PK Parameters			
				Part 1: Fed (high fat)				
				Treatment A = DTG 50 mg tablet (clinical image) plus a single EDURANT 25 mg tablet	101.3 (26.0)	5.00 (2.0 - 9.0)	3657 (31.0)	56.75 (41.6)
				Treatment B = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AS	92.64 (29.7)	4.00 (2.0 - 7.0)	3515 (31.5)	62.55 (38.0)
				Treatment C = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AM	107.9 (45.7)	4.00 (2.5 - 5.0)	3743 (34.1)	59.83 (26.9)
				Treatment D = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AQ	114.1 (27.5)	4.00 (2.0 - 7.0)	3764 (37.5)	50.73 (36.6)
				Treatment E = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AK	107.8 (31.7)	5.00 (2.5 - 9.0)	4006 (22.1)	52.86 (34.3)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
					Dolutegravir PK Parameters			
				Part 2:				
				Treatment A (Fasted)	2.27 (36.8)	2.00 (0.5 - 4.0)	39.91 (35.1)	14.47 (15.0)
				Treatment F = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AK				
				Fasted	1.95 (45.8)	3.00 (1.0 - 7.0)	35.64 (43.0)	14.85 (12.7)
				Fed (Moderate fat)	3.61 (15.4)	3.01 (1.0 - 4.0)	62.10 (22.0)	13.87 (13.3)
				Treatment G = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AM				
				Fasted	1.94 (63.2)	2.25 (1.0 - 5.0)	34.64 (57.1)	14.99 (20.3)
				Fed (Moderate fat)	3.40 (21.2)	3.51 (1.0 - 5.0)	64.62 (20.7)	15.45 (22.4)
				Treatment H = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AU				
				Fasted	1.92 (31.3)	2.50 (1.0 - 5.0)	37.26 (41.6)	14.56 (14.0)
				Fed (Moderate fat)	3.51 (11.2)	3.00 (1.0 - 5.0)	65.17 (25.9)	14.13 (17.5)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (ng/mL)	tmax (h) Median (Range)	AUC(0-∞) (ng.h/mL)	t1/2 (h)
					Rilpivirine PK Parameters			
				Part 2:				
				Treatment A (Fasted)	53.12 (66.3)	4.00 (2.0 - 6.0)	2134 (53.0)	48.61 (46.9)
				Treatment F = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AK Fasted	61.71 (31.0)	4.00 (2.5 - 9.0)	2427 (29.8)	45.63 (51.4)
				Fed (Moderate fat)	119.6 (28.3)	4.01 (2.0 - 5.0)	3498 (27.2)	44.53 (44.4)
				Treatment G = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AM Fasted	50.29 (92.2)	4.01 (2.0 - 5.0)	2236 (67.6)	64.60 (36.5)
				Fed (Moderate fat)	95.08 (35.9)	5.00 (2.0 - 5.0)	3508 (37.8)	62.29 (39.2)
				Treatment H = DTG/RPV Tablets, 50 mg/25 mg FDC Product Code AU Fasted	54.69 (65.8)	5.00 (3.0 - 12.0)	2016 (58.4)	40.66 (39.6)
				Fed(Moderate fat)	96.65 (26.1)	3.00 (1.5 - 5.0)	2849 (32.4)	41.21 (44.3)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
201676	To evaluate the bioequivalence between an FDC tablet formulation of DTG 50 mg and RPV 25 mg vs. co-administration of the separate tablet formulations of DTG 50 mg plus EDURANT (RPV 25 mg), in the fed state.	R, OL, XO,	Healthy subjects		**Dolutegravir PK Parameters**			
				Treatment A = DTG/RPV Tablet, 50 mg/25 mg FDC/single dose/Fed (Moderate fat)	3.65 (18.2)	3.02 (0.5 - 6.0)	65.0 (24.9)	14.5 (20.6)
				Treatment B = Co-administration of separate tablets of DTG 50 mg and RPV 25 mg/Fed (Moderate fat)	3.47 (18.8)	3.00 (0.5 - 8.0)	62.7 (25.3)	14.8 (21.0)
					Rilpivirine PK Parameters			
				Treatment A = DTG/RPV Tablet, 50 mg/25 mg FDC/single dose/Fed (Moderate fat)	0.0933 (42.2)	4.00 (1.0 - 9.0)	3.25 (42.8)	51.7 (40.9)
				Treatment B = Co-administration of separate tablets of DTG 50 mg and RPV 25 mg/Fed (Moderate fat)	0.0830 (38.2)	4.00 (1.5 - 9.0)	2.93 (43.7)	52.5 (41.2)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (μg/mL)	tmax (h) Median (Range)	AUC(0-∞) (μg.h/mL)	t1/2 (h)
Dolutegravir								
ING113674	To evaluate relative bioavailability study of three different tablet formulations of DTG 50 mg and effect of food on the selected formulation	R, O, XO	24: 10/14 38.6 (20-61) Healthy subjects	Part A DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AP	2.67 (35)	3.00 (1.0 - 5.0)	53.2 (34)	14.2 (19)
				DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AW	2.64 (30)	2.56 (1.0 - 6.0)	50.6 (27)	14.1 (21)
				DTG/ 50 mg/ tablet/ oral/ single dose/ formulation AX	2.77 (32)	2.04 (1.0 - 4.0)	53.7 (34)	14.4 (19)
				Part B (formulation AW) DTG/ 50 mg/ tablet/ oral/ single dose, fasted	2.65 (28)	2.06 (1.0 - 5.0)	50.3 (27)	14.1 (22)
				DTG/ 50 mg/ tablet/ oral/ single dose, low fat	3.88 (21)	3.0 (2.0 - 5.1)	66.7 (35)	13.4 (19)
				DTG/ 50 mg/ tablet/ oral/ single dose, high fat	4.44 (24)	5.0 (1.0 - 8.0)	83.6 (35)	13.4 (21)
				DTG/ 50 mg/ tablet/ oral/ single dose, moderate fat	4.03 (19)	4.0 (2.0 - 6.0)	71.0 (31)	13.5 (19)

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

Protocol No.	Study Objective(s)	Study Design	No. of Subjects (M/F) Age Mean(Range) Subject type	Treatment Details (Drug/Dose/ Form/Route/ Frequency)	Geometric Mean Parameters (CV%)			
					Cmax (ng/mL)	tmax (h) Median (Range)	AUC(0-∞) (ng.h/mL)	t1/2 (h)
Rilpivirine								
TMC278-TiDP6-C137	Determine the effect of different types of meals on the oral bioavailability of RPV after a single dose, formulated as the Phase III tablet	R, O, XO	20: 18/2: 36.7 (21-55) Healthy subjects	Treatment A: RPV/ 75 mg/ tablet/ oral/ single dose, normal-fat breakfast	270.7 (40)	5.0 (2.0 - 9.0)	10550 (39)	43.7 (46)
				Treatment B: RPV/ 75 mg/ tablet/ ora/ single dose, fasted	148.8 (39)	4.0 (2.0 - 24.0)	6269 (42)	48.9 (51)
				Treatment C: RPV/ 75 mg/ tablet/ oral/ single dose, high-fat breakfast	255.6 (37)	5.0 (3.0 - 9.0)	9682 (41)	40.0 (40)
				Treatment D: RPV/ 75 mg/ tablet/ oral/ single dose, protein-rich nutritional drink.	138.4 (38)	5.0 (4.0 - 9.0)	5378 (50)	42.8 (48)

Cmax = maximum concentration; tmax = first occurrence of Cmax ; AUC(0-∞) = area under the plasma concentration versus time curve from time 0 and extrapolated to infinity; t½ = apparent plasma half-life; R&D=research and development

Module 2.7.2

Summary of Clinical Pharmacology

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ABBREVIATIONS

AAG	α1-acid glycoprotein
ABC	Abacavir
ALAG	Absorption lag time
ALT	Alanine aminotransferase
ARV	Antiretroviral
AST	Aspartate aminotransferase
ATV	Atazanavir
AUC	Area under the concentration-time curve
AUC24h	Area under the plasma concentration-time curve from time of administration up to 24 hours post dosing
AUC(0-24h)	Area under the concentration-time curve from zero (pre-dose) to 24 hours post dosing
AUC∞	AUC extrapolated to infinity
AUC(0-∞)	Area under the concentration-time curve from time zero (pre-dose) extrapolated to infinite time
%AUCex	Percentage of AUC(0-∞) obtained by extrapolation
AUC(0-t)	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
AUClast	Area under the curve from from time zero (pre-dose) until last measured time point
AZT	Zidovudine
BA	Bioavailability
BCV	Boceprevir
BE	Bioequivalence
BMI	Body mass index
C0avg	Average pre-dose concentration
C0h	Observed plasma concentration prior to the beginning of a dosing interval
C24h	Plasma concentration after 24 hours
c/mL	Copies/mL
CAR	Current antiretroviral regimen
CBZ	Carbamazepine
CDC	Centers for Disease Control
CI	Confidence interval
CL	Systemic clearance of parent drug
CL/F	Apparent clearance following oral dosing
CL/F/kg	Apparent oral clearance adjusted for body weight
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CrCL	Creatinine clearance
CSF	Cerebrospinal fluid
CSR	Clinical study report

Css,avg	Average steady-state plasma concentration, calculated by AUC24h/τ at steady-state (τ = dosing interval)
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
Ct	Last observed quantifiable concentration
CV	Coefficient of variance
%CVb	Between-subject coefficient of variation on the geometric mean
CYP	Cytochrome P450
DCV	Daclatasvir
ddI	Didanosine
DDI	Drug-drug interaction
DRV	Darunavir
DTG	Dolutegravir, TIVICAY
DTG + RPV	DTG 50 mg + RPV 25 mg
DTG/RPV	DTG/RPV 50 mg/25 mg
DTG/RPV FDC	DTG/RPV 50 mg/25 mg FDC
EC90	Concentration at which 90% of the maximal effect is achieved
ECG	Electrocardiogram
EE	Ethinyl estradiol
EFV	Efavirenz
ERPF	Effective renal plasma flow
ESRD	End-stage renal dysfunction
ETR	Etravirine
EU	European Union
F	Absolute bioavailability
FDC	Fixed-dose combination
FI	Fluctuation index
FPV	Fosamprenavir
FTC	Emtricitabine
GFR	Glomerular filtration rate
GLS	Geometric Least-Squares
h or hr	Hour(s)
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HSA	Human serum albumin
IIV	Inter-individual variability
IC50	Concentration at which 50% inhibition was observed
INI	Integrase inhibitor
INSTI	Integrase strand transfer inhibitor
IR	Immediate release
ITT	Intent-to-treat
IV	Intravenous
Ka	First-order rate of absorption
KTZ	Ketoconazole
λz	Terminal phase rate constant

LC-MS-MS	Liquid chromatography tandem mass spectroscopy
LDL	Low-density lipoprotein
LPV/RTV	Lopinavir/ritonavir
LS	Least square
MATE	Multidrug and toxin extrusion transporter
MDZ	Midazolam
NA	Not applicable
NGMN	Norelgestromin/norgestimate
NNRTI	Non-nucleoside HIV-1 reverse transcriptase inhibitor
NQ	Non-quantifiable (<4 ng/mL)
NRTI	Nucleoside HIV-1 reverse transcriptase inhibitor
N(t)RTI	Nucleotide HIV-1 reverse transcriptase inhibitor
NVP	Nevirapine
OBT	Optimized background therapy
OC	Oral contraceptive
OCT2	Organic cation transporter 2
OMP	Omeprazole
PAH	Para-aminohippurate
PA IC90	Protein-adjusted concentration required for 90% viral inhibition
PD	Pharmacodynamic
PDVF	Protocol-defined virologic failures
P-gp	P-glycoprotein
PGx	Pharmacogenetics
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per protocol
QTc	QT interval corrected for heart rate
QTcB	QT duration corrected for heart rate by Bazett's formula
QTcF	QT duration corrected for heart rate by Fridericia's formula
RAL	Raltegravir
RAM	Resistance-associated mutation
RBT	Rifabutin
RIF	Rifampin
RNA	Ribonucleic acid
RPV	Rilpivirine, EDURANT
RT-PCR	Reverse transcriptase polymerase chain reaction
SD	Standard deviation
SE	Single entity
SPV	Simeprevir
t	Time of last observed quantifiable concentration
t½	Terminal phase half-life
τ	Dosing interval
TDF	Tenofovir
tlag	Lag time before observation of drug concentrations in sampled matrix
tlast	Time of last quantifiable concentration
TLOVR	Time to loss of virologic response

TLOVR (non-VF)	Time to loss of virologic response imputation where all premature discontinuations due to virologic failure were considered to be events
tmax	Time of occurrence of Cmax
TPV	Tipranavir
TVR	Telaprevir
UDP	Uridine diphosphate
UGT	Uridine diphosphate glucuronosyltransferase
UGT1A1	Uridine diphosphate glucuronosyltransferase isozyme 1A1
US	United States
VF	Virologic failure
V/F or Vd/F	Apparent volume of distribution after extravascular (e.g., oral) administration

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1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

Dolutegravir (TIVICAY™, GSK1349572), a HIV INSTI, and RPV (TMC278; EDURANT, GSK1329758), a NNRTI, are currently under clinical development as a FDC tablet. Both DTG and RPV are commercially available products in many markets worldwide. TIVICAY (DTG) Tablets, 50 mg are available in over 85 countries, including the US, EU, and Canada. Dolutegravir was developed by GSK on behalf of ViiV Healthcare. EDURANT (RPV) Tablets, 25 mg have been approved for the treatment of HIV-1 infection in ARV treatment-naïve adult patients in over 85 countries including the US, EU, and Canada. In most countries, the indication is further restricted to patients with plasma viral load ≤100,000 c/mL. Rilpivirine was developed by Janssen Sciences Ireland UC. The new formulation being developed is a FDC of DTG/RPV 50 mg/25 mg (GSK3365791) with a proposed indication for the treatment of HIV-1 infection in virologically-suppressed (HIV-1 RNA <50 c/mL) adults without known or suspected resistance to either ARV component. The proposed recommended oral dose for adults is 1 tablet administered once daily with a meal.

This document summarizes the relevant human PK, PD, and PK/PD relationships of the FDC consisting of DTG/RPV 50 mg/25 mg referred to as DTG/RPV FDC and the SEs DTG and RPV.

1.1. Organization of Data

All data pertaining to the DTG/RPV FDC development is considered "pivotal" and is presented with this application. Where no studies have been performed with DTG and RPV, additional previously submitted studies from DTG or RPV SE development programs support this application and are categorized as "key" studies or "supportive" studies:

Key SE Studies: these studies provide data that may be included in labeling, and were conducted during the individual agent development programs. Summaries of key clinical pharmacology studies are presented in Table 1 and CSRs for these studies have been previously submitted.

Supportive SE Studies: these studies are not essential for the FDC Benefit Risk assessment, but are considered helpful to the reviewer and supportive of the proposed indication. A summary of supportive studies is presented in Table 2, but reports will be made available upon request for the convenience of the reviewer.

Table 1 Summary of Completed Clinical Pharmacology Studies that were Previously Submitted as Part of the TIVICAY or EDURANT Registration and are "Key"Studies to the DTG/RPV FDC Submission

Study	Study Design	Population	Treatment Details	Main Conclusions
Single-dose PK/Mass Balance				
TMC278-C119 (RPV) Status: Complete	Open label, single-dose, mass-balance study	Healthy adult male subjects	RPV 150 mg (^{14}C-labeled and unlabeled); oral solution, single dose.	Most of the radioactivity was recovered in feces (on average 85.1% of the dose). The mean recovery of radioactivity in urine was 6.1% of the administered dose. RPV was extensively metabolized, with more than 15 metabolites detected. The major fecal metabolites originated from oxidative pathways. The most abundant metabolite in feces, metabolite 42, originated from oxidation at the 5-position of the pyrimidinyl moiety and accounted for a mean of 16.1% of the dose. In urine, apart from the carboxylic acid metabolite (metabolite 30), all metabolites were phase-2 metabolites (glucuronides or glutathione-derived conjugates). Unchanged drug accounted for the major part of the radioactivity in plasma.
ING111853 (DTG) GSK Document Number: RM2009/00293/00 Status: Complete	Open-label, single-dose study	Healthy adult subjects	DTG 20 mg (^{14}C-labeled and unlabeled); oral suspension; single dose; fasted.	Following oral administration, the total mean recovery of DTG was 95.6% of the administered dose, with a mean recovery of 64.0% in feces and 31.6% in urine. DTG was the predominant circulating compound in plasma. Low mean blood:plasma concentration ratios indicated minimal association of radioactivity with the blood cellular components.
Repeat-dose PK				
ING111322 (DTG) GSK Document Number: RM2008/00375/00 Status: Complete	Part 1: double-blind, randomized, placebo-controlled, repeat-dose, escalation study	Healthy adult subjects	Part 1: DTG 10, 25, and 50 mg; oral suspension; once daily; 10 days; fasted.	Following repeat-dose administration, plasma concentrations of DTG reached steady state by approximately 5 days of dosing. DTG AUC and $C\tau$ increased proportionally between 10 and 50 mg once daily. The increase in DTG Cmax was slightly less than dose-proportional. Accumulation was observed in AUC, Cmax, and $C\tau$ following repeat-dose administration of DTG once daily, with accumulation ratios estimated to be 1.24 to 1.42, 1.16 to 1.36, and 1.29 to 1.53, respectively, across 10 to

Study	Study Design	Population	Treatment Details	Main Conclusions
				50 mg once daily dose levels. DTG showed time-invariant PK.
TMC278-C103 (RPV)	Open-label, randomized, multiple-dose ranging, parallel-group study	Healthy adult subjects	Treatment A: RPV 25 mg; tablet; oral; once daily; 14 days. Treatment B: RPV 50 mg; oral; once daily; 14 days. Treatment C: RPV 100 mg; oral; once daily; 14 days. Treatment D: RPV 150 mg; oral; once daily; 14 days.	The single dose and steady-state PK parameters of RPV (Cmax and AUC24h) increased proportional to the dose across the dose range of 25 mg to 150 mg once daily. Steady state was reached before Day 7 for all dose levels. The inter-individual variability was low to moderate and independent of the dose.
Special Populations: Intrinsic Factors				
ING115381 (DTG) GSK Document Number: 2011N123593_00 Status: Complete	Open-label, single-dose study	Healthy adult Japanese subjects	DTG 50 mg; tablet; oral; single dose.	The PK of DTG following single-dose oral administration to Japanese healthy subjects were similar to previously observed parameters in US healthy subjects, mainly Caucasian. Dose adjustment of DTG in Japanese subjects solely based on PK is not necessary.
ING113097 (DTG) GSK Document Number: 2011N115189_00 Status: Complete	Single-dose, open-label, parallel-group, 2-part, adaptive study	Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function	DTG 50 mg; tablet; oral; single dose.	Total DTG exposure in plasma was similar between subjects with moderate hepatic impairment and matched healthy subjects. DTG can be taken without dose adjustment in subjects with mild to moderate hepatic impairment.
ING113125 (DTG); GSK Document Number: 2011N130599_00 Status: Complete	Single-dose, open-label, parallel-group, 2-part study	Subjects with severe renal impairment and matched, healthy control subjects with normal renal function	DTG 50 mg; tablet; oral; single dose.	DTG exposure was lower in subjects with severe renal impairment (CrCL< 30 mL/min) than in healthy, matched subjects: AUC(0-∞) and Cmax were 40% and 23% lower, respectively. The moderate reduction in DTG exposure in subjects with severe renal impairment was not considered clinically significant. No dose adjustment of DTG is needed in subjects with mild to severe renal impairment (not on renal replacement therapy).
TMC278-TiDP6-C130 (RPV) Status: Complete	Open-label, parallel, controlled, sequential study	Subjects with mild or moderate hepatic impairment and matched; healthy control subjects	RPV 25 mg; oral; once daily; 11 days	After a single dose, RPV Cmax and AUC24h were 6% and 18% higher, respectively, in subjects with mild hepatic impairment, compared with healthy subjects. At steady-state (Day 11) Cmax, AUC24h, Cmin and C24h were

Study	Study Design	Population	Treatment Details	Main Conclusions
		with normal hepatic function		27%, 47%, 31% and 76% higher, respectively. After a single dose in subjects with moderate hepatic impairment, Cmax and AUC24h were 29% and 24% lower, respectively, compared with healthy subjects. At steady-state, Cmax was 5% lower and AUC24h was 5% higher. Mean Cmin and C24h were increased by 11% and 28%, respectively, in subjects with moderate hepatic impairment as compared with healthy subjects. The results of the trial also demonstrate that administration of RPV 25 mg once daily was generally safe and well tolerated and that no dose adjustment of RPV is needed in subjects with mild or moderate hepatic impairment.
Drug-drug Interactions				
Dolutegravir				
ING111322 (MDZ) GSK Document Number: RM2008/00375/00 Status: Complete	Part 1: double-blind, randomized, placebo-controlled, repeat-dose, escalation study	Healthy adult subjects	Part 1: DTG 25 mg; oral suspension; once daily; 10 days; fasted. MDZ 3 mg; oral single dose on Day -1 and Day 10.	Co-administration of repeat doses of DTG 25 mg once daily with a single dose of 3 mg MDZ resulted in no significant change in MDZ plasma AUC, indicating no induction or inhibition effect of DTG on CYP3A activity. Thus, DTG will not affect exposure of CYP3A substrates following co-administration.
ING111405 (LPV/RTV, DRV/RTV) GSK Document Number: RM2008/00863/00 Status: Complete	Randomized, open-label, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	DTG 30 mg; tablet; oral; once daily; 5 days. DTG 30 mg; tablet; oral; once daily + LPV/RTV 400/100 mg; tablet; oral; q12h; 14 days. DTG 30 mg; tablet; oral; once daily + DRV (tablet) /RTV (capsule) 600/100 mg; oral; q12h; 14 days.	Co-administration of LPV/RTV had no effect on plasma DTG PK. Co-administration of DRV/RTV resulted in decreased plasma DTG exposures (DTG AUC(0-∞), Cmax, and Cτ were decreased by 22%, 11%, and 38%, respectively); however, these decreases are not considered to be clinically significant. DTG can be co-administered with DRV/RTV or LPV/RTV with no dose adjustment.
ING111602 (Antacid, Multivitamins) GSK Document Number: UM2009/00142/00	Open-label, single-dose, randomized, 4-period crossover study	Healthy adult subjects	DTG 50 mg; tablet; oral; single dose. DTG 50 mg; tablet; oral; single dose + multivitamin; tablet; oral; single dose.	Concurrent administration of a multivitamin decreased DTG AUC, Cmax, and C24 by 33%, 35%, and 32%, respectively, on average. The decrease is not considered clinically relevant and DTG may be taken concomitantly with a multivitamin without dose adjustment.

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			DTG 50 mg; tablet; oral; single dose + Maalox Advanced Maximum Strength; 20mL suspension; single dose. DTG 50 mg; tablet; oral; single dose 2 hrs prior to Maalox Advanced Maximum Strength 20mL; suspension; single dose.	Concurrent administration of Maalox decreased DTG AUC, Cmax, and C24 by 74%, 72%, and 74%, respectively, on average. Administration of Maalox 2 hours after DTG decreased DTG AUC, Cmax, and C24 by 26%, 18%, and 30%, respectively, on average. Concomitant administration of DTG and antacids should be avoided. It is recommended that DTG should be administered 2 hours before or 6 hours after antacids.
ING111603 (ETR) GSK Document Number: RM2008/00859/00 Status: Complete	Open-label, repeat-dose, 2-period, single-sequence study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily + ETR 200 mg; tablet; oral; q12h; 14 days.	Co-administration of DTG and ETR resulted in decreased steady-state plasma DTG AUC(0-τ), Cmax, and Cτ by 71%, 52%, and 88%, respectively. Co-administration of DTG and ETR is not recommended.
Study ING111604 (TDF) GSK Document Number: RM2008/00793/00 Status: Complete	Open-label, repeat-dose, single-sequence, 3-period study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. TDF 300 mg; tablet; oral; once daily; 7 days. DTG 50 mg; tablet; oral; once daily + TDF 300 mg; tablet; oral; once daily; 5 days.	PK parameters of DTG and TDF during combination therapy were similar to those when either drug was given alone, demonstrating no drug interaction. Therefore, these 2 drugs can be taken together without dose adjustment
ING111854 (ATV, ATV/RTV) GSK Document Number: UM2009/00075/00 Status: Complete	Randomized, open-label, repeat-dose, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	Period 1: DTG 30 mg; tablet; oral; once daily; 5 days; fed. Period 2: DTG 30 mg; tablet; oral; once daily + ATV (capsule) /RTV (capsule) 400/100 mg; once daily; 14 days. DTG 30 mg; tablet; oral; once daily + ATV 400 mg; capsule; oral; once daily;	Co-administration of DTG with ATV/RTV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 62%, 34%, and 121%, respectively. Co-administration of DTG with ATV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 91%, 50%, and 180%, respectively. Although co-administration of ATV/RTV or ATV with DTG resulted in increased DTG plasma exposure, this effect is not considered clinically significant based on accumulated toxicity data in animals, and safety and tolerability data in humans receiving DTG to date. Therefore it is recommended that no dose adjustment is necessary

Study	Study Design	Population	Treatment Details	Main Conclusions
			14 days.	when DTG is co-administered with ATV/RTV or ATV.
ING111855 (EE/NGMN) GSK Document Number: 2012N134648_00 Status: Complete	Randomized, 2-period, double-blind study	Healthy adult female subjects	DTG 50 mg or placebo; oral; tablet; once daily; Days 1-11 and DTG 50 mg or placebo; tablet; oral; once daily; Days 12-21. EE/NGMN; tablet; oral; once daily; Days 1-21.	Co-administration with DTG had no effect on the PK of NGMN and EE in healthy female subjects receiving Ortho-Cyclen. DTG and common oral contraceptives can be co-administered without dose adjustment.
ING112934 (ETR/LPV/RTV, ETR/DRV/RTV) GSK Document Number: UM2009/00077/00 Status: Complete	Randomized, open-label, repeat-dose, 3-period, single-sequence, 2-cohort adaptive study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily + ETR/LPV/RTV 200/400/100 mg; tablet; oral; q12h; 14 days. DTG 50 mg; tablet; oral; once daily + ETR (tablet) DRV (tablet)/RTV (capsule) 200/600/100 mg; oral; once daily; 14 days.	Co-administration of DTG with ETR/LPV/RTV had no effect on DTG AUC(0-τ) and Cmax, while increasing Cτ by 28% and t1/2 by 36%. Co-administration of DTG with ETR/DRV/RTV resulted in decreased plasma DTG exposures, with plasma DTG AUC(0-τ), Cmax, and Cτ on average 25%, 12%, and 37% lower when co-administered with ETR/DRV/RTV compared with DTG given alone. These effects of ETR/LPV/RTV and ETR/DRV/RTV on DTG exposures are not considered clinically relevant. Co-administration of LPV/RTV and DRV/RTV attenuated the effect of ETR on DTG exposure. DTG may be co-administered with ETR without a dosage adjustment if the subject is receiving concomitant LPV/RTV or DRV/RTV.
ING112941 (OMP) GSK Document Number: RM2009/00534/00 Status: Complete	Part 1: Randomized, open-label, 2-sequence, 3-treatment crossover study	Healthy adult subjects	Part 1: DTG 50 mg; tablet; oral; single dose; fasted. DTG 50 mg; tablet; oral; single dose; within 30 minutes after the start of a high-fat meal. DTG 50 mg; tablet; oral; single dose + OMP 40 mg; capsule; oral; once daily; fasted; 5 days.	Co-administration with OMP had no significant effect on plasma DTG AUC(0-τ), AUC(0-∞), Cmax, and C24. DTG can be co-administered with OMP without dose adjustment.
ING113068 (FPV/RTV) GSK Document Number: 2010N110708_00	Part A: open-label, repeat-dose, 2-period, single-sequence	Healthy adult subjects	Part A: DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral;	Amprenavir concentrations in combination with DTG were similar to literature values suggesting that DTG does not have a significant effect on amprenavir exposure. Co-administration of FPV/RTV decreased DTG plasma

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			once daily + FPV 700 mg; tablet / RTV 100 mg; capsule; oral; q12h; 10 days.	exposures: AUC(0-τ), Cmax, and Cτ decreased by 35%, 24%, and 49% , respectively. The effect of FPV/RTV on DTG exposure is not considered clinically significant, therefore no DTG dose adjustment is necessary when co-administered with FPV/RTV. However caution should be given to INSTI-resistant subjects.
ING113096 (TPV/RTV) GSK Document Number: RM2010/00261/00 Status: Complete	Randomized, open-label, repeat-dose, 3-period, single-sequence, study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. TPV/RTV 500/200 mg; capsule; oral; BID; 7 days DTG 50 mg; tablet; oral; once daily and TPV/RTV 500/200 mg; capsule; oral; BID; 5 days	Co-administration of DTG with TPV/RTV resulted in a 59%, 46%, and 76% decrease in plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. DTG 50 mg BID dosing is recommended when co-administered with TPV/RTV based on clinical efficacy data.
ING113099 (RIF, RBT) GSK Document Number: 2011N119786_00 Status: Complete	Randomized, open-label, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 7 days. DTG 50 mg; tablet; oral; BID; 7 days then DTG 50 mg; tablet; oral; BID + RIF 600 mg; capsule; oral; once daily; 14 days. DTG 50 mg; tablet; oral; once daily for 7 days then DTG 50 mg; tablet; oral BID+ RBT 300 mg; capsule; oral; once daily; 14 days.	Co-administration of DTG 50 mg BID with RIF 600 mg once daily significantly reduced plasma DTG concentrations relative to DTG 50 mg BID alone, but resulted in 18 to 33% higher plasma DTG Cmax, AUC(0-24), and Cτ than DTG 50 mg once daily alone. Co-administration of DTG 50 mg once daily with RBT 300 mg once daily resulted in a 16% increase in DTG Cmax, no change in AUC(0-τ), and a 30% reduction in Cτ compared with DTG 50 mg once daily alone. DTG 50 mg BID is recommended when co-administered with RIF. No dose adjustment is needed when DTG is co-administered with RBT.
ING114005 (EFV) GSK Document Number: RM2010/00328/00 Status: Complete	Open-label, repeat-dose, 3-period, single-sequence study	Healthy adult subjects	DTG 100 mg; tablet; oral; single dose. DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily in AM + EFV 600 mg; tablet; oral; once daily in PM; 14 days.	Co-administration of EFV with DTG did not affect EFV exposure. Co-administration of DTG with EFV resulted in a 57%, 39%, and 75% decreased plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. DTG 50 mg BID is recommended when co-administered with EFV based on clinical efficacy data

Study	Study Design	Population	Treatment Details	Main Conclusions
ING115696 (Prednisone) GSK Document Number: 2011N126791_00 Status: Complete	Open-label, repeat-dose, 2-period, single-sequence study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily; Days 1-10 + prednisone; tablet; oral; once daily (60 mg Days 1-5; 50 mg Day 6; 40 mg Day 7; 30 mg Day 8; 20 mg Day 9; 10 mg Day 10).	DTG PK parameters were similar between Day 5 and Day 10 in Period 2. Co-administration of prednisone 60 mg once daily x 5 days + 5 days of taper with DTG (Day 10 in Period 2) resulted in an increase in the mean DTG AUC, Cmax and Cτ by 11%, 6%, and 17%, respectively. Steady state was reached for DTG following 5 days co-administration of DTG with prednisone. No dose adjustment is needed for DTG when co-administered with prednisone.
ING115697 (TVR, BCV) GSK Document Number: 2012N140471_01 Status: Complete	Randomized, open-label, 2-period, single-sequence, 2-cohort study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days. DTG 50 mg; tablet; oral; once daily + TVR 750 mg; tablet; oral; q8h; 10 days. DTG 50 mg; tablet; oral; once daily + BCV 800 mg; capsule; oral; q8h; 10 days.	Co-administration of DTG with BCV had no effect on plasma exposure of DTG. Co-administration of DTG with TVR resulted in increased DTG plasma exposures: AUC(0-τ), Cmax, Cτ, increased by 25%, 19%, 37%, respectively. Co-administration of BCV or TVR with DTG had no clinically significant effect on DTG PK. Plasma BCV and TVR PK data for the DTG-TVR and DTG-BCV combination treatment were similar to historical TVR data, indicating no effect of DTG on BCV or TVR exposure.
ING115698 (Methadone) GSK Document Number: 2012N133261_00 Status: Complete	Open-label, repeat-dose, 2-period, single-sequence study	Healthy adult subjects enrolled in a methadone maintenance program	Stable methadone dose; oral solution; once daily; 3 days. Stable methadone dose; oral solution + DTG 50 mg; tablet; oral; BID; 5 days.	Co-administration of methadone with repeat doses of 50 mg DTG had no effect on total, R-, and S-methadone PK. No dose adjustment in methadone is required when given in combination with DTG.
LAI116181 (RPV) GSK Document Number: 2011N130484_00 Status: Complete	Cohort 1: Open-label, repeat-dose, single-sequence, 3-period study	Healthy adult subjects	Cohort 1: Treatment A = DTG 50 mg; tablet; oral; q24h; 5 days. Treatment B = RPV 25 mg; tablet; oral; q24h; 11 days. Treatment C = RPV 25 mg; tablet; oral; q24h +	Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ) and Cmax, and a 22% increase in Cτ. Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in Cτ. There was no significant drug interaction between DTG and RPV. DTV and RPV can be co-administered without dose adjustment.

Study	Study Design	Population	Treatment Details	Main Conclusions
			DTG 50 mg; tablet; oral; q24h; 5 days.	
ING116898 (Calcium & Iron Supplements) GSK Document Number: 2013N163904_00 Status: Complete	A phase 1 open-label, randomized, 2-cohort, 4-period, crossover study	Healthy adult subjects	Cohort 1: DTG 50 mg; tablet; oral; single dose; fasted. DTG 50 mg; tablet; oral; single dose + calcium carbonate 1200 mg; tablet; oral; fasted. DTG 50 mg, tablet; oral; sinlge dose + calcium carbonate 1200 mg; tablet; oral; fed. DTG 50 mg, tablet, oral, single dose, fasted, 2 hours prior to calcium carbonate 1200 mg, tablet, oral. Cohort 2: DTG 50 mg; tablet; oral; single dose; fasted. DTG 50 mg; tablet; oral; single dose + 324 mg ferrous fumarate; oral, fasted. DTG 50 mg; tablet; oral; sinlge dose + 324 mg ferrous fumarate; oral; fed. DTG 50 mg; tablet; oral;	Under fasted conditions, co-administration of calcium carbonate reduced DTG exposure by 37 to 39% and ferrous fumarate reduced DTG exposure by 54 to 57%. Co-administration of DTG with calcium carbonate or ferrous fumarate under fed conditions or dosing DTG 2 hours prior to these supplements showed DTG exposure similar to those when DTG was given alone under fasted conditions. DTG can be given concurrently with calcium or iron supplements with food; without food, DTG should be given 2 hours prior to or 6 hours after calcium or iron supplements.

Study	Study Design	Population	Treatment Details	Main Conclusions
			single dose; fasted; 2 hours prior to 324 mg ferrous fumarate; oral,	
200901 (CBZ) GSK Document Number: 2013N185729_00 Status: Complete	A phase 1, open-label, 3-period, fixed-sequence crossover study	Healthy adult subjects	Period 1: DTG 50 mg; tablet; oral; once daily (Days 1-5) Period 2: CBZ 100 mg; tablet; oral; BID (Days 1-3); CBZ 200 mg; tablet; oral; BID (Days 4-6); CBZ 300 mg; tablet; oral; BID (Days 7-16) Period 3: DTG 50 mg; tablet; oral, once daily + CBZ 300 mg; tablet; oral; BID (Days 1-5)	Co-administration of DTG with CBZ resulted in decreases in DTG Cmax, AUC, and $C\tau$ by approximately 33%, 49%, and 73%, respectively, compared with DTG administered alone. DTG dose adjustment from 50 mg once daily to 50 mg twice daily is recommended when DTG is co-administered with CBZ.
201102 (DCV) GSK Document Number: 2014N203043_00 Status: Complete	A single-center, open-label, 3-period, crossover study	Healthy adult subjects	Treatment A = DTG 50 mg, tablet, oral, q24h x 5 days Treatment B = DCV 60 mg, tablet, oral, q24h x 5 days Treatment C = DCV 60 mg, tablet, oral, q24h + DTG 50 mg, tablet, oral, q24h x 5 days	Plasma exposure of DCV did not appear to be meaningfully affected when co-administered with DTG compared with DCV administered alone. Co-administration of DTG 50 mg q24h with DCV 60 mg q24h increased DTG AUC(0-τ), Cmax, and $C\tau$ by approximately 33%, 29%, and 45%, respectively, compared with DTG administered alone. DTG and DCV can be co-administered without dose adjustment.

Study	Study Design	Population	Treatment Details	Main Conclusions
201167 (Metformin) GSK Document Number: 2014N203038_00 Status: Complete	Phase I, open-label, parallel group, 3-period, fixed-sequence study	Healthy adult subjects	Cohort 1: Period 1: Metformin IR 500 mg, tablet, oral, q12h (Days 1-5); fed Period 2: Metformin IR 500 mg, tablet, oral, q12h + DTG 50 mg, tablet, oral, q24h (Days 1-7); fed Period 3: Metformin IR 500 mg, tablet, oral, q12h (Days 1-10); fed Cohort 2: Period 1: Metformin IR 500 mg, tablet, oral, q12h (Days 1-5); fed Period 2: Metformin IR 500 mg, tablet, oral, q12h + DTG 50 mg, tablet, oral, q12h (Days 1-7); fed Period 3: Metformin IR 500 mg, tablet, oral, q12h (Days 1-10); fed	Co-administration of DTG 50 mg q24h with metformin 500 mg q12h resulted in increases in metformin AUC(0-τ) and Cmax by 79% and 66%, respectively, compared with metformin administered alone. Co-administration of DTG 50 mg q12h with metformin 500 mg q12h resulted in increases in metformin AUC(0-τ) and Cmax by 145% and 111%, respectively, compared with metformin administered alone. Effects were DTG dose dependent. Subjects should be monitored when starting and stopping co-administration of DTG with metformin and a dose adjustment of metformin should be considered to maintain glycemic control
Rilpivirine				
TMC278-C104 (TDF) Status: Complete	Open-label, 2-period, randomized study	Healthy adult subjects	Session I: RPV 150 mg once daily; Days 1-8; oral. Session II: Group 1: TDF 300 mg once daily; Days 1-16 + RPV 150 mg once daily; Days 9-16; oral. Group 2: TDF 300 mg once daily; Days 1-16 + RPV 150 mg once daily; Days 1-8; oral	No relevant changes were observed in the steady-state PK of RPV during co-administration with TDF as compared with administration of RPV alone. The mean exposure to TDF (AUC24h) was increased 1.23-fold when co-administered with RPV, but this increase is not considered to be clinically relevant. No treatment effect was shown for the urinary excretion of TDF in the presence of RPV.

Study	Study Design	Population	Treatment Details	Main Conclusions
TMC278-C106 (ddI) Status: Complete	Open-label, randomized study	Healthy adult subjects	Session I: Groups I & II RPV 150 mg once daily; Days 1-7; oral. Session II: Group I: ddI 400 mg once daily; Days 1-14 + RPV 150 mg once daily on Days 8-14; oral. Group II: ddI 400 mg once daily; Days 1-14 + RPV 150 mg once daily; Days 1-7; oral.	No relevant changes were observed in the steady-state PK of RPV or ddI during co-administration of these drugs compared with their administration alone.
TMC278-C105 (LPV/RTV) Status: Complete	Open-label, randomized, 2-way crossover study	Healthy adult subjects	Treatment A: RPV 150 mg once daily; Days 1-10; oral. Treatment B: LPV/RTV 400/100 mg BID; Days 1-20 + RPV 150 mg once daily; Days 11-20; oral.	The mean exposure (AUC24h) to RPV was increased 1.52-fold during co-administration with LPV/RTV, as compared with RPV administration alone. The mean Cmin of RPV was increased more than the mean Cmax (1.74-fold and 1.29-fold, respectively). RPV did not affect the PK of LPV or low-dose RTV.
TMC278-C112 (DRV/RPV) Status: Complete	Open-label, randomized, 2-way crossover study	Healthy adult subjects	Treatment A: RPV 150 mg once daily; Days 1-11; oral. Treatment B: DRV/RTV 800/100 mg once daily; Days 1-22 + RPV 150 mg once daily; Days 12-22; oral.	The mean exposure (AUC24h) to RPV was increased 2.30-fold during co-administration with DRV/RTV when compared with administration of RPV alone. RPV did not affect the mean exposure (AUC24h) to DRV. The mean exposure (AUC24h) to RTV was decreased by 15% compared with administration of DRV/RTV alone.
R278474-C101 (EFV/NVP) Status: Complete	Open-label, parallel group, add-on study	HIV-1 infected male subjects	Group 1: At least 2 N(t)RTIs + EFV 600 mg once daily + RPV 50 mg; single dose; oral. Group 2: At least 2 N(t)RTIs + NVP 200 mg BID + RPV 50 mg; single dose; oral.	In HIV-1 infected subjects, the exposure to RPV (AUClast) after a single dose of 50 mg was decreased by approximately 67% when co-administered with EFV and at least 2 N(t)RTIs compared with historical controls of RPV administered alone in healthy subjects. Co-administration of a single 50 mg dose of RPV with NVP and at least 2 N(t)RTIs did not affect the systemic exposure to RPV compared with historical controls of RPV administered alone in healthy subjects.

Study	Study Design	Population	Treatment Details	Main Conclusions
TMC278-TiDP6-C153 (RAL) Status: Complete	Open-label, 2-way crossover study	Healthy adult subjects	Treatment 1: RPV 25 mg once daily; Days 1-11, oral Treatment 2: RAL 400 mg BID; Days 1-15 + RPV 25 mg once daily; Days 5-15, oral	The values for the metabolic ratios of the PK parameters (RAL-glucuronide/RAL) were comparable after intake of RAL alone or co-administered with RPV, indicating that RPV does not affect the glucuronidation metabolic pathway of RAL.
R278474-C108 (RIF) Status: Complete	Randomized, open-label, 3-way crossover study	Healthy adult subjects	Treatment 1: RPV 150 mg once daily; Days 1-7, oral Treatment 2: RIF 600 mg once daily; Days 1-7, oral Treatment 3: RPV 150 mg once daily + RIF 600 mg once daily; Days 1-7, oral	The mean exposure (AUC24h) to RPV was decreased by 80% when RPV was co-administered with RIF compared with administration of RPV alone. RPV did not affect PK of RIF or 25-desacetylrifampin.
TMC278-C125 (RBT) Status: Complete	Randomized, open-label, 3-way crossover study	Healthy adult subjects	Treatment 1: RPV 150 mg once daily; Days 1-11, oral Treatment 2: RBT 300 mg once daily; Days 1-11, oral Treatment 3: RPV 150 mg once daily; + RBT 300 mg once daily; Days 1-11, oral	The mean exposure (AUC24h) to RPV was decreased by 46% during co-administration with RBT compared with RPV administration alone. RPV had no relevant effect on the PK of RBT or its metabolite 25-O-desacetyl-RBT.
TMC278IFD1003 (RBT) Status: Complete	Open-label, 3-period study	Healthy adult subjects	Treatment 1: RPV 25 mg once daily; Days 1-11, oral Treatment 2: RBT 300 mg once daily; Days 1-17 + RPV 50 mg once daily; Days 1-11, oral Treatment 3: RBT 300 mg once daily; Days 1-17 + RPV 25 mg once daily; Days 1-11, oral	For RPV 25 mg once daily in the presence of RBT, RPV Cmin, Cmax, and AUC24h were 48%, 31%, and 42% lower, respectively, compared with RPV alone at the same dose level. For RPV 50 mg once daily in the presence of RBT, RPV Cmax was 43% higher compared with RPV 25 mg once daily alone, while Cmin was similar (90% CI within 80% to 125%) and AUC24h was 16% higher compared with RPV 25 mg once daily alone, with the upper limit of the 90% CI just above 125%. These changes in Cmax and AUC24h are not considered clinically relevant. While the RPV 25 mg once daily exposure was significantly reduced by the potent CYP3A4 enzyme activity inducer, RBT, doubling the RPV dose (50 mg once daily) was able to overcome this interaction.
TMC278-C127 (KTZ)	Open-label, randomized, 2-way crossover study	Healthy adult subjects	Treatment A: RPV 150 mg once daily; Days 1-11; oral	The mean exposure to RPV was increased 1.49-fold (AUC24h) and 1.30-fold (Cmax) when RPV was co-

Study	Study Design	Population	Treatment Details	Main Conclusions
Status: Complete			Treatment B: KTZ 400 mg once daily; Days 1-22 + RPV 150 mg once daily; Days 12-22; oral	administered with KTZ. The mean exposure (AUC24h) to KTZ was decreased by 24%.
TMC278-TiDP6-C123 (Sildenafil) Status: Complete	Open-label, randomized, 2-way crossover study	Healthy adult subjects	Treatment A: Sildenafil 50 mg single dose; Day 1; oral. Treatment B: RPV 75 mg once daily; Days 1-12 + Sildenafil 50 mg single dose; Day 12; oral	The steady-state PK of RPV was not affected by a single dose of sildenafil, and the exposure to sildenafil and its active metabolite, N-desmethyl sildenafil, were unaffected when RPV was co-administered at steady state.
TMC278-C116 (Atorvastatin) Status: Complete	Open-label, randomized, 2-way crossover study	Healthy adult subjects	Treatment A: Atorvastatin 40 mg once daily; Days 1-4; oral Treatment B: RPV 150 mg once daily; Days 1-15 + atorvastatin 40 mg once daily; Days 12-15; oral	The steady-state exposures (AUC24h) of RPV and atorvastatin were not affected by co-administration of the 2 drugs. However, the mean Cmax and Cmin values of atorvastatin were increased 1.35-fold and decreased by 15%, respectively, during co-administration with RPV. The mean AUC24h of the inactive metabolite atorvastatin lactone was decreased by 18%, while the AUC24h of the total HMG-CoA reductase activity (calculated as the sum of atorvastatin and the active metabolites 2-hydroxy- and 4-hydroxy-atorvastatin) was increased 1.21-fold when co-administered with RPV, as compared with atorvastatin alone. The changes in total HMG-CoA reductase activity during co-administration of atorvastatin and RPV were not considered to be clinically relevant.
TMC278-C120 (EE/Norethindrone) Status: Complete	Open-label, single-sequence study	Healthy female adult subjects	Treatment A: EE/ norethindrone 0.035 mg/1 mg once daily; Days 1-21; no trial drug on Days 22-28; oral Treatment B: EE/ norethindrone 0.035 mg/1 mg once daily; Days 29-49 + RPV 150 mg once daily; Days 29-43; no trial drug on Days 50-56;	The PK parameters of RPV were not influenced to any relevant degree by co-administration of RPV with EE and norethindrone when compared with administration of RPV alone in other trials. The PK parameters of EE were not affected by co-administration with RPV. The mean exposure (AUC24h) to norethindrone was decreased by 41% when RPV was co-administered with EE and norethindrone at a dose of 150 mg once daily. Although there were no marked effects of co-administration of RPV with EE and norethindrone on the luteinizing hormone, follicle stimulating hormone, and progesterone levels, the

Study	Study Design	Population	Treatment Details	Main Conclusions
			oral	results of this trial cannot discount the efficacy of OCs being compromised when combined with RPV at a dose of 150 mg once daily, given the reduction in exposure to norethindrone.
TMC278-TiDP6-C136 (EE/Norethindrone) Status: Complete	Open-label, single-sequence study	Healthy female adult subjects	Treatment A: EE/ norethindrone 0.035 mg/1 mg once daily; Days 1-21; no trial drug on Days 22-28; oral. Treatment B: EE/ norethindrone 0.035 mg/1 mg once daily; Days 29-49 + RPV 25 mg once daily; Days 29-43; no trial drug on Days 50-56; oral.	The steady-state PK parameters of RPV were not influenced by co-administration of RPV, given at a dose of 25 mg once daily with EE and norethindrone, compared with administration of RPV 25 mg once daily alone in another trial. The PK of EE and norethindrone were unaffected by co-administration of RPV 25 mg once daily apart from a 17% increase in the Cmax of EE that is not considered to be clinically relevant. No marked effects on the concentrations of luteinizing hormone, follicle stimulating hormone, or progesterone were observed with co-administration of RPV 25 mg once daily.
TMC278-TiDP6-C121 (Methadone) Status: Complete	Open-label, single-sequence study	HIV-negative subjects on stable methadone maintenance therapy	Individualized stable methadone therapy (60 to 150 mg once daily); Days -14-12 + RPV 25 mg once daily; Days 1-11, oral	Co-administration of RPV with stable individualized methadone maintenance therapy resulted in a 16% decrease in the AUC24h of R(–) methadone and S(+) methadone compared with administration of methadone alone. The AUC24h ratio of S(+) methadone and R(–) methadone was comparable between both treatments, indicating that the effects were not specific to a stereoisomer. The exposure to RPV when administered in the presence of methadone was within the range observed in other trials in healthy subjects. Co-administration of RPV 25 mg once daily and methadone did not have a clinically relevant effect on PD parameters.
TMC278-C114 (OMP) Status: Complete	Randomized, open-label, 2-way crossover study	Healthy adult subjects	Treatment A: RPV 150 mg once daily; Days 1-11; oral Treatment B: OMP 20 mg once daily; Days 1-22 + RPV 150 mg once daily; Days 12-22; oral	Co-administration of OMP resulted in a 56% decrease in the AUC24h of RPV after a single 150 mg dose of RPV and a 40% decrease after multiple 150 mg once daily doses of RPV at steady state compared with administration of RPV alone. A single dose of 150 mg RPV did not have a relevant influence on the AUC24h of OMP or its metabolites 5-hydroxy-OMP and OMP sulfone. Multiple 150 mg once daily doses of RPV decreased the

Study	Study Design	Population	Treatment Details	Main Conclusions
				AUC24h of OMP and OMP sulfone by 14% and 24%, respectively, compared with administration of OMP alone. The ratio of OMP sulfone to OMP AUC24h was not significantly affected by RPV, suggesting that RPV did not significantly influence the CYP3A4-mediated metabolism of OMP. The ratio of 5-hydroxy-OMP to OMP AUC24h increased 1.27-fold after co-administration of OMP with multiple 150 mg once daily doses of RPV at steady state, suggesting a modest induction of CYP2C19-mediated metabolism after repeated administration of RPV.
TMC278-C140 (Famotidine) Status: Complete	Randomized, open-label, 4-way crossover study	Healthy adult subjects	Treatment A: RPV 150 mg, single dose, Day 1; oral Treatment B: RPV 150 mg, single dose, Day 1, and famotidine 40 mg, single dose, Day 1, oral (2h before RPV intake) Treatment C: RPV 150 mg, single dose, Day 1, and famotidine 40 mg, single dose, Day 1, oral (4 hours after RPV intake); Treatment D: RPV 150 mg, single dose, Day 1, and famotidine 40 mg, single dose, Day -1, oral (12 hours before RPV)	The absorption of RPV is pH-dependent. When a single dose of RPV was administered 2 hours after a single dose of famotidine, the exposure to RPV (AUC∞) was decreased by 76% compared with administration of RPV alone. There was a negative relationship between RPV exposure and intragastric pH after famotidine administration. When RPV was administered 4 hours before famotidine or 12 hours after famotidine, the BA of RPV was only slightly increased or decreased. Based on these results, the combined use of RPV and famotidine is possible when their administration is separated in time (i.e., famotidine given 4 hours after RPV or 12 hours before RPV) to prevent reduced absorption of RPV due to the effects of famotidine on intragastric pH.
TMC278-C109 (Paracetamol) Status: Complete	Open-label, randomized, 2-way crossover study	Healthy adult subjects	Treatment A: Single dose paracetamol 500 mg; Day 1; oral Treatment B: RPV 150 mg once daily; Days 1-11 + single dose paracetamol 500 mg; Day 11; oral	The steady-state exposure to RPV (AUC24h) was not affected after co-administration of a single dose of paracetamol. There were no relevant changes in the PK of paracetamol or the glucuronide or sulfate conjugates of paracetamol after co-administration of a single dose of paracetamol with RPV at steady state compared with administration of paracetamol alone.

Study	Study Design	Population	Treatment Details	Main Conclusions
TMC278-C139 (Chlorzoxazone) Status: Complete	Open-label study	Healthy adult subjects	Single doses of chlorzoxazone 500 mg; Days 1, 4, and 19 + RPV 150 mg once daily; Days 4-19; oral	The mean exposure (AUC24h) to RPV was increased 1.25-fold after a single dose of chlorzoxazone. The mean exposures to chlorzoxazone and its metabolite 6-hydroxy-chlorzoxazone were unaffected by a single dose or multiple doses of RPV, as was the ratio of 6-hydroxy-chlorzoxazone to chlorzoxazone AUClast values. These data indicate that RPV does not inhibit or induce CYP2E1 activity in vivo.
TMC278IFD1001 (Digoxin) Status: Complete	Open-label, 2-way crossover study	Healthy adult subjects	Treatment 1: 1 x digoxin 0.5 mg once daily; Day 1, oral Treatment 2: RPV 25 mg once daily; Days 1-16 + 1 x digoxin 0.5 mg; Day 11, oral	The plasma and urine PK of the prototype permeability P-gp substrate digoxin were unaffected by co-administration of steady-state RPV. The 90% CIs of the LS means ratios of the main PK parameters were contained within the 0.80 - 1.25 boundaries of no effect. These results indicate that RPV at the recommended dose of 25 mg once daily does not influence P-gp activity in vivo.
TMC278IFD1004 (Metformin) Status: Complete	Phase I, open-label, single-sequence drug interaction study	Healthy adult subjects	Treatment A: Metformin 850 mg single dose; Day 1 Treatment B: RPV 25 mg once daily; Day 5 - 17 + Metformin 850 mg single dose; Day 15	RPV did not affect the plasma or urine PK parameters of metformin when co-administered. The 90% CIs of the LS means ratios for Cmax, AUClast, AUC∞, and renal clearance of metformin were all contained within the 0.80-1.25 boundaries of no effect. The mean percentage of the administered metformin dose that was excreted in the urine was comparable after intake of metformin alone and in the presence of RPV. For RPV administered in combination with a single dose of metformin, the steady-state PK parameters were in the same range as those observed for RPV alone at the same dose regimen in previous studies in healthy subjects.
TMC435-TiDP6-C114[a] (SPV)	Phase I, open-label, 3-way cross-over drug interaction study between repeated doses of SPV and RPV or TDF.	Healthy adult subjects	**Panel 1:** Treatment 1: SPV 150 mg; once daily; Days 1-11; oral Treatment 2: RPV 25 mg once daily; Days 1-11; oral Treatment 3: SPV 150 mg once daily + RPV 25 mg once daily; Days 1-11; oral	

Study	Study Design	Population	Treatment Details	Main Conclusions
			Panel 2: Treatment 4: SPV 150 mg; once daily; Days 1-7; oral Treatment 5: TDF 300 mg; once daily; Days 1-7; oral Treatment 6: SPV 150 mg; once daily + TDF 300 mg; once daily; Days 1-7; oral	
Efficacy and Safety Trials				
TMC278-TiDP6-C209 (RPV) Status: Complete	96-week, randomized, double blind, double dummy, activecontrolled, international Phase III trial	HIV-1 infected, treatment-naïve adult subjects	RPV 25 mg + EFV placebo once daily + fixed background regimen (TDF 300 mg/FTC 200 mg once daily) from for 96 weeks, oral Or EFV 600 mg + RPV placebo once daily + fixed background regimen (TDF 300 mg/FTC 200 mg once daily) from for 96 weeks, oral	RPV demonstrated substantial and sustained efficacy in a manner that was non-inferior to control, and was shown to be generally safe and well tolerated. At Week 48, the proportions of virologic responders (ITT-TLOVR) were 82.9% and 82.8% for the RPV and control group, respectively. From the primary analysis (i.e., logistic regression adjusted for stratification factor for viral load <50 c/mL TLOVR), non-inferiority was demonstrated at the 12% and 10% margins; superiority could not be claimed. Except for the TLOVR (non-VF), the results for virologic response and non-inferiority were robust and consistent across different populations and imputation methods, including the PP population and the Snapshot analysis. The response rates in the two treatment groups were similar throughout the 48 weeks of treatment. The time to virologic response was slightly longer with RPV, but the time to virologic failure was similar with RPV and control. At baseline, similar proportions of subjects were sensitive to RPV and EFV, and to both their background N(t)RTIs. The proportion of RPV and control VFs with at least one treatment-emergent NNRTI RAM (Extended list) was comparable at the time of failure (failure). Most of the RT mutations emerging in the TMC278 VFs were not found in the control VFs, and vice versa. At failure, 52.6% of TMC278 VFs and 38.5% of control VFs were resistance to their treatment NNRTI. The majority of RPV VFs resistant

Study	Study Design	Population	Treatment Details	Main Conclusions
				to RPV at failure were resistant to ETR and EFV, while all of the control VFs resistant to EFV were sensitive to ETR and RPV. The response rates were high in all the RPV AUC quartiles, ranging from 73.2% (lowest quartile of exposure) to 92.7% (highest quartile of exposure). Both baseline plasma viral load and RPV exposure were significantly associated with a viral load <50 c/mL at week 48 (TLOVR [non-VF]). There were no apparent relationships between the PK of RPV and safety parameters.
TMC278-TiDP6-C215 (RPV) Status: Complete	96-week, randomized, double-blind, double-dummy, activecontrolled, international Phase III trial	HIV-1 infected, treatment-naïve adult subjects	RPV 25 mg + EFV placebo once daily + fixed background regimen containing ABC 600 mg/3TC 300 mg, AZT 300 mg/3TC 300 mg BID, or TDF 300 mg/FTC 200 mg once daily for 96 weeks, oral. Or EFV 600 mg + RPV placebo once daily + fixed background regimen containing ABC 600 mg/3TC 300 mg, AZT 300 mg/3TC 300 mg BID, or TDF 300 mg/FTC 200 mg once daily for 96 weeks, oral	RPV demonstrated substantial and sustained efficacy in a manner that was non-inferior to control. RPV was shown to be generally safe and well tolerated. At Week 48, the proportions of virologic responders (ITT-TLOVR) were 85.6% and 81.7% for the RPV and control group, respectively. From the primary analysis (i.e. logistic regression adjusted for stratification factors for viral load <50 c/mL TLOVR), non-inferiority was demonstrated at the 12% and 10% margins; superiority could not be claimed. The results for virologic response and non-inferiority were robust and consistent across different populations and imputation methods, including the PP population and the Snapshot analysis. At baseline, similar proportions of subjects were sensitive to RPV and EFV, and to both their background N(t)RTIs. The proportion of RPV and control VFs with at least one treatment-emergent NNRTI RAM (Extended list) was comparable at the time of failure (failure). Most of the RT mutations emerging in the RPV VFs were not found in the control VFs, and vice versa. The proportion of RPV and control VFs resistant to their treatment NNRTI was comparable at failure. The majority of RPV VFs resistant to RPV at failure were resistant to ETR and EFV, while all of the control VFs resistant to EFV were sensitive to ETR

Study	Study Design	Population	Treatment Details	Main Conclusions
				and RPV. The response rates were high in all the RPV AUC quartiles, ranging from 83.5% to 98.8%. Both baseline plasma viral load and RPV exposure, but not NRTI background regimen, were significantly associated with a viral load <50 c/mL at week 48 (TLOVR [non-VF]). There were no apparent relationships between the PK of RPV and safety parameters.
Pharmacodynamics				
Dolutegravir				
ING111856 (TQT) GSK Document Number: RM2010/00046/00 Status: Complete	Randomized, partial-blind, single-dose, 3-period, crossover study	Healthy adult subjects	DTG 250 mg; oral suspension; single dose Placebo; oral suspension; single dose Moxifloxacin 400 mg; tablet; oral; single dose	DTG had no effect on cardiac repolarization at a supratherapeutic dose of 250 mg suspension. The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QTcF, which confirmed that this study was valid for assessing the effects of DTG on cardiac repolarization.
ING114819 (Effect of DTG on Renal Functions) GSK Document Number: 2010N110959_00 Status: Complete	Open-label, randomized, 3-arm, parallel, placebo-controlled study	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 14 days DTG 50 mg; tablet; oral; q12h; 14 days Placebo; tablet; oral; once daily; 14 days Omnipaque 300 (647 mg/mL of iohexol) 5 mL; solution; IV Aminohippurate Sodium 2 g/10 mL (20%) of Loading Dose : 8 mg/kg, Maintenance Dose: 12 mg/min; solution; IV	Administration of DTG caused a 10 to 14% reduction in plasma creatinine clearance, which is consistent with previous clinical studies. DTG had no effect on GFR or ERPF.
Rilpivirine				
TMC278-TiDP6-C131 (TQT) Status: Complete	Double-blind, double-dummy, randomized, 3-way crossover, placebo-controlled and positive-controlled study	Healthy adult subjects	Treatment A: RPV 75 mg; once daily; Days 1-11 + RPV placebo; Days 1-11 + moxifloxacin placebo; Day 12; oral Treatment B:	A positive relationship between plasma concentrations of RPV (administered at doses of 75 and 300 mg once daily) and changes in QTcF interval was observed at Day 11, i.e., higher concentrations of RPV were associated with larger changes in the QTcF interval. This relationship was

Study	Study Design	Population	Treatment Details	Main Conclusions
			RPV 300 mg; once daily; Days 1-11 + moxifloxacin placebo; Day 12; oral Treatment C: RPV placebo; Days 1-11 + 400 mg moxifloxacin; Day 12; oral	gender-dependent, with higher RPV plasma concentrations leading to a larger difference between females and males. RPV administered at doses of 75 and 300 mg once daily had a mild CYP3A4 inducing effect, which appeared to be dose-related.
TMC278-TiDP6-C152 (TQT) Status: Complete	Randomized, double-blind, double-dummy, placebo- and active-controlled, crossover study	Healthy adult subjects	RPV Panel: Treatment 1: RPV 25 mg once daily; Days 1-11 + 1 x moxifloxacin placebo; Day 11 Treatment 2: RPV placebo once daily; Days 1-11 + 1 x moxifloxacin placebo; Day 11 Treatment 3: RPV placebo once daily; Days 1-11 + 1 x moxifloxacin 400 mg; Day 11 EFV Panel: Treatment 4: EFV 600 mg once daily; 11 days Treatment 5: EFV placebo once daily; 11 days	At steady state (Day 11), RPV 25 mg once daily and EFV 600 mg once daily were not associated with clinically relevant effects on QTcF interval, as indicated by the 90% CIs of the observed time-matched differences vs. placebo in QTcF interval not exceeding the 10 ms threshold at any time point. At a dose of 25 mg once daily, no relationship was observed between RPV plasma concentrations and changes in QTcF interval from baseline, i.e., higher plasma concentrations did not result in notable changes in QTcF interval. There was no clear gender-dependent relationship. There was also no relationship between EFV plasma concentrations and changes in QTcF interval from baseline.

Study	Study Design	Population	Treatment Details	Main Conclusions
Population PK				
Population PK Analysis of DTG in HIV-Infected Treatment-Naïve Patients GSK Document Number: 2012N149219_00 Status: Complete	DTG concentration-time, dosing, demographic, and covariate data from the following studies were combined: proof of concept (PoC: ING111521), Phase IIb (SPRING-1: ING112276), and Phase III (SPRING-2: ING113086)	ARV-naïve and experienced (INSTI inhibitor-naïve) HIV-infected patients, not currently receiving ART therapy HIV-infected treatment-naïve patients	DTG 10 and 50 mg tablet; oral; once daily for 10 days DTG 10, 25, and 50 mg tablet; oral; once daily with either ABC/3TC (600 mg/300 mg) or TDF/FTC (300 mg/200 mg) FDC for 96 weeks DTG 50 mg tablet; oral; once daily with either ABC/3TC (600 mg/300 mg) or TDF/FTC (300 mg/200 mg) FDC	<u>Population PK Modelling</u>: The PK of DTG in subjects with HIV following repeat-oral administration were adequately described by a 1-compartment model with first-order absorption and absorption lag-time and first-order elimination. Weight, smoking status, age, and total bilirubin were predictors of CL/F; weight was a predictor of V/F, and gender was a predictor of F. The effect of these covariates were not considered clinically significant, therefore, no DTG dose adjustment by these covariates is necessary. For a typical 40-year-old male, non-current smoker subject that weighed 70 kg with total bilirubin of 9 μmol/L, the estimated mean (95% CI) parameter values were: CL/F=0.901 (0.864, 0.938) L/h, V/F=17.4 (16.5, 18.3) L, Ka=2.24 (1.56-2.92) h-1, and ALAG=0.263 (0.0942, 0.432) h. Race/ethnicity, HCV co-infection, CDC classification, albumin, CrCL, ALT, or AST did not influence the PK of DTG in this analysis. There were limited PK data on subjects with HBV co-infection (n=8, 1%) and subjects of ≥65 years of age (n=1). The PK of DTG were dose proportional for the range of doses between 25 and 50 mg, but a greater-than-dose-proportional PK was found at the 10-mg dose due to its 24% higher oral BA compared with the 25 and 50 mg doses. Inter-individual variability for CL/F and V/F was relatively low (23.5% and 13.7%), but was high for Ka (50.1%). Inter-occasion variability on CL/F was 17% over the course of studies.

Study	Study Design	Population	Treatment Details	Main Conclusions
				PK-PD Relationship: There was no correlation between DTG exposure (AUC0-τ, Cmax, and Cmin) and antiviral response and CD4+ cell count change from Baseline. There was no correlation between DTG exposure (AUC0-τ, Cmax, and Cmin) and safety measures except for change from Baseline in serum creatinine and CrCL. Change from Baseline in serum creatinine and CrCL appeared correlated with DTG exposure, however, it was not clinically significant due to the small magnitude of change.
Population PK Analysis of DTG in HIV-1 Infected Treatment-Experienced Adults GSK Document Number: 2012N149456_01 Status: Complete	DTG concentration-time, dosing, demographic, and covariate data from the following studies were combined: ING112961 (VIKING, Phase IIb RAL-resistant), ING112574 (VIKING-3, Phase III INSTI-resistant), ING111762 (SAILING, Phase III, treatment-experienced and INSTI-naïve), and ING116529 (VIKING-4, Phase III, treatment-experienced and INSTI-resistant).	HIV-1 infected, ARV-experienced adults with RAL resistance HIV-1 infected, ART-experienced adults with INSTI resistance HIV-1 infected, ARV-experienced, INSTI-naïve adults	DTG 50 mg once daily and BID with continuation of the current failing ARV regimen for 10 days, then in combination with OBT for a minimum of 24 weeks. DTG 50 mg BID with continuation of the current failing antiretroviral regimen for 7 days, then in combination with OBT for a minimum of 24 weeks. DTG 50 mg QD with an investigator-selected background regimen for 48 weeks DTG 50 mg BID or placebo with continuation of the current failing ARV regimen for 7 days, then	The PK of DTG following repeat oral administration in HIV-1-infected, treatment-experienced adults were adequately described by a 1-compartment model with first-order absorption, absorption lag-time, and first-order elimination. The structural model resembled PK in HIV-1-infected, treatment-naïve adults. Weight, smoking status, concomitant use of metabolic inducers (DRV-RTV, FPV-RTV, ETR or EFV without RTV-boosted PIs, or TPV-RTV) as part of background ARV classified by their level of induction, concomitant use of metabolic inhibitors (ATV-RTV) as part of background ARV, and albumin level were predictors of CL/F; weight and albumin level were predictors of V/F; and gender and concomitant use of metal cation-containing vitamin/mineral supplements were predictors of F. The estimated effect size of the metabolic inducers or inhibitors in the final model was consistent with observations in Phase 1 drug interaction studies and supports the use of Phase 1 data for informing the need for dosage adjustments. The effect of weight, gender, smoking status, albumin, concomitant use of mild metabolic inducers (DRV-RTV or

Study	Study Design	Population	Treatment Details	Main Conclusions
			50 mg BID in combination with OBT for a minimum of 24 weeks	FPV-RTV) and inhibitors (ATV or ATV-RTV) as part of background ARV, and concomitant use of metal cation-containing vitamin/mineral supplements are unlikely to be clinically significant due to the small magnitude of effects. For a typical 70-kg male, non-current smoker, not currently receiving metabolic inducers or inhibitors as part of background ARV, not taking any metal cation-containing vitamin/supplements, with albumin of 43 g/L, the estimated mean (95% CI) parameter values CL/F=1.00 (0.942, 1.06) L/hr, V/F=18.9 (17.8, 20.0) L, Ka=1.99 (1.62, 2.36) hr-1, and ALAG=0.333 (fixed) hr. Race/ethnicity, HCV co-infection, CDC classification, mild to moderate renal impairment as judged by estimated CrCL, ALT, or AST did not influence the PK of DTG in this analysis. The PK of DTG appeared to be dose proportional between 50 mg once daily and 50 mg BID regimens. Inter-individual variability for CL/F was relatively low (CV=28%). IIV for V/F and Ka could not be estimated due to lack of PK samples during the absorption phase. Inter-occasion variability on CL/F was moderate, at 29.5% over the course of studies in treatment-experienced subjects, somewhat higher than that estimated in treatment-naïve subjects (17%).
Population PK Report TMC278-0016435 (Pooled data from TMC278-TiDP6-C209 and TMC278-TiDP6-C215)	TMC278 Phase III (48 week) Population Pharmacaokinetic Modeling, Empirical Bayesian Feedback and Covariate Analysis	HIV-infected treatment-naïve adult patients	TMC278-TiDP6-C209 RPV 25 mg + EFV placebo once daily + fixed background regimen (TDF 300 mg/FTC 200 mg once daily) from for 96 weeks, oral	The population PK model that best describes the PK of RPV is a 2-compartment disposition model in which absorption is described by a lag time followed by a sequential zero- and first-order absorption process. In HIV-1 infected subjects, the apparent clearance of RPV was estimated to be 11.8 L/h (inter-individual variability 39%) and the apparent volume of the central

Study	Study Design	Population	Treatment Details	Main Conclusions
			Or EFV 600 mg + RPV placebo once daily + fixed background regimen (TDF 300 mg/FTC 200 mg once daily) from for 96 weeks, oral TMC278-TiPD6-C215 RPV 25 mg + EFV placebo once daily + fixed background regimen containing ABC 600 mg/3TC 300 mg, AZT 300 mg/3TC 300 mg BID, or TDF 300 mg/FTC 200 mg once daily for 96 weeks, oral. Or EFV 600 mg + RPV placebo once daily + fixed background regimen containing ABC 600 mg/3TC 300 mg, AZT 300 mg/3TC 300 mg BID, or TDF 300 mg/FTC 200 mg once daily for 96 weeks, oral	compartment was estimated to be 152 L. In univariate analyses, a statistically significant effect of gender and of race on the exposure to RPV was observed, with a somewhat higher exposure in females, and a somewhat higher exposure in Asian/Other subjects compared with the rest of the population. In a multivariate analysis, including gender, trial, race, and region as factors, the effect of gender and of race was still statistically significant. In the covariate analysis of the population pharmacokinetic analysis, a statistically significant effect of gender and of race on the CL/F of RPV was observed, resulting in a slightly lower CL/F in females (13.6% lower) compared with males, and a slightly lower CL/F in Asian subjects (17.2% lower) compared with the rest of the population. The magnitude of both effects was not considered clinically meaningful and therefore there is no need for dose adjustments based on gender or race. Age, body weight, baseline GFR, HBV and/or HCV co-infection status did not have a statistically significant effect on the exposure to RPV in the Phase III trials. This was confirmed in the covariate analysis, where age, body weight, BMI, GFR, HBV and/or HCV co-infection status were not retained as significant covariates affecting the CL/F of RPV.
Pharmacogenetics				
ING116265 (PGx432 Evaluation of the effect of UGT1A1 polymorphisms on DTG PK)	Meta-analysis of 9 clinical pharmacology studies with DTG steady-state PK data from 50 mg once daily	Healthy adult subjects	DTG 50 mg tablet; oral; once daily; 5 days	Subjects with genotypes conferring poor metabolizer status of UGT1A1 (*28/*28; *28/*37; *37/*37) had a 32% lower clearance, 46% higher AUC, and 32% higher Cmax of DTG compared with subjects with genotypes associated with normal UGT1A1 activity (*1/*1, *1/*36). Subjects with genotypes conferring intermediate and poor metabolizer status of UGT1A1 had a 23% lower clearance

Study	Study Design	Population	Treatment Details	Main Conclusions
				of DTG and 31% higher AUC compared with subjects with genotypes associated with normal UGT1A1 activity. Polymorphisms in CYP3A4, CYP3A5, and NR1I2 were not associated with differences in the PK of DTG. Increases in DTG exposure due to UGT1A1 polymorphisms are not considered clinically significant based on the accumulated safety data for DTG.

a. Available upon request

Table 2 Summary of Completed Clinical Pharmacology Studies that were Previously Submitted as Part of the TIVICAY or EDURANT Registration and are "Supportive" Studies to the DTG/RPV FDC Submission

Study	Study Title	Main Conclusions
Special Populations: Intrinsic Factors		
TMC114HIV3015 (RPV) Status: Complete	A single-arm, open-label study to assess the pharmacokinetics of darunavir and ritonavir, darunavir and cobicistat, etravirine, and rilpivirine in HIV-1 Infected pregnant women: Results for the rilpivirine Arm	The results of this study demonstrate that exposure to RPV after intake of RPV 25 mg once daily as part of an ARV regimen was lower during pregnancy (similar for the 2nd and 3rd trimester) compared with postpartum. The decrease in unbound (i.e., active) RPV PK parameters during pregnancy compared with postpartum was less pronounced than for total RPV. The virologic response was generally preserved throughout the study period: of the 12 subjects who completed the study, 10 subjects were suppressed at the end of the study. Two subjects in the study experienced (suspected) virologic failure (both had suspected non-adherence to ARV treatment based on undetectable RPV plasma concentrations). One subject had 2 consecutive viral load measurements >200 c/mL at the last 2 study visits and was considered to have completed the study. One subject was withdrawn after the 4-weeks post-baseline due to suspected virologic failure (i.e., HIV RNA levels did not decrease by at least 0.5 $\log_{10}$ 4 weeks after Baseline) but was suppressed at time of withdrawal. No mother-to-child transmission was observed in all 10 infants who had HIV-1 test results available out of the 12 mothers who completed the study.
PK and PK/PD relationships		
ING111521 (DTG) GSK Document Number: RM2008/00548/00 Status: Complete	A Phase 2a, multicenter, randomized, parallel, double-blind, dose ranging, placebo-controlled study to compare antiviral effect, safety, tolerability and PK of GSK1349572 monotherapy versus placebo over 10 days in HIV-1 infected adults	PK: Following oral dosing using the tablet formulation, DTG was rapidly absorbed with maximal concentration observed at 1.5 to 2 hours post dose. Following repeat-dose administration, plasma concentrations of DTG reached steady state by 7 days of dosing, and accumulation ratios ranged from 1.25 to 1.42 across doses. The increase in DTG exposure (AUC and Cmax) was less than dose proportional following both single- and repeat-dose administration. DTG showed time-invariant PK and moderate between-subject variability with %CVb ranging from 16 to 51%. PK/PD Relationship: A mean decrease from Baseline on Day 11 in plasma HIV-1 RNA of 1.51 to 2.46 $\log_{10}$ c/mL was observed across the DTG doses tested (2 mg, 10 mg, 50 mg once daily) compared with placebo (0.05 $\log_{10}$ c/mL increase). A dose response relationship was observed.

Study	Study Title	Main Conclusions
		The PK/PD analysis showed that greater antiviral activity was associated with higher DTG plasma exposure. The exposure-antiviral activity relationship was best described by an Emax model with Emax fixed to 2.6, Hill factor fixed to 1, and PK parameter on the linear scale. Cτ (concentration at end of dosing interval) was the PK parameter that best predicted Day 11 plasma viral load reduction from baseline or maximum plasma viral load reduction from baseline. DTG exposure from a 10 mg once daily dose is around EC90 and DTG exposure from 50 mg once daily is at the plateau of the curve.
ING112276 (DTG) GSK Document Number: 2011N117114_01 Status: Complete	A Phase IIb study to select a once daily oral dose of GSK1349572 administered with either abacavir/lamivudine or TDF/emtricitabine in HIV-1 infected antiretroviral therapy-naive adult subjects. (96-Week results)	PK: DTG exposure, including AUC(0-τ), Cmax, and Cτ, increased as dose increased from 10 mg to 50 mg; the increase in DTG exposure is dose proportional from 25 mg to 50 mg, but less than dose proportional from 10 mg to 25 mg. DTG PK parameters demonstrated moderate variability with %CVb estimated at 30 to 50% for AUC(0-τ) and Cmax and 60 to 70% for Cτ. DTG 50 mg once daily dose achieved Cτ of 1.2 μg/mL (geometric mean), which is ~18-fold higher than the in vitro PA IC90 of 0.064 μg/mL, supporting the dose selection of DTG 50 mg once daily in Phase III studies in INSTI-naïve subjects. PK/PD Relationship: No dose or exposure-response relationship was found for DTG antiviral activity due to combination therapy. There was a positive correlation between DTG dose/exposure and increase in serum creatinine from Baseline.
ING111762 (DTG) GSK Document Number: 2011N117609_00 Status: Complete	A Phase III randomized, double-blind study of the safety and efficacy of GSK1349572 50 mg once daily versus RAL 400 mg BID, both administered with an investigator-selected background regimen over 48 weeks in HIV-1 infected, INSTI-naïve, antiretroviral therapy-experienced adults	PK: Trough DTG concentrations observed in treatment-experienced subjects were lower than those observed in treatment-naïve subjects, likely due to drug interactions with concomitant medications, including antiretrovirals, and less optimal compliance. DTG should be given at 50 mg BID when co-administered with TPV/RTV and EFV. DTG can be co-administered with FPV/RTV without dose adjustment. DTG can be co-administered with once daily or BID DRV/RTV without dose adjustment. PK/PD Relationship: DTG drug exposure, C0, was a statistically significant predictor of Week 24 efficacy response using data from all subjects, but was not a predictor once subjects with evidence of non-compliance or on moderate/strong inducers were excluded. The only PK/PD relationship observed between DTG and safety measures was a correlation wtih total bilirubin and serum creatinine, likely due to benign competition between DTG and unconjugated bilirubin for UGT1A1 and an expected effect of DTG on OCT2, respectively.

1.2. Dolutegravir/Rilpivirine Fixed-dose Combination

The main characteristics of clinical pharmacology related to the DTG/RPV FDC product are summarized below based upon information obtained from the SE development programs for DTG and RPV, food effect and bioequivalence studies of the DTG/RPV FDC, and 2 Phase III studies (201636 and 201637) in HIV-1 infected subjects who received co-administration of DTG with RPV.

Bioequivalence

- DTG/RPV 50/25 mg FDC is bioequivalent to TIVICAY 50 mg and EDURANT 25 mg (module 2.7.1) co-administered as single entities with a meal.

Food Effect

- DTG/RPV FDC should be taken with a meal (module 2.7.1). Taking DTG/RPV FDC in a fasted condition or with only a protein-rich nutritional drink may result in decreased plasma concentrations of RPV, which could potentially reduce the therapeutic effect of DTG/RPV FDC. This is consistent with the prescribing information for RPV to be administered with a meal.

Drug-drug Interactions

- There are no significant drug interactions between DTG and RPV – the 2 active components of the FDC tablet.
- DTG and RPV each have a generally favorable drug interaction profile with few clinically relevant interactions that require a dose adjustment, dose separation, or contraindication.
- Co-administration of DTG or RPV is contraindicated based either on the results of DDI studies or on the known metabolic and elimination pathways of DTG and RPV and those of the co-medications listed: dofetilide, pilsicainde, carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, rifapentine, proton pump inhibitors, systemic dexamethasone (more than single dose), and St. John's wort.
- The DTG + rifabutin DDI study showed no clinically relevant interaction; a RPV + rifabutin DDI study showed a reduction in RPV exposures which could be compensated for by increasing the total RPV dose to 50 mg once daily during rifabutin treatment. Therefore, to manage this interaction, an additional RPV 25 mg tablet should be administered once daily with the DTG/RPV FDC during the period of rifabutin co-administration.
- RPV did not have a clinically relevant effect on metformin PK; however, a DTG + metformin DDI study showed increased metformin plasma concentrations due to inhibition of OCT and MATE transporters by DTG. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/RPV FDC with metformin to maintain glycemic control.
- Co-administration of RPV and drugs that are strong CYP3A inducers are contraindicated because they may decrease RPV plasma concentrations.

- Co-administration of RPV and drugs that increase gastric pH may result in decreased plasma concentrations of RPV and loss of therapeutic effect. Co-administration of DTG and drugs that contain divalent metal cations may result in decreased DTG plasma concentrations. Therefore, avoidance or dose-separation strategies are needed to manage the following absorption-based drug interactions for DTG/RPV FDC:
    - Co-administration of proton pump inhibitors is contraindicated.
    - Administer DTG/RPV FDC at least 4 hours before or 6 hours after taking antacid products,
    - Administer DTG/RPV FDC at least 4 hours before or 6 hours after calcium or iron non-antacid products, or alternatively, co-administer with a meal,
    - DTG/RPV FDC should only be administered at least 4 hours before or at least 12 hours after H2-receptor antagonists.

Special populations

- DTG or RPV may be administered without dose adjustment in patients with mild and moderate hepatic impairment (Child-Pugh Grades A & B). The effect of severe hepatic impairment (Child-Pugh Grade C) on DTG or RPV has not been studied. Therefore, DTG/RPV FDC is not recommended for use in patients with severe hepatic impairment.
- DTG or RPV may be administered without dose adjustment in patients with mild and moderate renal impairment. DTG/RPV should be used with caution in patients with severe renal impairment or ESRD.
- HBV/HCV co-infection had no clinically relevant effect on DTG (HCV, limited data on HBV) or RPV. There is no drug interaction between DTG and commonly used or recently approved drugs for the treatment of HBV or HCV. DTG can be used in HBV or HCV co-infected subjects.
- No clinically relevant effect of gender, weight, age, race/ethnicity, UGT1A1 polymorphisms, or smoking on DTG or RPV PK in adults, and therefore no need for individualized dose adjustments based on these factors.

Description of DTG and RPV Phase III PK and PK/PD

- In the pooled analysis, the C0 for DTG in the overall and NNRTI Subset were similar across the Weeks 4 to 48 visits and were consistent with previously reported steady-state DTG and RPV trough concentrations in HIV-1-infected patients.
- Earlier PK sampling in a subset of subjects who switched from EFV- or NVP-based regimens showed that DTG and RPV pre-dose concentrations increased from Week 2 to steady-state concentrations at Week 4, indicating that any residual enzyme induction effects were diminished by Week 4. The efficacy and virology results, overall and in the NNRTI subgroup, demonstrate that the plasma concentrations of DTG and RPV during the immediate post-NNRTI switch period were sufficient to maintain virologic response.

- No association between DTG or RPV exposures and safety or efficacy parameters was observed.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Dolutegravir/Rilpivirine Fixed-dose Combination

A pivotal BE (Study 201676) and relative BA and food effect (Study 201674) study with the DTG/RPV FDC are described in module 2.7.1.

2.2. Dolutegravir + Rilpivirine

A summary of single and repeat dose DTG and RPV PK parameters following co-administration of DTG and RPV is provided in Table 1, Appendix Table 3.1 and Appendix Table 4.3 (DTG), and Appendix Table 3.2 and Appendix Table 4.4 (RPV).

2.2.1. Pharmacokinetics in Healthy Subjects

Study LAI116181 was a Phase I, open-label, crossover study to assess the potential for a drug interaction between DTG and RPV (Table 1). Sixteen subjects were enrolled in Cohort 1 and received DTG 50 mg once daily for 5 days in Period 1, RPV 25 mg once daily for 11 days in Period 2, and DTG 50 mg once daily in combination with RPV 25 mg once daily for 5 days in Period 3 (only Cohort 1 is described because Cohort 2 received cabotegravir + RPV). There was a 7-day washout between Period 1 and Period 2, and no washout between Period 2 and Period 3. Study drugs were taken with a moderate-fat meal. Co-administration of DTG with RPV resulted in no change in DTG AUC(0-τ) and Cmax, and a 22% increase in Cτ. Co-administration of DTG with RPV resulted in no change in RPV AUC(0-τ) and Cmax, and a 21% increase in Cτ. The results showed that there was no significant drug interaction between DTG and RPV. DTV and RPV can be co-administered without dose adjustment (Table 6, Table 7).

2.2.2. Pharmacokinetics in HIV-1 infected Subjects: Studies 201636, 201637, and Pooled Analyses of 201636 and 201637

2.2.2.1. Study 201636 and Study 201637 (Switching from current antiretroviral regimen CAR to DTG 50 mg + RPV 25 mg once daily vs. current antiretroviral regimen)

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

Location of Report: Study 201636 m5.3.5.1 and Study 201637 m5.3.5.1

Study Design: Study 201636 and Study 201637 were designed to demonstrate the non-inferior antiviral activity of switching to DTG 50 mg + RPV 25 mg oral tablets once daily compared with continuation of CAR up to 48 weeks. Eligible subjects were randomized 1:1 to continue their CAR or switched to DTG + RPV once daily (DTG +

RPV arm). At Week 52, subjects randomized to continue their CAR in the Early Switch Phase were switched to DTG + RPV and followed until Week 148. Subjects randomized to DTG + RPV in the Early Switch Phase continued receiving DTG + RPV until Week 148.

Summary of Pre-Dose Dolutegravir and Rilpivirine Plasma Concentrations in the Early Switch Phase

PK samples were collected to measure DTG and RPV pre-dose plasma concentrations in subjects who switched to DTG + RPV. For DTG and RPV, an evaluable pre-dose concentration (C0) was defined as having been collected within the visit window, within the window of 20 to 28 hours post last dose and subject properly administered the last 3 consecutive doses. The average C0 (C0avg) was defined as the average of DTG or RPV C0 across Weeks 4, 24, and 48. The pre-dose concentrations were summarized and used to investigate possible exposure-response relationships.

A pooled analysis of the DTG and RPV pre-dose plasma concentrations in subjects who switched to DTG + RPV in the 2 Phase III studies (201636 and 201637) was also performed.

Results: The PK Parameter Population was comprised of all subjects who received DTG + RPV and provided at least one evaluable estimate of C0. Evaluable DTG and RPV C0 at Weeks 4, 24, and 48, along with the average pre-dose concentration (C0avg), are summarized for subjects in the Early Switch group in Table 3. DTG and RPV C0 were relatively constant from Week 4 to Week 48.

Consistent with the individual study data, the pooled analysis of the PK results showed that DTG and RPV C0 were relatively constant from Week 4 to Week 48 in the Early Switch Phase (Table 3).

Summary of Pre-Dose Dolutegravir and Rilpivirine Plasma Concentrations and Efavirenz or Nevirapine Residual Plasma Concentrations in the NNRTI Subset

The data evaluated DTG and RPV pre-dose plasma concentrations and EFV or NVP residual plasma concentrations in subjects who switched from an enzyme-inducing NNRTI- (EFV or NVP) containing regimen to DTG + RPV. The PK Parameter NNRTI Subset Population was comprised of all subjects in the PK Parameter Population who switched from an EFV- or NVP- containing regimen to DTG + RPV. The PK Parameter NNRTI Subset with Extra Sampling Population was comprised of the first ~20 subjects per study in the PK Parameter NNRTI Subset Population who had extra PK samples collected at Weeks 2 and 8.

DTG and RPV pre-dose plasma concentrations over time are summarized for both the NNRTI Subset and NNRTI Subset with Extra Sampling in Table 4 for both the individual studies and pooled analysis. A summary of residual EFV or NVP concentrations obtained in the NNRTI Subset with Extra Sampling is provided in Table 5 for both the individual studies and pooled analysis.

Results: The results from the NNRTI Subset with Extra Sampling show that the DTG and RPV C0 increased from Week 2 through Week 4 post-switch and remained relatively constant from Week 4 to Week 48 following treatment with DTG + RPV (Table 4). Residual concentrations of EFV and NVP decreased over the 4-week post-switch period (Table 5).

The DTG and RPV C0 from Week 4 to Week 48 in the NNRTI Subset with Extra Sampling were comparable to the DTG and RPV C0 at Week 4, 24, and 48 in the larger NNRTI Subset of all patients who switched from NNRTIs (Table 4).

Consistent with the individual study data, the pooled analysis of results from the NNRTI Subset with Extra Sampling showed that the DTG and RPV C0 increased from Week 2 through Week 4 post-switch and remained relatively constant from Week 4 to Week 48 following treatment with DTG + RPV (Table 4). Residual concentrations of EFV and NVP decreased over the 4-week post-switch period (Table 5).

Conclusions:

In the pooled analysis, the C0 for DTG and RPV in the overall and NNRTI Subset were similar across the Weeks 4 to 48 visits and were consistent with previously reported steady-state DTG and RPV trough concentrations in HIV-1-infected patients (1.11 [46%] μg/mL; [TIVICAY Product Information, 2016]) and for RPV (79 ± 35 ng/mL, mean ± SD [EDURANT Product Information, 2015]).

In the NNRTI Subset with Extra Sampling, residual EFV and NVP decreased to negligible or non-quantifiable concentrations by Week 4 after DTG + RPV treatment was initiated. Although DTG and RPV C0 were slightly lower at Week 2 they were above their respective protein-adjusted IC90 values, as was expected based on PK results from prior EFV- and NVP-switch studies [GlaxoSmithKline document number 2015N261163_00; Mills, 2013; Rokx, 2015]. The efficacy and virology results, overall and in the NNRTI Subset, demonstrate that the plasma concentrations of DTG and RPV during the immediate post-NNRTI switch period were sufficient to maintain virologic suppression.

Table 3 Summary of Pre-dose Plasma Dolutegravir and Rilpivirine Concentrations by Visit and Average Pre-dose Plasma Concentration (C0avg) in Studies 201636, 201637, and Pooled (201636 + 201637) Data (PK Parameter Population)

Visit	Pre-Dose[a] Concentration (Geometric Mean [95% CI] [CVb%])											
	DTG (μg/mL)						RPV (ng/mL)					
	201636		201637		Pooled		201636		201637		Pooled	
	n		n		n		n		n		n	
Week 4	130	1.25 (1.10, 1.41) (84)	176	1.27 (1.16, 1.41) (73)	306	1.26 (1.17, 1.36) (78)	130	71.9 (64.8, 79.8) (66)	175	71.8 (66.8, 77.1) (51)	305	71.8 (67.7, 76.3) (57)
Week 24	210	1.52 (1.40, 1.66) (70)	207	1.22 (1.12, 1.33) (70)	417	1.36 (1.28, 1.45) (72)	210	80.0 (75.4, 84.9) (46)	207	79.7 (74.3, 85.5) (55)	417	79.8 (76.3, 83.6) (50)
Week 48	215	1.55 (1.42, 1.70) (76)	215	1.16 (1.07, 1.26) (65)	430	1.34 (1.26, 1.43) (72)	211	84.5 (79.0, 90.4) (53)	215	81.3 (76.1, 87.0) (53)	426	82.9 (79.1, 86.9) (53)
C0avg	239	1.58 (1.47, 1.69) (61)	242	1.27 (1.19, 1.36) (57)	481	1.41 (1.34, 1.49) (60)	239	81.8 (77.2, 86.6) (47)	242	79.2 (74.8, 83.7) (47)	481	80.4 (77.3, 83.7) (47)

Data Source: 201636 In-text Table 58; 201637 In-text Table 57; 201636/201637 Table 4.010, Table 4.040, Table 5.010, Table 5.020

Note:

N = 239 subjects in the PK Parameter Population who switched to DTG + RPV in Study 201636.

N = 242 subjects in the PK Parameter Population who switched to DTG + RPV in Study 201637.

N = 481 subjects in the PK Parameter Population who switched to DTG + RPV in Study 201636 and Study 201637

a. Pre-dose was defined as sample taken within 20-28 h after the last dose and correct administration of the last 3 doses

Table 4 Summary of Pre-Dose Dolutegravir and Rilpivirine Concentrations by Visit in Subjects who Switched from Efavirenz or Nevirapine in Studies 201636, 201637, and Pooled (201636 + 201637) Data (NNRTI Subset and NNRTI Subset with Extra Sampling)

Visit	Pre-Dose[a] Concentration (Geometric Mean [90% CI] [CVb%])											
	NNRTI Subset with Extra Sampling											
	201636				201637				Pooled			
	n	DTG (μg/mL)	n	RPV (ng/mL)	n	DTG (μg/mL)	n	RPV (ng/mL)	n	DTG (μg/mL)	n	RPV (ng/mL)
Week 2	16	0.665 (0.463, 0.957) (77)	15	57.6 (42.4, 78.3) (60)	19	0.702 (0.538, 0.916) (60)	19	51.1 (40.2, 64.9) (53)	35	0.685 (0.556, 0.843) (67)	34	53.9 (45.0, 64.5) (55)
Week 4	19	0.822 (0.598, 1.13) (74)	19	61.9 (50.1, 76.4) (46)	22	1.01 (0.770, 1.33) (68)	21	71.6 (58.0, 88.4) (49)	41	0.919 (0.751, 1.12) (71)	40	66.8 (57.8, 77.2) (47)
Week 8	19	1.17 (0.759, 1.81) (112)	19	70.0 (56.0, 87.4) (49)	26	1.28 (1.03, 1.59) (58)	26	68.8 (53.9, 87.8) (66)	45	1.24 (0.999, 1.53) (80)	45	69.3 (58.8, 81.5) (59)
Week 24	23	1.35 (0.970, 1.87) (89)	23	72.7 (58.9, 89.9 (52.0)	25	1.27 (0.922, 1.75) (91)	25	79.5 (66.4, 95.2) (46)	48	1.31 (1.05, 1.63) (89)	48	76.2 (66.7, 87.1) (48)
Week 48	23	1.12 (0.772, 1.63) (106)	23	72.0 (58.0, 89.3) (53)	27	0.965 (0.777, 1.20) (59)	27	78.9 (63.6, 97.8) (59)	50	1.03 (0.846, 1.27) (81)	50	75.6 (65.3, 87.7) (56)
	NNRTI Subset											
Week 4	56	1.08 (0.888, 1.31) (83)	54	63.1 (54.9, 72.6) (55)	93	1.27 (1.11, 1.44) (69)	92	72.6 (65.7. 80.2) (51)	149	1.19 (1.07, 1.33) (75)	146	68.9 (63.5, 74.7) (53)
Week 24	93	1.45 (1.27, 1.66) (71)	93	75.7 (69.2, 82.8) (46)	106	1.28 (1.13, 1.46) (74)	106	87.5 (79.2, 96.6) (55)	199	1.36 (1.24, 1.49) (73)	199	81.8 (76.4, 87.5) (51)
Week 48	94	1.45 (1.25, 1.69) (86)	91	81.7 (73.2, 91.2) (57)	111	1.26 (1.13, 1.40) (62)	111	84.8 (76.7, 93.7) (57)	205	1.34 (1.23, 1.47) (74)	202	83.4 (77.5, 89.8) (57)
C0avg[b]	105	1.46 (1.30, 1.63) (64)	105	77.0 (70.9, 83.6) (45)	120	1.32 (1.20, 1.45) (57)	120	82.4 (75.6, 89.7) (50)	225	1.38 (1.28, 1.49) (60)	225	79.8 (75.2, 84.7) (48)

Data Source: 201636 In-text Table 59; 201637 In-text Table 58; 201636/201637 Table 4.020, Table 4.030, Table 4.050, Table 4.060, Table 5.030, Table 5.040
Note:
N = 26 subjects in the PK Parameter NNRTI Subset with Extra Sampling Population Study 201636.
N = 28 subjects in the PK Parameter NNRTI Subset with Extra Sampling Population Study 201637.
N = 54 subjects in the NNRTI Subset with Extra PK Sampling in Study 201636 and Study 201637.
N = 54 subjects in the PK Parameter NNRTI Subset with Extra Sampling Population and N = 225 subjects in the PK Parameter NNRTI Subset for Study 201636.
a. Pre-dose was defined as sample taken within 20-28 h after the last dose and correct administration of the last 3 doses
b. C0avg: average of DTG or RPV plasma C0 across Weeks 4, 24 and 48

Table 5 Summary of Residual Plasma Concentrations of Efavirenz or Nevirapine by Visit in Subjects who Switched from Efavirenz or Nevirapine in Studies 201636, 201637, and Pooled (201636 + 201637) Data (NNRTI Subset with Extra Sampling)

Visit	Residual Concentration (Median [Range])											
	NNRTI Subset with Extra Sampling											
	201636				201637				Pooled			
	n	EFV (ng/mL)	n	NVP (ng/mL)	n	EFV (ng/mL)	n	NVP (ng/mL)	n	EFV (ng/mL)	n	NVP (ng/mL)
Week 2	13	79.40 (9.92, 855)	4	4.45 (NQ - 34.5)	16	89.4 (10.6, 269)	4	2.92 (NQ - 326)	29	82.6 (9.92 - 855)	8	2.92 (NQ - 326)
Week 4	17	7.30 (NQ - 45)	4	NQ	14	10.3 (NQ - 87.2)	4	NQ (NQ - 44.1)	31	7.95 (NQ - 87.2)	8	NQ (NQ - 44.1)

Data Source: 201636 In-text Table 60; 201637 In-text Table 59; 201636/201637 Table 4.070, Table 4.080.
Note:
N = 26 subjects in the PK Parameter NNRTI Subset with Extra Sampling Population Study 201636.
N = 28 subjects in the PK Parameter NNRTI Subset with Extra Sampling Population Study 201637
N = 54 subjects in the NNRTI Subset with Extra PK Sampling in Study 201636 and Study 201637
N = 55 subjects in the PK Parameter NNRTI Subset with Extra Sampling Population (Pooled)
NQ = Below the lower limit of quantitation (<4 ng/mL)

2.2.2.2. PK/PD relationships: Pooled Analyses of 201636 + 201637

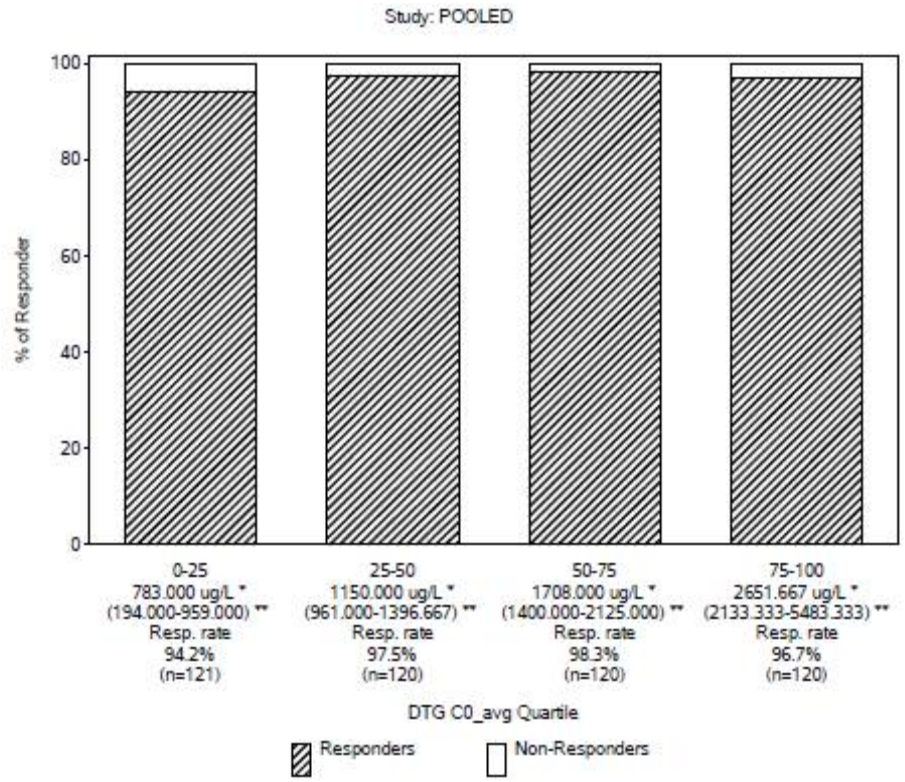
Exploration of Plasma Exposure-Response Relationships for Antiviral Efficacy

Potential exposure-response relationships between plasma C0avg and various measures of antiviral efficacy were explored graphically and by logistic regression. The C0avg was summarized for all subjects with evaluable data according to responder or non-responder (the Snapshot algorithm) status.

Results: Bar plots of the % responders (by Snapshot) at Week 48 by DTG or RPV C0avg quartile (Figure 1 and Figure 2) showed a high proportion of responders (>93%) across quartiles and did not reveal a relationship between DTG or RPV C0avg and virologic response. Likewise plots of DTG or RPV C0avg for Snapshot responders versus non-responders at Week 48 and logistic regression analyses did not indicate a clinically meaningful relationship between C0avg and virologic response.

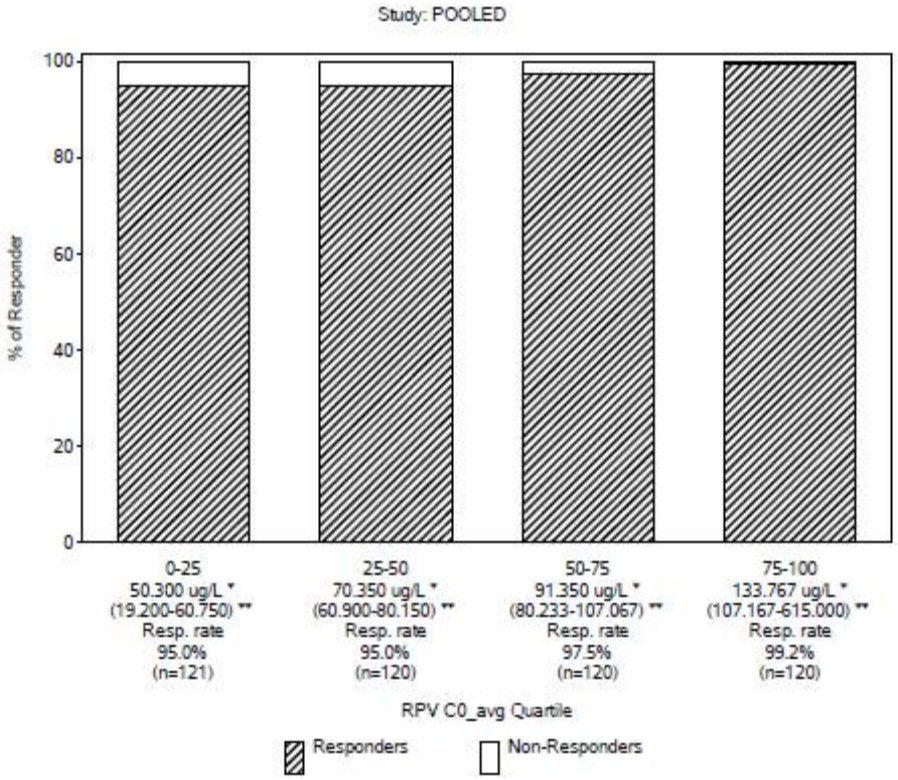
The analysis was limited by the small number of virologic failures in the 201636 and 201637 studies; however, the lack of an exposure-response relationship for efficacy was consistent with the high proportion of subjects who maintained virologic suppression in both studies.

Figure 1 Bar Plots of Percent of Snapshot Virologic Response at Week 48 by Dolutegravir Average Pre-Dose Plasma Concentration (C0avg) Quartile (Pooled Analysis)



Data Source: 201636/201637 Figure 5.030
*Median of DTG C0_avg values within the quartile.
**Range (Min - Max) of DTG C0_avg values within the quartile.

Figure 2 Pooled (Studies 201636 + 201637): Bar Plots of Percent of Snapshot Virologic Response at Week 48 by Rilpivirine Average Pre-Dose Plasma Concentration (C0avg) Quartile (Pooled Analysis)



Data Source: 201636/201637 Figure 5.040
*Median of RPV C0_avg values within the quartile.
**Range (Min - Max) of RPV C0_avg values within the quartile.

Exploration of Plasma Exposure-Response Relationships for Safety

Potential exposure-response relationships between plasma C0avg and various safety measures were explored graphically and by Pearson's correlation or logistic regression analyses.

Results: Individual and box plots of DTG and RPV C0avg, and the most frequent AEs (back pain, diarrhea, headache, nasopharyngitis, and upper respiratory tract infection) along with the summary of Pearson's correlations of selected laboratory parameters (creatinine, GFR, urine albumin/creatinine, ALT, bilirubin, LDL, and HDL), and the log-transformed DTG or RPV C0avg and logistic regression of selected AEs and the DTG or RPV C0avg, did not reveal any clinically meaningful associations between DTG or RPV exposures and safety parameters.

Conclusions: DTG and RPV were administered at approved once daily doses. No association between DTG or RPV exposures and safety or efficacy parameters was observed. The lack of an exposure-response relationship for efficacy was consistent with the high proportion of subjects who maintained virologic suppression in studies 201636 and 201637.

The overall efficacy and virology results suggest that lower DTG and RPV concentration in the immediate post-NNRTI switch period did not impact clinical efficacy.

2.3. Dolutegravir

A summary of single and repeat dose DTG PK parameters in clinical pharmacology studies discussed in this module are presented in Appendix Table 3.1 and Appendix Table 4.3, respectively. A summary of PK parameters for co-administered medications are provided in Appendix Table 5.1.

2.3.1. Pharmacokinetics and Mass Balance in Healthy Subjects

The PK profile of repeat doses of DTG 10, 25, and 50 mg suspensions in healthy subjects was investigated in Study ING111322. Table 1 provides a summary of the study design and the main results. Following repeat dosing, steady state was achieved after approximately 5 days of dosing, and DTG showed time-invariant PK; accumulation ratios after 50 mg once daily dosing were 1.43, 1.36, and 1.42 for AUC(0-∞), Cmax, and Cτ, respectively.

Study ING111853 was conducted to investigate the recovery, excretion, and PK of DTG administered as a single, oral suspension 20-mg dose containing ^{14}C-DTG in healthy adult subjects (Table 1). Unchanged DTG was eliminated primarily through hepatic metabolism with minimal renal excretion (<1% of dose administered orally); UDP glucuronosyltransferase isozyme 1A1 (UGT1A1) was the primary route of metabolism with CYP3A4 as a notable secondary metabolic pathway.

2.3.2. Pharmacokinetics in Special Populations

The PK of DTG was investigated in healthy Japanese subjects (ING115381), and in subjects with moderate hepatic impairment (ING113097) and severe renal impairment (ING113125). A summary of the study design and main conclusions are provided in Table 1. In summary, no dose adjustment of DTG is needed in Japanese subjects, in subjects with mild to moderate hepatic impairment, or in subjects with mild to severe renal impairment (not on renal replacement therapy).

2.3.3. Pharmacokinetic Interactions

Summaries of study design, treatments, and the main conclusions from 24 previously completed DDI studies from the DTG single agent development program that are key to the DTG/RPV FDC submission are provided in Table 1. In summary, no clinically significant drug interactions were observed between DTG and MDZ, oral contraceptives containing NGMN and EE, methadone, multivitamins, OMP, prednisone, RBT, TDF, RPV, DRV/RTV, LPV/RTV, ETR/LPV/RTV, ETR/DRV/RTV, FPV/RTV, BCV, and TVR. There are few clinically relevant interactions that require dose adjustment, dose separation, or contraindication. DTG inhibited the renal transporter OCT2, a mechanism that is consistent with a benign increase in serum creatinine. Based on this observation, DTG may reduce the excretion of dofetilide, thereby increasing plasma concentrations to toxic levels; therefore, co-administration of DTG and dofetilide is contraindicated.

2.3.4. Clinical Pharmacodynamics

2.3.4.1. Study ING111856 (Thorough QT) and Study ING114819 (Effect of Dolutegravir on Renal Function)

Study ING111856 investigated the effect of DTG on cardiac repolarisation compared with placebo in healthy adult subjects, and Study ING114819 was designed to confirm the mechanism behind the increase in serum creatinine observed during DTG therapy by investigating whether DTG had any effect on GFR or ERPF. Summaries of study designs, treatments, and conclusions from both studies from the SE development program for DTG are provided in Table 1. Study ING111856 showed that DTG had no effect on cardiac repolarization at a supratherapeutic dose of 250 mg suspension. In Study ING114819, DTG was shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without significantly affecting GFR or ERPF. DTG inhibits the renal transporter OCT2, a mechanism that is consistent with a benign increase in serum creatinine.

2.3.5. Pharmacokinetics and Pharmacokinetic-pharmacodynamic Relationships in Target Patient Population

Pharmacokinetics and any exposure-response relationships in the target population are described in Section 2.2.2 based on data from Study 201636 and Study 201637 which were conducted using approved doses of DTG and RPV and that are considered pivotal to the DTG/RPV FDC submission. The approved dose regimens for DTG and RPV were utilized in these studies.

Study ING111521 (10-day single agent study, DTG 2-50 mg once daily) and Study ING112276 (DTG 10 mg, 25 mg, or 50 mg, once daily + background therapy) are supportive studies to the DTG/RPV FDC submission and are summarized in Table 2.

2.4. Rilpivirine

A summary of single and repeat dose RPV PK parameters in clinical pharmacology studies discussed in this module are presented in Appendix Table 3.2 and Appendix Table 4.4, respectively. A summary of PK parameters for co-administered medications are provided in Appendix Table 5.2.

2.4.1. Pharmacokinetics and Mass Balance in Healthy Subjects

A mass balance study in healthy adults (TMC278-C119) showed that most of the administered ^{14}C-RPV-related radioactivity from a single 150 mg dose administered as an oral solution was excreted in feces. Unchanged RPV accounted for a mean of 25.5% of the dose in feces. The excretion of radioactivity in urine was limited, with a mean 6.1% of the administered radioactive dose (Table 1).

The PK profile of repeat doses of RPV 25, 50, 100 and 150 mg suspensions in healthy subjects was investigated in Study TMC278-C103. Table 1 provides a summary of the study design and the main results. The single dose and steady-state PK parameters of RPV (Cmax and AUC24h) increased proportional to the dose across the dose range of

25 mg to 150 mg once daily. Steady state was reached before Day 7 for all dose levels. The inter-individual variability was low to moderate and independent of the dose.

The effect of food on the BA of RPV (Study TMC278-TiDP6-C137) is presented in module 2.7.1, Section 2.4.1.

2.4.2. Pharmacokinetics in Special Populations

Study TMC278-TiDP6-C130 was conducted to investigate the effects of mild and moderate hepatic impairment on the PK of RPV administered at a dose of 25 mg once daily in subjects with mild or moderate hepatic impairment and matched healthy control subjects with normal hepatic function. Table 1 provides a summary of the study design and main results. In summary, the data suggest that no dose adjustment of RPV is needed in subjects with mild or moderate hepatic impairment.

2.4.3. Pharmacokinetic Interactions

Summaries of study designs, treatments, and conclusions from 22 previous DDI studies from the SE development program for RPV that are key to the DTG/RPV FDC submission are provided in Table 1. In summary, no clinically significant drug interactions were observed between RPV and TDF, ddI, LPV/RTV, DRV/RTV, RBT, KTZ, sildenafil, atorvastatin, oral contraceptives containing norethindrone and EE, methadone, paracetamol, chlorzoxazone, RAL, digoxin, and SPV. There are few clinically relevant interactions that require dose adjustment or dose separation. RPV is contraindicated with proton pump inhibitors (OMP) or CYP3A inducers (RIF) because co-administration may cause significant decreases in RPV plasma concentrations.

2.4.4. Clinical Pharmacodynamics

2.4.4.1. Study TMC278-TiDP6-C131 (Thorough QT) and Study TMC278-TiDP6-C152 (Thorough QT)

Two Phase I Thorough QT studies in healthy subjects (TMC278-TiDP6-C131 and TMC278-TiDP6-C152) evaluated the effect of RPV at different doses on cardiac rhythm and ECG parameters, specifically QTc. Table 1 provides a summary of the study designs and key results. In summary, there was no clinically relevant QTc interval prolongation with RPV 25 mg once daily, the dose utilized in Phase III trials and the recommended dose, as demonstrated by Study TMC278-TiDP6-C152. Increases in QTcF were observed in Study TMC278-TiDP6-C131 at supratherapeutic doses of RPV 75 mg once daily and 300 mg once daily, and were dose- and plasma concentration-dependent.

2.4.5. Pharmacokinetics and Pharmacokinetic-pharmacodynamic Relationships in Target Patient Population

Pharmacokinetics and any exposure-response relationships in the target population are described in Section 2.2.2 based on data from Study 201636 and Study 201637 which were conducted using approved doses of DTG and RPV and that are considered pivotal to the DTG/RPV FDC submission. The approved dose regimens for DTG and RPV were utilized in these studies.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. Absorption

3.1.1. Dolutegravir

Following oral administration of tablet formulations, DTG absorption is rapid with no absorption lag time and a median tmax of 2 to 3 hours post dose. DTG concentration declines mono-exponentially with an average t½ of approximately 14 hours.

DTG absorption is increased with co-administration of food (module 2.7.1, Section 2.4.1) and decreased when co-administered with polyvalent metal cation-containing products (Table 1). Following oral administration of tablet formulations, in general, DTG exhibits nonlinear PK with less than dose-proportional increases in plasma exposure from 2 to 100 mg (Study ING111521 and Study ING114005), likely due to different dispersion rates of various tablet strengths and solubility-limited absorption at higher doses; however, increase in DTG exposure appears dose proportional from 25 mg to 50 mg (as observed in Study ING112276).

The mean AUC(0-∞) value of the tablet was ~30% less than that of the suspension resulting in an estimated fraction absorbed from the tablet of 49 to 56%. Following single oral administration as a tablet formulation, food was noted to modestly increase systemic exposure to DTG (66%) resulting in an estimated fraction absorbed of 81 to 93%.

The absolute BA of DTG has not been directly measured due to low solubility and its non-specific binding, which present significant challenges to an IV formulation for DTG even at very low doses. However, based on accumulated data from in vitro permeability, metabolism, and biliary excretion in animals, and a human mass-balance study (ING111853, Table 1), the absolute BA of DTG is estimated to be approximately 67 to 80% from the suspension formulation and 49 to 56% from the tablet formulation.

3.1.2. Rilpivirine

In vitro evaluation of the cellular transport characteristics of ^{14}C-RPV indicated that RPV had intermediate permeability and, overall, RPV permeation is thought to occur predominantly via a passive transcellular diffusion mechanism.

Further, RPV, although not a substrate of P-gp, inhibits the P-gp mediated transport of paclitaxel in Caco-2 cells with an apparent IC50 value of 9.2 μM (3371 ng/mL). An in vivo effect of RPV at the intestinal absorption level is unlikely, given the low therapeutic dose of RPV (25 mg once daily) and the fact that the in vivo RPV total plasma concentrations at this dose are more than 10-fold lower than the IC50 value of 3371 ng/mL.

Provided that solubility and dissolution rate are not limiting, in vitro results indicated that RPV would likely exhibit sufficient membrane permeability to obtain adequate intestinal absorption.

The absolute BA of RPV has not been directly measured due to low solubility and its non-specific binding, which present significant challenges to an IV formulation for RPV even at very low doses.

The effect of concomitant food intake on the oral BA of RPV administered as a tablet was investigated in TMC278-TiDP6-C137 (module 2.7.1). The mean exposure to RPV administered as the 75 mg Phase III tablet was higher after a standardized (normal fat or high fat) breakfast than under fasted conditions. Administration of RPV after a high-fat breakfast or after a standard breakfast resulted in similar exposures. It is recommended that RPV is always taken with a meal. RPV was instructed to be taken with food in all trials in HIV-1 infected patients.

Administration of RPV under fasted conditions decreased RPV AUC(0-∞) by 41% and Cmax by 46%. Administration of RPV with only a protein-rich nutritional drink decreased RPV AUC(0-∞) by 49% and Cmax by 50% compared with a standard meal(Phase III tablet, TMC278-TiDP6-C137, module 2.7.1).

The highest solubility of RPV is obtained at pH 2.0 (0.003 g/100 mL). At pH values above 2.0, the solubility decreases (< 0.001 g/100 mL). Drugs that alter intragastric pH affect the solubility of RPV and thus indirectly affect the absorption of RPV. The effect of co-administering RPV 150 mg once daily with a drug that increases intragastric pH, i.e., proton pump inhibitors (OMP) was explored in Study TMC278-C114 (Table 1). Co-administration of OMP (20 mg once daily) resulted in a 56% decrease in the AUC24h of a single dose of RPV (150 mg) and a 40% decrease after multiple doses of RPV (150 mg once daily) at steady state compared with administration of RPV alone.

The effect of increased gastric pH was investigated further in a DDI Study (TMC278-C140) between RPV and famotidine, a histamine H2-receptor antagonist that inhibits gastric acid production. This study again demonstrated that the absorption of RPV is pH-dependent (Table 1). When a single dose of RPV was administered 2 hours after a single dose of famotidine, RPV AUC∞ was decreased by 76% compared with administration of RPV alone. There was an inverse relationship between intragastric pH and RPV exposure after famotidine administration. When RPV was administered 4 hours before famotidine or 12 hours after famotidine, there was no clinically relevant effect on the BA of RPV. Based on these results, the combined use of RPV and famotidine is possible when their administration is separated in time (i.e., DTG/RPV FDC should only be administered at least 4 hours before or at least 12 hours after H2-receptor antagonists such as famotidine) to prevent reduced absorption of RPV due to the effects of famotidine on intragastric pH.

3.2. Distribution

3.2.1. Dolutegravir

Apparent volume of distribution was estimated at 17.4 L following oral tablet dosing based on a population PK analysis in treatment-naïve subjects. The estimated Vd/F is greater than the total plasma volume (~3 L for a 70-kg person), but similar to the volume of total water in the extracellular space (~15 L for a 70-kg person). Total blood and

plasma drug-related radioactivity concentration ratios, as measured in the human mass balance Study ING111853 (Table 1), were averaged at 0.441 to 0.535, indicating minimal association of DTG with blood cellular components.

In vitro, the protein binding of DTG in human serum and plasma is high (approximately 99.3%). DTG appears to primarily bind to albumin based on the hepatic impairment Study ING113097 (Table 1) where the DTG unbound fraction showed better correlation with albumin than AAG.

DTG is present in CSF at levels similar to the unbound concentration in plasma. DTG is present in the female and male genital tract. AUC in cervicovaginal fluid, cervical tissue, and vaginal tissue were 6 to 10% of that in corresponding plasma at steady state, and AUC in semen and rectal tissue were 7% and 17%, respectively, of that in corresponding plasma at steady state. In the literature, median DTG concentrations in CSF were 18 ng/mL at Week 2 and 13 ng/mL at Week 16 in 13 HIV-1 infected male subjects receiving DTG (50 mg) + abacavir/lamivudine (600/300 mg) once daily. Ratios of DTG CSF to total plasma concentration were similar to the unbound fraction of DTG in plasma. Median changes from baseline in CSF (n = 11) and plasma (n = 12) HIV-1 RNA were -3.42 and -3.04 $\log_{10}$ c/mL, respectively. Nine of 11 subjects (82%) had plasma and CSF HIV-1 RNA levels <50 c/mL and 10 of 11 (91%) had CSF HIV-1 RNA levels <2 c/mL at Week 16 [Letendre, 2014].

3.2.2. Rilpivirine

After a single oral dose of 150 mg ^{14}C-RPV in healthy adults (TMC278-C119, Table 1), the blood-to-plasma ratios of total ^{14}C-radioactivity were time-independent, with values ranging between 0.65 and 0.75, indicating that RPV and its metabolites were not distributed to blood cells to any significant extent. 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 AAG. The blood-to-plasma concentration ratio was approximately 0.67, irrespective of the RPV concentration. 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. The distribution of RPV into compartments other than plasma (e.g., CSF or genital tract secretions) has not been evaluated in humans by Janssen. In the literature, individual RPV CSF concentrations were above the EC50 in 13 HIV-1 infected male subjects who switched from TDF + FTC + NVP (245 + 200 + 400 mg) once daily to TDF + FTC + RPV (245 + 200 + 25 mg) once daily and above the EC90 in 85% (11/13) of the subjects. HIV-1 RNA in CSF remained undetectable (<5 copies/mL) in all patients through 60 days. The mean plasma RPV trough concentration was 29.7 ng/mL and the mean RPV concentration in CSF was 0.8 ng/mL, representing a CSF:plasma ratio of 1.4% [Mora-Peris, 2014].

3.3. Metabolism

3.3.1. Dolutegravir

Following oral administration of 20 mg ^{14}C-DTG in humans, unchanged DTG is primarily eliminated through metabolism, and renal elimination of unchanged DTG represents less than 1% of the total dose administered. The quantified metabolites in humans include an ether glucuronide of DTG (M3), an N-dealkylation metabolite (M1), a product from oxidation at the benzylic carbon (M7), and a product of oxidative defluorination with cysteine addition (M13). M3 is the major metabolite observed in urine, and represents 18.9% of the total dose administered. The total radioactivity of the metabolites formed through oxidation (M1, M7, and M13) that are recovered in urine and feces accounts for approximately 9.7% (mean) of the total dose administered. The enzymes responsible for the formation of M3 are UDP glucuronosyl transferase (UGT) 1A1 (major), and UGT1A3 and UGT1A9 (minor). The enzyme responsible for forming M7 is CYP3A4, while the enzyme responsible for forming M13 is unknown. M1 is formed by hydrolysis of M7. Therefore, UGT1A1 is the primary route of metabolism, with CYP3A4 as a secondary metabolic pathway in humans. DTG is the predominant circulating compound in plasma, representing 97% of plasma total radiocarbon, while M3 represents <2.4% (Study ING111853). These human metabolites were observed in animals.

The primary metabolite, ether glucuronide of DTG (M3), in plasma shows formation rate-limited elimination following oral administration of DTG (Study ING113125). Apparent half-life of the ether glucuronide in plasma is similar to the parent compound, DTG, and renal excretion is a primary route of elimination of this metabolite (Study ING113125). In subjects with severe renal impairment (Study ING113125), exposure (AUC) of this metabolite is approximately 3-fold higher than that observed in healthy matching subjects, likely due to impaired renal elimination of the metabolite in subjects with renal impairment. However the apparent half-life of the metabolite is unchanged.

Co-administration of EFV decreases DTG systemic exposure (AUC) by 57% (Study ING114005). The plasma and urine metabolite profiling data suggests that EFV induces both UGT1A1 and CYP3A pathways. With presence of EFV, DTG is still the major component in plasma, while M3 is present at a mean value of <2% of DTG, similar to that observed from the treatment of DTG alone. DTG and 11 metabolites were identified in pooled human urine. The urine from subjects receiving DTG in combination with EFV displays an increase in the ratio of M3 relative to parent DTG, and a concomitant decrease in the ratio of M1 to DTG, when compared with the metabolic profile of DTG alone. No other significant urinary metabolite differences between the 2 treatments are noted.

As CYP3A4 is a secondary route of elimination of DTG, the first-pass metabolism of DTG following oral dosing is expected to be very low.

The primary metabolite, M3, is ether glucuronide of DTG, and is not expected to have antiviral activity. As M3 is presented at very low concentrations in plasma, it is not expected to exhibit pharmacological activity leading to toxicity.

3.3.2. Rilpivirine

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, Table 1). 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 Cmax, 51% based on AUClast). 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).

The primary RPV metabolism was mainly catalyzed by CYP3A enzymes, which play the major role in the biotransformation of RPV in vitro.

3.4. Excretion

3.4.1. Dolutegravir

Renal elimination of unchanged drug is low (<1% of the dose). Following oral administration of a ^{14}C-DTG in a suspension formulation, 31% of the total oral dose is excreted in the urine, represented by M3 (18.9% of total dose), M1 (3.6% of total dose), M7 (3.0% of total dose), and other minor metabolites. Sixty-four percent of the total oral dose is recovered in the feces, represented mainly by DTG (53% of total dose). It is unknown if all or part of the parent compound in feces is due to unabsorbed drug or biliary excretion of the glucuronide conjugate, which can be converted back to the parent compound in the gut lumen. In bile duct-cannulated animals, 7% of the administered dose was recovered as DTG in rat bile, and 12% in monkey bile; the percentage of administered drug recovered as DTG in feces was similar for humans (64%) and monkeys (59%), and higher in rats (88%). Other notable components in feces include M13 (1.8% of total dose) and M1 (1.3% of total dose) (Study ING111853).

DTG has a terminal half-life of ~14 hours and a low CL/F of 0.56 L/hr (Study ING111853), which represents <2% of liver plasma flow; therefore, the hepatic extraction ratio is low (lower than 2%). As CYP3A4 is a secondary route of elimination

of DTG, the first-pass metabolism of DTG following oral dosing is expected to be very low.

3.4.2. Rilpivirine

A mass-balance trial (TMC278-C119, Table 1) 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 hours 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.

After oral administration of the tablet formulation, the Cmax of RPV is generally achieved within 4 to 5 hours. The mean terminal elimination t1/2 of RPV is approximately 45 hours. The mean apparent oral clearance (CL/F) ranged from 6.89 to 8.66 L/h.

3.5. Intrinsic Factors

3.5.1. Dolutegravir

Effects of intrinsic factors on DTG PK were evaluated in either Phase I studies or through population PK modeling:

- Body size, age, gender, and smoking: these are statistically significant covariates of DTG CL/F, Vd/F, and/or F, but the effects are not considered clinically significant; no DTG dose adjustment according to these covariates is needed. Pharmacokinetic data of DTG in subjects of >65 years old are very limited;
- Race: race (Caucasian, African American, and Japanese ancestry) or ethnicity (Hispanic/Latino or Not-Hispanic/Latino) has no effect on DTG PK parameters; no DTG dose adjustment according to race or ethnicity is needed;
- Hepatic impairment: DTG PK are similar between healthy subjects and subjects with moderate hepatic impairment (Child-Pugh Grade B) (ING113097, Table 1); no DTG dose adjustment is needed in subjects with mild to moderate hepatic impairment (Child-Pugh Grade A or B); the effect of severe hepatic impairment on the PK of DTG has not been studied;
- Renal impairment: There is no clinically relevant difference in DTG PK in subjects with mild/moderate renal impairment (Population PK in treatment-experienced subjects, Table 1) or severe renal impairment (CrCL <30 mL/min) (Study ING113125, Table 1); no DTG dosage adjustment is needed for subjects with mild, moderate, and severe (CrCL<30 mL /min, not on dialysis) renal impairment; currently there is no data on DTG PK in subjects on hemodialysis although no effect of hemodialysis on DTG PK is expected due to high protein binding of DTG in plasma;
- *UGT1A1* polymorphism: subjects with genotypes conferring poor metabolizer status of UGT1A1 *(*28/*28*; **28/*37*; **37/*37*) had a 32% lower clearance, 46% higher AUC, and 32% higher Cmax of DTG compared with subjects with genotypes

associated with normal UGT1A1 activity (**1/*1*, **1/*36*) (ING116265, Table 1). Increases in DTG exposure due to UGT1A1 polymorphisms are not considered clinically significant. No DTG dose adjustment according to UGT1A1 polymorphism is needed;

- HBV/HCV co-infection: HCV co-infection has no effect on DTG PK exposure. There were limited PK data for subjects with HBV co-infection. There is no drug interaction between DTG and commonly used or recently approved drugs for the treatment of HBV or HCV (Section 3.6.1.2). DTG can be used in HBV or HCV co-infected subjects.

Results from subgroup analysis of integrated efficacy (module 2.7.3) and integrated safety (module 2.7.4) indicated that there was no apparent or consistent difference in efficacy and safety by age, gender, or race, supporting the conclusions of no dose adjustment for DTG by these intrinsic factors. Although no differences in DTG systemic exposure is seen with HBV/HCV co-infection, differences in the safety profile of DTG for HBV and HCV co-infected subjects are observed (module 2.7.4) and are likely due to the intrinsic nature of these diseases and to the more robust virologic and immunologic activity of DTG, especially in treatment-experienced subjects, rather than direct toxicity of DTG. Therefore, dose adjustment is also unnecessary due to this intrinsic factor.

3.5.2. Rilpivirine

The impact of intrinsic factors on the PK of RPV was evaluated in a specific study (TMC278-TiDP6-C130) or subgroup analyses and explored using covariate modeling in the population PK analysis of RPV for pooled data for 2 Phase III trials (TMC278-TiDP6-C209 and TMC278-TiDP6-C215) in HIV-1 infected subjects (Population PK Report TMC278-0016435).

- The pooled analysis of the Phase III trials assessed the effect of age, gender, race, body weight, baseline GFR, HBV and/or HCV co-infection status on RPV systemic exposure. Gender and race were statistically significant with a somewhat higher exposure in females (CL/F 13.6% lower in females compared with males) and in Asian/Other subjects (CL/F 17.2% lower in Asian subjects) compared with the rest of the population. The magnitude of both effects was not considered clinically meaningful and therefore there is no need for dose adjustments based on gender or race.
- The results from a study (TMC278-TiDP6-C130) conducted to investigate the effects of mild and moderate hepatic impairment on the PK of RPV administered at a dose of 25 mg once daily indicated that no dose adjustment of RPV is needed in subjects with mild or moderate hepatic impairment (Table 1).
- 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.

3.6. Extrinsic Factors

3.6.1. Dolutegravir

A total of 24 Phase I DDI studies in healthy subjects have been performed and completed to assess the interaction between DTG and various drugs, including ARV medications for HIV treatment and non-ARV medications expected to be used concomitantly with DTG.

3.6.1.1. Non-clinical transporter data

In vitro, DTG is an inhibitor of the basolateral renal OCT2 and the renal apical transporters: MATE1 transporter (IC50 = 6.34 μM) and MATE2-K (IC50 = 24.8 μM). Dolutegravir has a low potential to affect the transport of MATE2-K substrates. In vitro incubation with DTG concentrations that were observed in vivo after a 50 mg oral dose produced a 90% inhibition of OCT2. These in vitro results indicate the potential for a drug interaction in vivo with cationic compounds that are renally cleared by these transporters, such as the endogenous substrate, creatinine, the antiarrhythmic drugs, dofetilide and pilsicainide, and the anti-diabetic drug, metformin. Caution should be used when considering co-administration of narrow therapeutic index cationic drugs in which a significant part of their clearance is by renal proximal tubule secretion by OCT2 or MATE1 (see Section 3.6.1.2 for details).

3.6.1.2. Drug-drug interactions

Effect of Dolutegravir on the Pharmacokinetics of Co-administered Drugs

In vivo drug interaction studies with sensitive substrates for CYP3A4 (MDZ) and CYP2B6 (EFV) confirmed the low propensity of DTG to alter the PK of agents metabolized by either CYP3A4 or CYP2B6 by demonstrating a lack of effect of DTG on the PK of MDZ and EFV. Drug interaction studies also indicated no clinically meaningful effect of DTG on TDF (a renal OAT1, OAT3, MRP2, and MRP4 substrate), RPV (a CYP3A substrate), methadone (primarily metabolized by CYP2B6 and CYP2C19 with CYP3A as a minor route), and an OC containing NGMN and EE, which have complex metabolism, including oxidation, reduction, and conjugation (Table 6).

In vitro, metabolic or transporter-related DDI studies have been completed with DTG and the results for the PK parameters of DTG are presented in Table 6.

As noted in Section 3.6.1.1, DTG inhibited the renal transporter OCT2, a mechanism that is consistent with a benign increase in serum creatinine. Based on this observation, DTG may reduce the excretion of dofetilide, metformin, or pilsicainide, thereby increasing plasma concentrations to toxic levels. Co-administration of DTG and dofetilide or pilsicainide is contra-indicated. A drug interaction study (201167) showed that plasma exposures of metformin were significantly increased when co-administered with DTG, and the magnitude of the effect was DTG dose-dependent (Table 6). Co-administration of DTG 50 mg q24h with metformin 500 mg q12h increased metformin AUC(0-τ) by 79% and Cmax by 66%. Additionally, when co-administered with DTG 50 mg q12h; plasma metformin Cmax and AUC(0-τ) were approximately 111% and 145% higher, respectively. Metformin is primarily excreted unchanged in the urine mainly through

tubular secretion. In vitro, DTG inhibits OCT2 and MATE 1 which is known to be involved in the tubular secretion of metformin. Thus, an increase in plasma exposure of metformin when co-administered with DTG is not unexpected. However, the extent of increase in metformin plasma exposure is more than would be expected based on in vitro IC50 values of OCT2 (1.93 μM) and MATE 1 (6.34 μM) inhibition. Taken together, these findings suggest that mechanisms other than inhibition of metformin renal elimination through inhibition of OCT2 and MATE 1 may be involved in the observed drug interaction. Therefore, a dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/RPV FDC with metformin to maintain glycemic control. Monitoring of blood glucose when initiating concomitant use and after withdrawal of DTG is recommended.

Effects of Co-administered Drugs on the Pharmacokinetics of Dolutegravir

In general, the exposure to DTG can be affected by modulators of the enzymes UGT1A1 and CYP3A4, and by drugs containing divalent cations such as Mg or Al. A summary of the effects of co-administered drugs on DTG PK are presented in Table 7.

Table 6 Summary of Effects of Dolutegravir on Pharmacokinetics of Co-administered Drugs

Concomitant drug	Concomitant drug dose	DTG dose	N	GM Ratio (90% CI) Co-administered drug +DTG / co-administered drug alone			Study	Conclusion
				C24/Cτ	AUC	Cmax		
MDZ (CYP 3A4 substrate)	3 mg single dose	25 mg once daily (suspension)	10	NA	0.945 (0.815, 1.095)	NA	ING111322	No effect on MDZ
TDF	300 mg once daily	50 mg once daily	15	1.186 (1.042-1.350)	1.119 (1.012-1.238)	1.094 (0.974-1.228)	ING111604	No TDF dose adjustment
Methadone	Individualized dose	50 mg BID	11	Total methadone 0.99 (0.91, 1.07) R-methadone 0.95 (0.89, 1.02) S-methadone 1.02 (0.93, 1.12)	0.98 (0.91, 1.06) 0.95 (0.89, 1.02) 1.01 (0.93, 1.09)	1.00 (0.94, 1.06) 0.97 (0.91, 1.03) 1.03 (0.97, 1.10)	ING115698	No methadone dose adjustment
Oral Contraceptive (EE/NGMN)	NGMN 0.25 mg EE 0.035 mg	50 mg BID	15	0.932 (0.846, 1.027) 1.019 (0.934, 1.112]	0.975 (0.910, 1.044) 1.032 (0.964, 1.105)	0.890 (0.815, 0.973) 0.988 (0.907, 1.077)	ING111855	No OC dose adjustment
RPV	25 mg once daily	50 mg once daily	16	1.214 (1.070, 1.378)	1.063 (0.976, 1.158)	1.102 (0.992, 1.224)	LAI116181	No RPV dose adjustment
Metformin	500 mg BID	50 mg once daily	15	NA	1.79 (1.65, 1.93)	1.66 (1.53, 1.81)	201167	Metformin dose adjustment[a]
		50 mg BID		NA	2.45 (2.25, 2.6)	2.11 (1.91, 2.33)		

Data Source: ING111322, Table 11.15; ING111604, Table 11.10; ING115698, Table 11.8; ING111855, Table 3.6, Table 3.10; LAI116181, Table 11.12; 201167, Table 10.051, Table 10.052

a. Subjects should be monitored when starting and stopping co-administration of DTG with metformin

Table 7 Summary of Effects of Co-administered Drugs on Dolutegravir Pharmacokinetics

Co-administered Drug	Co-administered Drug Dose	DTG Dose	N	Geometric Mean Ratio (90% CI) of DTG PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	DTG Dose Recommendation
				Cτ/C24	AUC	Cmax		
TDF	300 mg once daily	50 mg once daily	15	0.920 (0.816-1.036)	1.005 (0.908-1.113)	0.969 (0.867-1.083)	ING111604 Table 11.6	No dose adjustment
DRV/RTV	600/100 mg BID	30 mg once daily	15	0.620 (0.555-0.694)	0.782 (0.722-0.848)	0.892 (0.825-0.965)	ING111405 Table 11.6	No dose adjustment
LPV/RTV	400/100 mg BID	30 mg once daily	15	0.944 (0.848-1.052)	0.973 (0.911-1.039)	1.000 (0.937-1.066)	ING111405 Table 11.6	No dose adjustment
ETR	200 mg BID	50 mg once daily	15	0.121 (0.093-0.157)	0.294 (0.257-0.337)	0.484 (0.433-0.542)	ING111603 Table 11.6	Not recommended
ETR/LPV/RTV	200/400/ 100 mg BID	50 mg once daily	8	1.278 (1.130-1.445)	1.105 (1.017-1.201)	1.072 (1.020-1.128)	ING112934 Table 11.6	No dose adjustment
ETR/DRV/RTV	200/600/ 100 mg BID	50 mg once daily	9	0.629 (0.523-0.758)	0.750 (0.691-0.814)	0.882 (0.781-0.997)	ING112934 Table 11.6	No dose adjustment
Multivitamins	One-a-Day	50 mg single dose	16	0.679 (0.560-0.824)	0.668 (0.553-0.806)	0.646 (0.540-0.774)	ING111602 Table 11.4	No dose adjustment
Maalox	20 mL	50 mg single dose	16	0.256 (0.211-0.311)	0.264 (0.218-0.318)	0.276 (0.231-0.331)	ING111602 Table 11.4	DTG should be taken 2 hours before or 6 hours after antacid
Maalox 2 hrs after	20 mL	50 mg single dose	16	0.703 (0.579-0.853)	0.743 (0.615-0.897)	0.821 (0.686-0.984)	ING111602 Table 11.4	
Calcium carbonate (fasted)	1200 mg	50 mg single dose	12	0.61 (0.47, 0.80)	0.61 (0.47, 0.79)	0.63 (0.50, 0.81)	ING116898 Table 3.5	DTG should be taken 2 hours before or 6 hours after supplement if taken without food; or alternatively, take with food
Calcium carbonate (fed)	1200 mg	50 mg single dose	11	1.08 (0.81, 1.42)	1.09 (0.84, 1.43)	1.07 (0.83, 1.38)	ING116898 Table 3.5	
Calcium carbonate 2hrs prior (fasted)	1200 mg	50 mg single dose	11	0.90 (0.68, 1.19)	0.94 (0.72, 1.23)	1.00 (0.7, 1.29)	ING116898 Table 3.5	
Ferrous Fumarate (fasted)	324 mg	50 mg single dose	11	0.44 (0.36, 0.54)	0.46 (0.38, 0.56)	0.43 (0.35, 0.52)	ING116898 Table 3.5	DTG should be taken 2 hours before or 6 hours after supplement if taken without food; or alternatively, take with food
Ferrous Fumarate (fed)	324 mg	50 mg single dose	11	0.99 (0.80, 1.22)	0.97 (0.80, 1.19)	1.03 (0.85, 1.26)	ING116898 Table 3.5	
Ferrous Fumarate 2hrs prior (fasted)	324 mg	50 mg single dose	10	0.92 (0.74, 1.13)	0.95 (0.78, 1.15)	0.99 (0.81, 1.21)	ING116898 Table 3.5	

Co-administered Drug	Co-administered Drug Dose	DTG Dose	N	Geometric Mean Ratio (90% CI) of DTG PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	DTG Dose Recommendation
				Cτ/C24	AUC	Cmax		
ATV/RTV	300/100 mg once daily	30 mg once daily	12	2.206 (1.972-2.468)	1.617 (1.500-1.743)	1.336 (1.254-1.423)	ING111854 Table 11.6	No dose adjustment
ATV	400 mg once daily	30 mg once daily	12	2.802 (2.523-3.113)	1.911 (1.802-2.026)	1.495 (1.404-1.591)	ING111854 Table 11.6	No dose adjustment
OMP	40 mg once daily	50 mg single dose	12	0.954 (0.752-1.209)	0.971 (0.783-1.203)	0.915 (0.754-1.111)	ING112941 Table 11.4	No dose adjustment
TPV/RTV	500/200 mg BID	50 mg once daily	14	0.239 (0.212-0.270)	0.409 (0.379-0.443)	0.535 (0.500-0.572)	ING113096 Table 11.6	DTG 50 mg BID[a]
EFV	600 mg once daily	50 mg once daily	12	0.245 (0.179-0.336)	0.431 (0.346-0.536)	0.608 (0.506-0.730)	ING114005 Table 11.10	DTG 50 mg BID[a]
FPV/RTV	700/100 mg BID	50 mg once daily	12	0.510 (0.413-0.629)	0.651 (0.542-0.782)	0.763 (0.632-0.921)	ING113068 Table 11.12	No dose adjustment
RIF	600 mg once daily	50 mg BID[b]	11	1.220 (1.005, 1.480)	1.327 (1.152, 1.529)	1.184 (1.026, 1.366)	ING113099 Table 11.5	DTG 50 mg BID
		50 mg BID[c]	11	0.277 (0.228, 0.336)	0.460 (0.384, 0.552)	0.565 (0.489, 0.652)		
RBT	300 mg once daily	50 mg once daily	9	0.700 (0.566, 0.866)	0.947 (0.816, 1.098)	1.156 (0.978, 1.365)	ING113099 Table 11.6	No dose adjustment
Prednisone	60 mg once daily	50 mg once daily	12	1.167 (1.062, 1.281)	1.111 (1.030, 1.198)	1.062 (0.991, 1.139)	ING115696 Table 11.5	No dose adjustment
BCV	800 mg three times daily	50 mg once daily	13	1.080 (0.911, 1.281)	1.068 (0.948, 1.203)	1.052 (0.960, 1.153)	ING115697 Table 3.7	No dose adjustment
TVR	750 mg three times daily	50 mg once daily	15	1.368 (1.290, 1.450)	1.253 (1.196, 1.314)	1.185 (1.111, 1.264)	ING115697 Table 3.8	No dose adjustment
RPV	250 mg once daily	50 mg once daily	16	1.223 (1.149, 1.302)	1.121 (1.053, 1.194)	1.130 (1.055, 1.210)	LAI116181 Table 11.5	No dose adjustment
CBZ	300 mg BID	50 mg once daily	16	0.274 (0.240, 0.313)	0.512 (0.477, 0.549)	0.666 (0.610, 0.726)	200901 Table 10.3	DTG 50 mg BID
DCV	60 mg once daily	50 mg once daily	12	1.45 (1.25, 1.68)	1.33 (1.11, 1.59)	1.29 (1.07, 1.57)	201102 Table 10.6	No dose adjustment

Data Source: see table.

a. Caution should be given to INSTI-resistant subjects.
b. Comparison was between DTG 50 mg BID + RIF (test treatment) vs DTG 50 mg once daily (reference treatment).
c. Comparison was between DTG 50 mg BID + RIF (test treatment) vs DTG 50 mg BID (reference treatment).

3.6.1.3. Effect of food on Pharmacokinetic Parameters

The effect of food on the BA of the DTG/RPV FDC (Study 201674) and a selected DTG formulation (Study ING113674) is presented in module 2.7.1, Section 2.4.1 and Section 2.4.2, respectively. Co-administration of various DTG/RPV FDC formulations with a moderate-fat meal increased DTG AUC(0-∞) by 74 to 87% and Cmax by 75 to 88% (Study 201674).

3.6.2. Rilpivirine

A total of 21 Phase I DDI studies in healthy subjects and 1 study in HIV-1 infected subjects have been performed and completed to assess the interaction between RPV and various drugs, including ARV medications for HIV treatment and non-ARV medications expected to be used concomitantly with RPV.

3.6.2.1. Drug-drug interactions

Effect of Rilpivirine on the Pharmacokinetics of Co-administered Drugs

Overall, RPV at the dose of 25 mg once daily is not likely to have a clinically relevant effect on the exposure of co-administered drugs. Most of the DDI studies were performed with a RPV dose of 150 mg once daily, which was the highest dose studied in the Phase IIb dose-finding trial, to assess the maximal effect of RPV on other drugs within the dose range studied. With the RPV dose of 25 mg once daily, any observed effect on the PK of other drugs would either be similar or, more likely, lower than that observed with the RPV dose of 150 mg once daily because of the lower exposure to RPV. The PK parameters for the co-administered drugs in the presence of RPV are presented in Table 8.

Effects of Co-administered Drugs on the Pharmacokinetics of Rilpivirine

In general, the exposure to RPV can be affected by modulators of CYP3A enzyme activity and by drugs that increase gastric pH. Drugs that alter intragastric pH may affect the solubility of RPV in vivo and can therefore also indirectly affect the absorption of RPV, as evidenced by a decrease in RPV AUC after co-administration of a single 150 mg dose of RPV with OMP (TMC278-C114, Table 9) or administration of a single dose of RPV 2 hours after a single dose of famotidine (TMC278-C140; Table 9). The metabolism of RPV is mainly catalyzed by CYP3A enzymes (see Section 3.3.2). Therefore, co-administration of RPV and drugs that induce CYP3A could decrease RPV plasma concentrations. This was indeed shown in vivo by the results of DDI studies with RIF (R278474-C108, Table 9) and RBT (TMC278-C125, Table 9), which both significantly decreased the exposure to RPV. Conversely, co-administration of RPV and drugs that inhibit CYP3A may increase RPV plasma concentrations, as evidenced in vivo by the results of DDI studies with KTZ (TMC278-C127, Table 9) and RTV-boosted PIs (TMC278-C105 and TMC278-C112, Table 9). The PK parameters for RPV in the presence of co-administered drugs are presented in Table 9.

Table 8 Summary of Effects of Rilpivirine on Pharmacokinetics of Co-administered Drugs

Concomitant drug	Concomitant drug dose	RPV dose	N	Ratio of the Least Square Means (90% CI) Co-administered drug +RPV / co-administered drug alone			Study	Conclusion
				Cmin	AUC24h	Cmax		
TDF	300 mg once daily	150 mg once daily	16	1.24 (1.10 - 1.38)	1.23 (1.16 - 1.31)	1.19 (1.06 - 1.34)	TMC278-C104	No TDF dose adjustment
ddI	400 mg once daily	150 mg once daily	13	NA	1.12 (0.99 - 1.27)	0.96 (0.80 - 1.14)	TMC278-C106	No ddI dose adjustment[a]
LPV	400 mg BID	150 mg once daily	15	0.89 (0.73 - 1.08)	0.99[b] (0.89 - 1.10)	0.96 (0.88 - 1.05)	TMC278-C105	No LPV/RTV dose adjustment
RTV	100 mg BID	150 mg once daily	15	1.07 (0.89 - 1.28)	0.96[b] (0.84 - 1.11)	0.89 (0.73 - 1.08)	TMC278-C105	
DRV	800 mg once daily	150 mg once daily	15	0.89 (0.68 - 1.16)	0.89 (0.81 - 0.99)	0.90 (0.81 - 1.00)	TMC278-C112	No DRV/RTV dose adjustment
RTV	100 mg once daily	150 mg once daily	15	0.78 (0.68 - 0.90)	0.85 (0.78 - 0.91)	0.83 (0.72 - 0.95)	TMC278-C112	
RIF	RIF 600 mg once daily	150 mg once daily	16	NA	0.99 (0.92 - 1.07)	1.02 (0.93 - 1.12)	R278474-C108	RIF is contraindicated with RPV
25-desacetylrifampin			16	NA	0.91 (0.77 - 1.07)	1.00 (0.87 - 1.15)	R278474-C108	
RBT	RBT 300 mg once daily	150 mg once daily	17	1.01 (0.94 - 1.09)	1.03 (0.97 - 1.09)	1.03 (0.93 - 1.14)	TMC278-C125	No RBT dose adjustment[c]
25-O-desacetyl-RBT			17	1.12 (1.03 - 1.22)	1.07 (1.02 - 1.11)	1.07 (0.98 - 1.17)	TMC278-C125	
Ketoconazole	400 mg once daily	150 mg once daily	14	0.34 (0.25 - 0.46)	0.76 (0.70 - 0.82)	0.85 0.80 - 0.90)	TMC278-C127	No ketoconazole dose adjustment
Sildenafil	Sildenafil 50 mg single dose	75 mg once daily	16	NA	0.97 (0.87 - 1.08)[e]	0.93 (0.80 - 1.08)	TMC278-TiDP6-C123	No sildenafil dose adjustment
N-desmethyl sildenafil			16	NA	0.92 (0.85 - 0.99)[d]	0.90 (0.80 - 1.02)	TMC278-TiDP6-C123	

Concomitant drug	Concomitant drug dose	RPV dose	N	Ratio of the Least Square Means (90% CI) Co-administered drug +RPV / co-administered drug alone			Study	Conclusion
				Cmin	AUC24h	Cmax		
Atorvastatin	Atorvastatin 40 mg once daily	150 mg once daily	16	0.85 (0.69 - 1.03)	1.04 (0.97 - 1.12)	1.35 (1.08 - 1.68)	TMC278-C116	No atorvastatin dose adjustment
Atorvastatin lactone			16	0.74 (0.63 - 0.86)	0.82 (0.77 - 0.88)	0.93 (0.84 - 1.03)	TMC278-C116	
2-hydroxy-atorvastatin			16	1.32 (1.10 - 1.58)	1.39 (1.29 - 1.50)	1.58 (1.33 - 1.87)	TMC278-C116	
4-hydroxy-atorvastatin			16	NA	1.23 (1.13 - 1.33)	1.28 (1.15 - 1.43)	TMC278-C116	
Total HMG CoA reductase activity			16	1.13 (0.92 - 1.39)	1.21 (1.12 - 1.30)	1.39 1.14 - 1.70)	TMC278-C116	
EE	35 μg once daily	150 mg once daily	15	0.83 (0.75 - 0.91)	0.99 (0.93 - 1.06)	1.12 (1.01 - 1.24)	TMC278-C120	No EE dose adjustment
Norethindrone	1 mg once daily		15	0.54 (0.49 - 0.59)	0.59 (0.56 - 0.61)	0.67 (0.60 - 0.74)	TMC278-C120	
EE	35 μg once daily	25 mg once daily	17	1.09 (1.03 - 1.16)	1.14 (1.10 - 1.19)	1.17 (1.06 - 1.30)	TMC278-TiDP6-C136	No EE dose adjustment
Norethindrone	1 mg once daily	25 mg once daily	17	0.99 (0.90 - 1.08)	0.89 (0.84 - 0.94)	0.94 (0.83 - 1.06)	TMC278-TiDP6-C136	
R(-) Methadone	60 to 100 mg once daily individualized dose	25 mg once daily	13	0.78 (0.67 - 0.91)	0.84 (0.74 - 0.95)	0.86 (0.78 - 0.95)	TMC278-TiDP6-C121	No methadone dose adjustment
S(+) Methadone			13	0.79 (0.67 - 0.92)	0.84 (0.74 - 0.96)	0.87 (0.78 - 0.97)	TMC278-TiDP6-C121	
OMP	OMP 20 mg once daily	150 mg single dose	15	NA	0.99 (0.89 - 1.11)	0.94 (0.75 - 1.18)	TMC278-C114	OMP is contraindicated with RPV
5-hydroxy-OMP			15	NA	1.06 (0.99 - 1.12)	1.03 (0.87 - 1.22)	TMC278-C114	
OMP sulfone			15	0.94 (0.78 - 1.13)	0.94 (0.83 - 1.06)	0.90 (0.75 - 1.07)	TMC278-C114	

Concomitant drug	Concomitant drug dose	RPV dose	N	Ratio of the Least Square Means (90% CI) Co-administered drug +RPV / co-administered drug alone			Study	Conclusion
				Cmin	AUC24h	Cmax		
OMP	OMP 20 mg once daily	150 mg once daily	15	NA	0.86 (0.76 - 0.97)	0.86 (0.68 - 1.09)	TMC278-C114	
5-hydroxy-OMP			15	NA	1.09 (1.02 - 1.16)	1.07 (0.91 - 1.25)	TMC278-C114	
OMP sulfone			15	NA	0.76 (0.65 - 0.88)	0.85 (0.69 - 1.03)	TMC278-C114	
Paracetamol	500 mg single dose	150 mg once daily	16	NA	0.91 (0.86 - 0.97)[d]	0.97 (0.86 - 1.10)	TMC278-C109	No paracetamol dose adjustment
Paracetamol glucuronide			16	NA	0.98 (0.94 - 1.03)[d]	0.96 (0.90 - 1.03)	TMC278-C109	
Paracetamol sulfate			16	NA	0.97 (0.91 - 1.03)d	1.00 (0.94 - 1.07)	TMC278-C109	
Chlorzoxazone	500 mg single dose	150 mg single dose	16	NA	0.97 (0.87 - 1.07)[e]	0.96 (0.82 - 1.12)	TMC278-C139	No chlorzoxazone dose adjustment
6-hydroxy-chlorzoxazone			16	NA	0.94 (0.90 - 0.98)[e]	0.99 (0.94 - 1.04)	TMC278-C139	
Chlorzoxazone		150 mg once daily	16	NA	1.03 (0.95 - 1.13)[e]	0.98 (0.85 - 1.13)	TMC278-C139	
6-hydroxy-chlorzoxazone			16	NA	0.97 (0.87 - 1.07)[e]	0.97 (0.90 - 1.05)	TMC278-C139	
RAL	400 mg BID	25 mg once daily	23	1.27 (1.01 - 1.60)	1.09 (0.81 - 1.47)	1.10 (0.77 - 1.58)	TMC278-TiDP6-C153	No RAL dose adjustment
Digoxin	0.5 mg single dose	25 mg once daily	22	NA	0.98[d] (0.93 - 1.04)	1.06 (0.97 - 1.17)	TMC278 IFD1001	No digoxin dose adjustment
Metformin	850 mg single dose	25 mg once daily	20	NA	0.97 (0.90-1.06)[e]	1.02 (0.95-1.10)	TMC278 IFD1004	No metformin dose adjustment

Data Source: TMC278-C104, Table 11; TMC278-C106, Table 14; TMC278-C105, Table 10, Table 12; TMC278-C112, Table 10, Table 12; R278474-C108, Table 12; TMC278-C125, Table 10, Table 12; TMC278-C127, Table 10; TMC278-TiDP6-C123, Table 8, Table 10; TMC278-C116, Table 10, Table 12, Table 14, Table 16, Table 18; TMC278-C120, Table 9, Table 11; TMC278-TiDP6-C136, Table 6, Table 8; TMC278-TiDP6-C121, Table 5, Table 7; TMC278-C114, Table 10, Table 11, Table 13, Table 14, Table 17, Table 18; TMC278-C109, Table 10, Table 12, Table 14; TMC278-C139, Table 9, Table 10, Table 12, Table 13; TMC278-TiDP6-C153; synopsis CSR; TMC278IFD1001, Table 6; TMC278IFD1004, Table 6

a. As ddI is administered on an empty stomach, ddI should be administered at least 1 hour before or 2 hours after RPV (which should be administered with a meal).
b. AUC = AUC12h
c. For patients concomitantly receiving RBT, the RPV dose should be increased to 50 mg once daily, taken with a meal. When RBT co-administration is stopped, the RPV dose should be decreased to 25 mg once daily, taken with a meal.
d. AUC = AUC∞
e. AUC = AUClast

N = Maximum number of subjects with data

Table 9 Summary of Effects of Co-administered Drugs on Rilpivirine Pharmacokinetics

Co-administered Drug	Co-administered Drug Dose	RPV Dose	N	Ratio of the Least Square Means (90% CI) of RPV PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	RPV Dose Recommendation
				Cmin	AUC24h	Cmax		
TDF	300 mg once daily	150 mg once daily	16	0.99 (0.83 - 1.16)	1.01 (0.87 - 1.18)	0.96 (0.81 - 1.13)	TMC278-C104 Table 9	No dose adjustment
ddI	400 mg once daily	150 mg once daily	21	1.00 (0.92 - 1.09)	1.00 (0.95 - 1.06)	1.00 (0.90 - 1.10)	TMC278-C106 Table 12	No dose adjustment[a]
LPV/RTV	400/100 mg BID	150 mg once daily	15	1.74 (1.46 - 2.08)	1.52 (1.36 - 1.70)	1.29 (1.18 - 1.40)	TMC278-C105 Table 8	No dose adjustment
DRV/RTV	800/100 mg once daily	150 mg once daily	14	2.78 (2.39 - 3.24)	2.30 (1.98 - 2.67)	1.79 (1.56 - 2.06)	TMC278-C112 Table 8	No dose adjustment
RIF	600 mg once daily	150 mg once daily	16	0.11 (0.10 - 0.13)	0.20 (0.18 - 0.23)	0.31 (0.27 - 0.36)	R278474-C108 Table 9	RIF is contraindicated with RPV
RBT	300 mg once daily	150 mg once daily	16	0.51 (0.48 - 0.54)	0.54 (0.50 - 0.58)	0.65 (0.58 - 0.74)	TMC278-C125 Table 8	No dose adjustment
RBT	300 mg once daily	25 mg once daily	18	0.52 (0.46 - 0.59)	0.58 (0.52 - 0.65)	0.69 (0.62 - 0.76)	TMC278 IFD1003 Table 6 Table 7	Increase RPV dose to 50 mg once daily[c]
	300 mg once daily	50 mg once daily	18	0.93[b] (0.85 - 1.01)	1.16[b] (1.06 - 1.26)	1.43[b] (1.30 - 1.56)		
Ketoconazole	400 mg once daily	150 mg once daily	15	1.76 (1.57 - 1.97)	1.49 (1.31 - 1.70)	1.30 (1.13 - 1.48)	TMC278-C127 Table 8	No dose adjustment
Sildenafil	50 mg	75 mg once daily	16	1.04	0.98	0.92	TMC278-	No dose adjustment

Co-administered Drug	Co-administered Drug Dose	RPV Dose	N	Ratio of the Least Square Means (90% CI) of RPV PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	RPV Dose Recommendation
				Cmin	AUC24h	Cmax		
	single dose			(0.98 - 1.09)	(0.92 - 1.05)	(0.85 - 0.99)	TiDP6-C123 Table 6	
Atorvastatin	40 mg once daily	150 mg once daily	16	0.90 (0.84 - 0.96)	0.90 (0.81 - 0.99)	0.91 (0.79 - 1.06)	TMC278-C116 Table 8	No dose adjustment
EE/Norethindrone	35 μg/1 mg once daily	150 mg once daily	15	No change[d]	No change[d]	No change[d]	TMC278-C120 Table 7	No dose adjustment
EE/Norethindrone	35 μg/1 mg once daily	25 mg once daily	15	No change[d]	No change[d]	No change[d]	TMC278-TiDP6-C136[e]	No dose adjustment
Methadone	60 to 100 mg once daily individualized dose	25 mg once daily	12	No change[d]	No change[d]	No change[d]	TMC278-TiDP6-C121 Table 8	No dose adjustment
OMP	20 mg once daily	150 mg single dose	16	NA	0.44 (0.35 - 0.55)	0.42 (0.32 - 0.54)	TMC278-C114 Table 7	OMP is contraindicated with RPV
		150 mg once daily	16	0.67 (0.58 - 0.78)	0.60 (0.51 - 0.71)	0.60 (0.48 - 0.73)	TMC278-C114 Table 8	
Famotidine	40 mg single dose 2h before RPV	150 mg single dose	23	NA	0.24 (0.20 - 0.28)[f]	0.15 (0.12 - 0.19)	TMC278-C140 Table 8	Co-administration of RPV with famotidine should be used with caution[g]
	40 mg single dose 4h after RPV	150 mg single dose	24	NA	1.13 (1.01 - 1.27)[f]	1.21 (1.06 - 1.39)	TMC278-C140 Table 9	

Co-administered Drug	Co-administered Drug Dose	RPV Dose	N	Ratio of the Least Square Means (90% CI) of RPV PK Parameters with/without Co-administered Drugs No Effect = 1.00			Data Source	RPV Dose Recommendation
				Cmin	AUC24h	Cmax		
	40 mg single dose 12h before RPV	150 mg single dose	24	NA	0.91 (0.78 - 1.07)[f]	0.99 (0.84 - 1.16)	TMC278-C140 Table 10	
Paracetamol	500 mg single dose	150 mg once daily	16	1.26 (1.16 - 1.38)	1.16 (1.10 - 1.22)	1.09 (1.01 - 1.18)	TMC278-C109 Table 8	No dose adjustment
Chlorzoxazone	500 mg single dose	150 mg once daily	16	1.18 (1.09 - 1.28)	1.25 (1.16 - 1.35)	1.17 (1.08 - 1.27)	TMC278-C139 Table 7	No dose adjustment
RAL	400 mg BID	25 mg once daily	23	1.03 (0.96 - 1.12)	1.12 (1.05 - 1.19)	1.12 (1.04 - 1.20)	TMC278-TiDP6-C153 Synopsis	No dose adjustment
Simeprevir	150 mg once daily	25 mg once daily	23	1.25 (1.16-1.35)	1.12 (1.05-1.19)	1.04 (0.95-1.13)	TMC435-TiDP16-C114	No dose adjustment

Data Source: see table.

a. As ddI is administered on an empty stomach, ddI should be administered at least 1 hour before or 2 hours after RPV (which should be administered with a meal)
b. Compared with RPV 25 mg once daily alone
c. For patients concomitantly receiving RBT, the RPV dose should be increased to 50 mg once daily, taken with a meal. When RBT co-administration is stopped, the RPV dose should be decreased to 25 mg once daily, taken with a meal.
d. Comparison based on historical controls
e. No table of statistical analysis for RPV is presented in the CSR
f. AUC = AUC∞
g. H2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV.

N = Maximum number of subjects with data

3.6.2.2. Effect of food on Pharmacokinetic Parameters

The effect of food on the BA of RPV from the single entity development program (Study TMC278-TiDP6-C137) and from the DTG/RPV FDC (Study 201674) is presented in module 2.7.1. RPV systemic exposure was 1.6- to 1.9-fold higher when DTG/RPV FDC was administered with moderate-fat meal compared with a fasted state. Taking DTG/RPV FDC in a fasted condition or with only a protein-rich nutritional drink may result in decreased plasma concentrations of RPV, which could potentially reduce the therapeutic effect of DTG/RPV FDC.

3.6.3. Management of Drug-drug Interactions for Dolutegravir/Rilpivirine Fixed-dose Combination

Recommendations for the management of expected DDIs for the DTG/RPV FDC are presented in Table 10. These recommendations are based on DDI studies from the DTG or RPV SE development programs.

Table 10 Recommendations for the Management of DTG/RPV FDC Based on Expected Drug-drug Interactions for DTG and RPV Single Entity Development Programs

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug	Clinical Comment
Carbamazepine (CBZ)	Co-administration of DTG with CBZ resulted in decreases in DTG Cmax, AUC, and Cτ by approximately 33%, 49%, and 73%, respectively.	Metabolic inducers may significantly decrease DTG or RPV plasma concentrations, resulting in loss of therapeutic effect. Co-administration of DTG/RPV FDC with these metabolic inducers is contraindicated
Omeprazole (OMP)	**Effect of OMP on RPV:** Co-administration of RPV with OMP resulted in decreases in RPV Cmax, AUC24h, and Cmin by 40%, 40%, and 33%, respectively **Effect of RPV on OMP** A decrease of 14% in both OMP Cmax and AUC24h was observed during co-administration with multiple doses of RPV. Cmin: not evaluated	Proton pump inhibitors may significantly decrease RPV plasma concentrations, resulting in loss of therapeutic effect. Co-administration of DTG/RPV FDC with proton pump inhibitors is contraindicated.
Rifampin (RIF)	**Effect of RIF on DTG:** Co-administration of DTG with RIF resulted in decreases in DTG AUC(0-τ), Cmax, and Cτ by 54%, 43%, and 72%, respectively. RIF ↔ **Effect of RIF on RPV:** Co-administration of RPV with RIF decreased RPV AUC24h, Cmax, and Cmin by 80%, 69%, and 89%, respectively	RIF may significantly decrease DTG or RPV plasma concentrations, resulting in loss of therapeutic effect. Co-administration of DTG/RPV FDC with RIF is contraindicated.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug**	**Clinical Comment**
Tipranavir (TPV)/RTV	**DTG:** Co-administration of DTG with TPV/RTV resulted in a 59%, 46%, and 76% decrease in plasma DTG AUC(0-τ), Cmax, and Cτ, respectively. TPV ↔ RTV ↔	TPV/RTV may increase RPV plasma concentrations and decrease DTG concentrations. Co-administration of DTG/RPV FDC with TPV/RTV is not recommended
Famotidine	**Famotidine taken 12h before RPV**: AUClast and AUC∞ of RPV were each decreased by 9%. Cmax: ↔, Cmin: not evaluated. **Famotidine taken 2h before RPV**: AUClast, AUC∞, and Cmax of RPV were decreased by 77%, 76%, and 85%, respectively. Cmin not evaluated. **Famotidine taken 4h after RPV**: AUClast, AUC∞, and Cmax of RPV were increased by 12%, 13%, and 21%, respectively. Cmin not evaluated.	H2-receptor antagonists may significantly decrease RPV plasma concentrations. DTG/RPV FDC should only be administered at least 4 hours before or at least 12 hours after H2-receptor antagonists.
Aluminium magnesium hydroxide, and/or calcium carbonate	**DTG:** Co-administration of DTG with Maalox decreased DTG AUC, Cmax, and C24 by 74%, 72%, and 74%, respectively.	Use with caution as co-administration may significantly decrease DTG or RPV plasma concentrations, resulting in loss of therapeutic effect. DTG/RPV FDC should only be administered at least 4 hours before or 6 hours after taking antacid products
Calcium or iron supplements	**DTG:** Co-administration of DTG with calcium carbonate reduced DTG AUC(0-∞), Cmax, and C24 by 39%, 37%, and 39%, respectively. **DTG:** Co-administration of DTG with ferrous fumarate reduced DTG AUC(0-∞), Cmax, and C24 by 54%, 57%, and 56%, respectively.	DTG/RPV FDC is recommended to be administered at least 4 hours before or 6 hours after taking calcium or iron non-antacid products, or alternatively, co-administer together with a meal.
Metformin	**DTG:** Co-administration of DTG with metformin resulted in increases in metformin AUC(0-τ) and Cmax by 79% and 66%, respectively. Cmin not evaluated. **RPV:** Co-administration of RPV with metformin did not affect Cmax, AUClast, and AUC∞ values of metformin	Co-administration of DTG/RPV FDC may increase metformin plasma concentrations. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/RPV FDC with metformin to maintain glycemic control.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug	Clinical Comment
Rifabutin (RBT)	**DTG**: Co-administration of DTG with RBT resulted in a 16% increase in DTG Cmax, no change in AUC(0-τ), and a 30% reduction in Cτ. RBT ↔ **RPV:** Co-administration of RPV 25 mg with RBT decreased RPV AUC24h, Cmax, and Cmin by 42%, 31%, and 48%, respectively. Co-administration of RPV 50 mg with RBT increased RPV AUC24h and Cmax by 16% and 43%, respectively. Cmin ↔ compared with RPV 25 mg alone.	RBT decreased the plasma concentrations of RPV. During co-administration with RBT an additional 25-mg dose of RPV should be taken at the same time with DTG/RPV FDC.
Didanosine (ddI)	**RPV** : RPV ↔ **Effect of RPV on ddI:** Co-administration of RPV with ddI increased plasma ddI AUC24h by 12%. Cmax ↔ Cmin: not evaluated	ddI did not change RPV plasma concentrations to a clinically relevant extent. No dose adjustment of DTG/RPV FDC is necessary. ddI should be administered on an empty stomach at least 2 hours before or 4 hours after DTG/RPV FDC (which should be taken with a meal).
Methadone	**Effect of DTG on methadone** Co-administration of DTG with methadone resulted in decreased methadone AUC(0-τ) and Cτ by 2% and 1%, respectively, and no effect on Cmax. **Effect of RPV on methadone** Co-administration of RPV with methadone resulted in decreased methadone AUC24h, Cmax, and Cmin by 16%, 14% and 22%, respectively.	DTG or RPV did not change methadone plasma concentrations to a clinically relevant extent. No dose adjustment of methadone is necessary when initiating co-administration with DTG/RPV FDC. However, clinical monitoring is recommended as methadone maintenance therapy may need to be adjusted in some patients.
Atazanavir (ATV)	**DTG:** Co-administration of DTG with ATV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 91%, 50%, and 180%, respectively. ATV ↔	ATV may increase DTG or RPV plasma concentrations. No dose adjustment is necessary.
ATV/ritonavir (RTV)	**DTG:** Co-administration of DTG with ATV/RTV resulted in an increase in plasma DTG AUC(0-τ), Cmax, and Cτ by 62%, 34%, and 121%, respectively. ATV↔ RTV↔	ATV/RTV may increase DTG or RPV plasma concentrations. No dose adjustment is necessary.

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug	Clinical Comment
Fosamprenavir (FPV)/RTV	**DTG:** Co-administration of DTG with FPV/RTV decreased DTG plasma AUC(0-τ), Cmax, and Cτ by 35%, 24%, and 49%, respectively. FPV ↔ RTV ↔	FPV/RTV may increase RPV plasma concentrations and decrease DTG concentrations. No dose adjustment is necessary.
Lopinavir/RTV (LPV + RTV)	**DTG:** Co-administration of DTG with LPV/RTV decreased plasma DTG AUC(0-τ) and Cτ by 4% and 6%, respectively. There was no effect of LPV/RTV on DTG Cmax. LPV ↔ RTV ↔ **RPV:** Co-administration of RPV with LPV/RTV increased RPV plasma AUC24h, Cmax, and Cmin by 52%, 29%, and 74%, respectively.	LPV/RTV did not change DTG or RPV plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Darunavir (DRV)/RTV	**DTG:** Co-administration of DTG with DRV/RTV decreased plasma DTG AUC(0-τ), Cmax, and Cτ by 22%, 11%, and 38%, respectively. DRV ↔ RTV ↔ **RPV:** Co-administration of RPV with DRV/RTV increased plasma RPV AUC24h, Cmax, Cmin by 130%, 79%, and 178%, respectively.	DRV/RTV did not change DTG or RPV plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Tenofovir disoproxil fumarte (TDF)	**DTG:** Co-administration of DTG with TDF decreased plasma DTG Cmax and Cτ by 3%, and 8%, respectively. TDF had no effect on DTG AUC(0-τ). **Effect of DTG on TDF:** Co-administration of DTG with TDF increased plasma TDF AUC(0-τ), Cmax, and Cτ by 12%, 9%, and 19%, respectively. **RPV** : RPV ↔ **Effect of RPV on TDF**: Co-administration of RPV with TDF increased plasma TDF AUC24h, Cmax, Cmin by 23%, 19%, and 24%, respectively.	TDF did not change DTG or RPV plasma concentrations to a clinically relevant extent. No dose adjustment is necessary.
Daclatasavir (DCV)	**DTG:** Co-administration of DTG with DCV increased DTG AUC(0-τ), Cmax, and Cτ by 33%, 29%, and 45%, respectively. DCV: ↔	DCV did not change DTG plasma concentrations to a clinically relevant extent. DTG did not change DCV plasma concentrations. No dose adjustment is necessary.

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug**	**Clinical Comment**
Simeprevir (SPV)	**RPV:** Co-administration of RPV with SPV increased RPV plasma Cmin by 25%. AUCτ ↔ Cmax ↔ **Effect of RPV on SPV:** Co-administration of RPV with SPV increased plasma Cmax by 10%. AUCτ ↔ Cmin ↔	No dose adjustment is necessary.
Oral contraceptives (Ethinyl estradiol [EE)] and Norelgestromin [NGMN]) or Norethindrone	**Effect of DTG on EE** Co-administration of DTG with EE increased EE AUC(0-τ) and Cmin by 3% and 2%, respectively, whereas Cmax decreased by 1%. **Effect of DTG on NGMN** Co-administration of DTG with NGMN resulted in decreased NGMN AUC(0-τ), Cmax, and Cmin by 2%, 11%, and 7%, respectively. **Effect of RPV on EE** Co-administration of RPV with EE increased EE Cmax by 17%. RPV had no effect on AUC24h or Cmin. **Effect of RPV on Norethindrone** Norethindrone ↔	DTG or RPV did not change EE and NGMN/norethindrone plasma concentrations to a clinically relevant extent. No dose adjustment of OCs is necessary when co-administered with DTG/RPV FDC.
Azole Antifungals: Ketoconazole (KTZ) Fluconazole Itraconazole Posaconazole Voriconazole	**Effect of KTZ on RPV:** Co-administration of RPV with KTZ resulted in increased RPV AUC24h, Cmax, and Cmin by 49%, 30% and 76%, respectively. **Effect of RPV on KTZ:** Co-administration of RPV with KTZ resulted in decreased KTZ AUC24h, Cmax, and Cmin by 24%, 15% and 66%, respectively.	Azole antifungal agents may increase RPV plasma concentrations. No dose adjustment is necessary when co-administered with DTG/RPV FDC.
HMG CO-A Reductase Inhibitors: Atorvastatin Fluvastatin Lovastatin Pitavastatin Pravastatin Rosuvastatin Simvastatin	**Effect of atorvastatin on RPV:** Co-administration of RPV with atorvastatin resulted in decreased RPV Cmax by 9%. AUC24 ↔ Cmin ↔. **Effect of RPV on atorvastatin**: Co-administration of RPV with atorvastatin resulted in increased atorvastatin Cmax by 35% and a decrease in Cmin by 15%. AUC24h ↔	No dose adjustment is necessary when co-administered with DTG/RPV FDC.
Phosphodiesterase type 5 (PDE-5) inhibitors: Sildenafil Vardenafil Tadalafil	**Effect of sildenafil on RPV:** Sildenafil had no effect on RPV AUC24h, Cmax, or Cmin. **Effect of RPV on sildenafil:** RPV had no effect on sildenafil AUClast, AUC∞, or Cmax. Cmin not evaluated.	No dose adjustment is necessary when co-administered with DTG/RPV FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Dolutegravir, Rilpivirine, or Concomitant Drug	Clinical Comment
Digoxin	**Effect of RPV on digoxin:** AUC ↔ Cmax ↔ Cmin: not evaluated	No dose adjustment is necessary when co-administered with DTG/RPV FDC

↑ = Increase; ↓ =decrease; ↔ = no significant change

4. SPECIAL STUDIES

Please note that m2.7.2.4, Special Studies (Summary of Microbiology/Virology), is provided as a standalone module.

5. CONCLUSIONS

- There were no significant drug interactions between DTG and RPV – the 2 active components of the FDC tablet. Therefore, DTG and RPV can be co-administered without dose adjustment.
- Co-administration of DTG/RPV FDC may increase metformin plasma concentrations due to inhibition of OCT and MATE transporters. A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG/RPV FDC with metformin to maintain glycemic control.
- Rifabutin decreased the plasma concentrations of RPV. Therefore, during co-administration with rifabutin an additional 25-mg dose of RPV should be taken at the same time with DTG/RPV FDC.
- Co-administration of RPV with drugs that increase gastric pH may significantly decrease RPV plasma concentrations, resulting in loss of therapeutic effect of RPV. Co-administration of proton pump inhibitors is contraindicated. H2-receptor antagonists may significantly decrease RPV plasma concentrations. Therefore, DTG/RPV FDC should only be administered at least 4 hours before or at least 12 hours after H2-receptor antagonists.
- Co-administration of antacid products may significantly decrease DTG or RPV plasm concentrations resulting in loss of therapeutic effect, therefore, DTG/RPV FDC should only be administered at least 4 hours before or 6 hours after taking antacid products,
- Co-administration of DTG and drugs that contain divalent metal cations may result in decreased DTG plasma concentrations. Co-administer DTG/RPV FDC at least 4 hours before or 6 hours after calcium or iron non-antacid products, or alternatively, co-administer together with a meal,
- In the Phase III studies, plasma C0 for DTG and RPV were similar across the Weeks 4 to 48 visits and were consistent with previously reported steady-state DTG and RPV trough concentrations in HIV-1-infected patients.

- Earlier PK sampling in a subset of subjects who switched from EFV- or NVP-based regimens showed that DTG and RPV pre-dose concentrations increased from Week 2 to steady-state concentrations at Week 4, indicating that any residual enzyme induction effects were diminished by Week 4. The efficacy and virology results, overall and in the NNRTI subgroup, demonstrate that the plasma concentrations of DTG and RPV during the immediate post-NNRTI switch period were sufficient to maintain virologic response.
- Overall, the DDI profile, PK, and PK/PD support the dose recommendation for a FDC of DTG/RPV 50 mg/25 mg (GSK3365791) once daily with a meal and the proposed indication.

6. APPENDIX

Appendix Table 1 Tabular Listing of all Dolutegravir Clinical Pharmacology Studies

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
Pharmacokinetic Studies in HIV-Negative Subjects										
ING111207 (Dose Linearity) GSK	1 US	Start 13 Nov 2007; Completed 18 Feb 2008; 25/20	To assess safety, tolerability and PK of single doses of DTG	Double-Blind, Randomized, Placebo-Controlled	18-55yrs, Healthy subjects, male/ female	DTG 2 to 100 mg; oral suspension; single dose; fasted	25 Enrolled, 13 Completed	20/5; 31.8yrs (19 - 54)	DTG safety parameters AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and t½ following single dose administration	Completed CPSR
ING111322 (Dose Linearity) GSK	1 US	Start 27 Feb 2008; Completed 12 Jun 2008; Part 1: 32/32, Part 2: 12/12	Part 1: To assess safety, tolerability and PK of repeat doses of DTG Part 2: To assess safety, tolerability and PK of single doses of DTG suspension and single	Part 1: Double-Blind, Randomized, Placebo-Controlled Part 2: Randomized, 3-Period, Balanced, Crossover	18-50yrs, Healthy subjects, male/ female	Part 1: DTG 10 to 50 mg; oral suspension; once daily; 10 days; fasted Part 2:	Part 1: 32 (includes 5 placebo; 1 subject assigned to placebo received a single dose of DTG in error) Enrolled, 31 Completed Part 2:	Part 1: 27/5; 31.7yrs (18 - 50) Part 2: 12/0; 30.8yrs (18 - 50)	Part 1: DTG safety parameters from pre-dose values DTG PK parameters following single dose administration on Day 1: AUC(0-∞) and AUC(0-24), Cmax, tmax, C24, t1/2, tlag, and CL/F; and	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			doses of DTG tablets with or without food			DTG 20 mg; oral suspension; singe dose; fasted DTG 10 mg x2 (20 mg); tablet; oral; single dose; fasted DTG 10 mg x2 (20 mg); tablet; oral; single dose; fed	12 Enrolled, 12 Completed		(AUC(0-t), C0, Ct, Cmin, Cmax, tmax, t1/2, and CL/F on Day 10 Part 2: Single dose plasma DTG PK parameters: AUC(0-t), AUC(0-∞), Cmax, and C24	
ING111853 (Mass Balance) GSK	1 US	Start 17 Feb 2009; Completed 21 Apr 2009; 6/6	To investigate the recovery, excretion, and PK of ^{14}C-DTG	Open-label, single dose study	30-55yrs, Healthy subjects, male	DTG 20 mg; oral suspension; single dose; fasted	6 Enrolled, 6 Completed	6/0; 37.5yrs (32 - 46)	Percent recovery of total radiocarbon in urine and feces. AUC(0-t), AUC(0-∞), Cmax, tmax, λz, tlag, and t½ of total drug-related material (radiocarbon) in blood and plasma following oral suspension [^{14}C]-DTG dosing	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									AUC(0-t), AUC(0-∞), Cmax, tmax, λz, tlag, CL/F, Vz/F, and t½ of DTG in plasma following oral suspension [^{14}C]-DTG dosing Collection of samples for use in a separate study for characterization and quantification of DTG-related metabolites in plasma, urine and fecal homogenates	

Protocol No. (Study Type) Sponsor	**No. Study Centres Location(s)**	**Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment**	**Study Objectives**	**Study Design**	**Diagnosis; Key Inclusion Criteria**	**Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)**	**No. of Subjects by Group Entered/ Completed[a]**	**Gender M/F; Mean Age (Range)**	**Primary Endpoint(s)**	**Study Reporting Status (Type of Report)**
ING113125 (PK) ViiV Healthcare	1 US	Start 28 Jun 2011; Completed 20 April 2012; 16/16	To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with severe renal impairment	Single dose, open-label, parallel group, 2-part study	18-70yrs, Severe renal impairment subjects and matched, healthy control subjects with normal renal function, male / female	DTG 50 mg; tablet; oral; single dose	Renal: 8 Enrolled, 8 Completed Healthy: 8 Enrolled, 8 Completed	Renal: 5/3; 56.8yrs (47-65) Healthy: 5/3; 56.1yrs (43 - 68)	Plasma DTG tlag, tmax, Cmax, AUC(0-t), AUC(0-∞), %AUCex, t½, CL/F and Vz/F	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING113097 (PK) ViiV Healthcare	1 US	Start 19 Nov 2010; Completed 04 Jun 2011; 16/16	To evaluate the single dose PK and safety of DTG in healthy subjects and in subjects with mild or moderate hepatic impairment based on Child-Pugh category	Single dose, open-label, parallel group, 2-part, adaptive study	18-70yrs, Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function, male / female	DTG 50 mg; tablet; oral; single dose	Hepatic Impaired: 8 Enrolled, 8 Completed Healthy Controls: 8 Enrolled, 8 Completed	Hepatic Impaired : 5/3; 55.5yrs (50 - 61) Healthy Controls: 5/3; 57.0yrs (42 - 67)	Plasma DTG AUC(0-t), AUC(0-∞), Cmax, C24, apparent t½, apparent clearance (CL/F), and Vz/F	Completed CPSR
ING115381 (PK) ViiV Healthcare	1 US	Start 20 Apr 2011; Completed 27 May 2011; 10/10	To assess safety, tolerability and PK of single doses of DTG in healthy Japanese subjects	Open label, single dose study	20-55yrs, Healthy Japanese subjects, male /female	DTG 50 mg; tablet; oral; single dose	10 Enrolled, 10 Completed	6/4; 33.4yrs (22-52)	Plasma DTG following single dose administration: AUC(0-t), AUC(0-∞), Cmax, and C24	Completed CPSR
ING113099 (Drug Interaction) ViiV Healthcare	1 US	Start 13 May 2011; Completed 28 Nov 2011; 27/24	To assess the potential for a drug interaction between DTG and RIF and between DTG	Randomized , open-label, 2-period, single-sequence, 2 cohort study	18-65yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 7 days. DTG 50 mg;	Arm 1: 12 Enrolled, 11 Completed Arm 2:	ITT-E: 19/7; 44.7yrs (26 - 59)	Plasma DTG Cτ, Cmax, and AUC(0-τ), and AUC(0-24) for comparison between once	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			and RBT			tablet; oral; BID; 7 days then DTG 50 mg; tablet; oral; BID + RIF 600 mg; capsule; oral; once daily; 14 days DTG 50 mg; tablet; oral; once daily for 7 days then DTG 50 mg; tablet; oral BID+ RIF 300 mg; capsule; oral; once daily; 14 days	14 Enrolled, 9 Completed		daily and BID regimens only	
ING115696 (Drug Interaction) ViiV Healthcare	1 US	Start 01 Sep 2011; Completed 17 Oct 2011; 12/12	To investigate the effects of prednisone on the steady-state PK of DTG	Open-label, repeat dose, 2-period, single-sequence	18-65yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily; Days 1-10 +	12 Enrolled, 12 Completed	5/7; 28.5yrs (23 - 38)	DTG PK parameters on Day 5 and Day 10: AUC(0-τ), Cmax, C0, Cτ, Cmin, CL/F, and t½	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						prednisone; tablet; oral; once daily (60 mg Days 1-5; 50 mg Day 6; 40 mg Day 7; 30 mg Day 8; 20 mg Day 9; 10 mg Day 10)				
ING115697 (Drug Interaction) ViiV Healthcare	1 US	Start 13 Mar 2012; Completed 23 May 2012; 32/32	To assess the potential for a drug interaction between DTG and TVR and between DTG and boceprevir (BCV)	Randomized, open-label, 2-period, single-sequence, 2 cohort study	18-65yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + TVR 750 mg; tablet; oral; q8h; 10 days DTG 50 mg; tablet; oral; once daily + BCV 800 mg; capsule; oral; q8h; 10 days	DTG + BCV 16 Enrolled, 13 Completed DTG + TVR 16 Enrolled, 15 Completed	19/13; 42.5yrs (19 - 65)	Plasma steady-state DTG AUC(0-τ), Cmax, Cmin, Cτ, following administration of DTG 50 mg once daily (q24h) for 5 days and following co-administration with BCV 800 mg q8h for 10 days or TVR 750 mg q8h for 10 days	Completed CPSR
ING115698 (Drug	1 Canada	Start 02 Dec 2011;	To assess the potential for a	Open-label, repeat dose,	18-65yrs, Healthy	Stable methadone	11 Enrolled, 10	6/5; 34.5yrs	Steady-state total and R-	Completed CPSR

Protocol No. (Study Type) Sponsor	**No. Study Centres Location(s)**	**Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment**	**Study Objectives**	**Study Design**	**Diagnosis; Key Inclusion Criteria**	**Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)**	**No. of Subjects by Group Entered/ Completed[a]**	**Gender M/F; Mean Age (Range)**	**Primary Endpoint(s)**	**Study Reporting Status (Type of Report)**
Interaction) ViiV Healthcare		Completed 30 Dec 2011; 11/12	drug interaction between DTG and methadone	2-period, single-sequence	subjects enrolled in a methadone maintenanc e program, male / female	dose; oral solution; once daily; 3 days Stable methadone dose; oral solution + DTG 50 mg; tablet; oral; BID; 5 days	Completed	(24 - 44)	Methadone PK parameters: AUC(0-τ), Cmax, and Cτ	

Protocol No. (Study Type) Sponsor	**No. Study Centres Location(s)**	**Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment**	**Study Objectives**	**Study Design**	**Diagnosis; Key Inclusion Criteria**	**Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)**	**No. of Subjects by Group Entered/ Completed[a]**	**Gender M/F; Mean Age (Range)**	**Primary Endpoint(s)**	**Study Reporting Status (Type of Report)**
ING111405 (Drug Interaction) GSK	1 US	Start 09 Oct 2008; Completed 12 Dec 2008; 31/30	To assess the potential for a drug interaction between DTG and LPV/ RTV and between DTG and DRV/ RTV	Randomized , open-label, 2-period, single-sequence, 2 cohort study	18-50yrs, Healthy subjects, male / female	DTG 30 mg; tablet; oral; once daily; 5 days DTG 30 mg; tablet; oral; once daily + LPV/RTV 400/100 mg; tablet; oral; q12h; 14 days DTG 30 mg; tablet; oral; once daily + DRV (tablet) /RTV (capsule) 600/100 mg; oral; q12h; 14 days	31 Enrolled, 30 Completed	31/0; 29.4yrs (18 - 50)	Plasma DTG steady-state AUC(0-τ), Cmax, Cτ, Cmin, CL/F, t½ and t1/2 following administration of DTG 30 mg q24h for 5 days and following co-administration with LPV/RTV 400/100 mg q12h or DRV/RTV 600/100 mg q12h for 14 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING111602 (Drug Interaction) GSK	1 US	Start 07 Jan 2009; Completed 05 Mar 2009; 16/16	To assess the potential for a drug interaction between DTG and multivitamin and between DTG and Maalox	Open-label, single dose, randomized, 4-period crossover study	18-65yrs, Healthy subjects, male/ female	DTG 50 mg; tablet; oral; single dose DTG 50 mg; tablet; oral; single dose + multivitamin; tablet; oral; single dose DTG 50 mg; tablet; oral; single dose + Maalox Advanced Maximum Strength; 20 mL suspension; single dose DTG 50 mg; tablet; oral; single dose 2 hrs prior to Maalox Advanced Maximum Strength	16 Enrolled, 16 Completed	16/0; 30.8yrs (18 - 53)	Single dose plasma DTG AUC(0-∞), Cmax, and C24	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						20 mL; suspension; single dose				
ING111603 (Drug Interaction) GSK	1 US	Start 16 Oct 2008; Completed 12 Dec 2008; 16/16	To assess the potential for a drug interaction between DTG and ETR	Open-label, repeat dose, 2-period, single-sequence study	18-65yrs, Healthy subjects, male/ female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETR 200 mg; tablet; oral; q12h; 14 days	16 Enrolled, 15 Completed	16/0; 41.5yrs (19 - 64)	Plasma DTG steady-state AUC(0-τ), Cmax, Cτ, Cmin, CL/F, t½ following administration of DTG 50 mg q24h for 5 days and following co-administration with ETR 200 mg q12h for 14 days	Completed CPSR
ING111604 (Drug Interaction) GSK	1 US	Start 11 Aug 2008; Completed 01 Oct 2008; 16/16	To assess the potential for a drug interaction between DTG and TDF	Open-label, repeat-dose, single-sequence, 3-period study	18-65yrs, Healthy subjects, male/ female	DTG 50 mg; tablet; oral; once daily; 5 days TDF 300 mg; tablet; oral; once daily; 7 days DTG 50 mg; tablet; oral; once daily + TDF 300 mg; tablet; oral;	16 Enrolled, 15 Completed	15/1; 38.6yrs (20 - 58)	Plasma DTG steady-state AUC[0-τ], Cmax and Cτ following administration of DTG 50 mg q24h for 5 days and following co-administration with TDF 300 mg q24h for 5 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						once daily; 5 days				
ING111854 (Drug Interaction) GSK	1 US	Start 07 Apr 2009; Completed 09 Jun 2009; 24/24	To assess the potential for a drug interaction between DTG and ATV and between DTG and ATV/RTV	Randomized, open-label, repeat dose, 2-period, single-sequence, 2-cohort study	18-65yrs, Healthy subjects, male / female	Period 1: DTG 30 mg; tablet; oral; once daily; 5 days; fed Period 2: DTG 30 mg; tablet; oral; once daily + ATV/RTV 300/100 mg; capsule; once daily; 14 days DTG 30 mg; tablet; oral; once daily + ATV 400 mg; capsule; oral; once daily; 14 days	24 Enrolled, 24 Completed	21/3; 37.2yrs (18 - 61)	Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 30 mg q24h for 5 days and following co-administration with ATV/RTV 300/100 mg q24h or ATV 400 mg q24h for 14 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING111855 (Drug Interaction) ViiV Healthcare	1 US	Start 13 Dec 2011; Completed 28 Mar 2012; 16/16	To assess the potential for a drug interaction between DTG and oral contraceptives (EE / NGMN)	Randomized, 2-period, double-blind study	18-40yrs, Healthy subjects, female	DTG 50 mg or placebo; oral; tablet; once daily Days 1-11 and DTG 50 mg or placebo; tablet; oral; once daily Days 12-21 EE / NGMN; tablet; oral; once daily Days 1-21	16 Enrolled, 15 Completed	0/16; 31.1yrs (20 - 40)	AUC(0-τ) of Norelgestromin and EE after Ortho-Cyclen alone and after Ortho-Cyclen with DTG	Completed CPSR
ING112934 (Drug Interaction) GSK	1 US	Start 02 Apr 2009; Completed 20 May 2009; 17/18	To assess the potential for a drug interaction between DTG, ETR, and LPV/RTV or DRV/RTV	Randomized, open-label, repeat dose, 3-period, single-sequence, 2-cohort adaptive study	18-65yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily + ETR/LPV/RTV 200/400/ 100 mg; tablet; oral; q12h; 14 days DTG 50 mg; tablet; oral;	17 Enrolled, 17 Completed	17/0; 37.6yrs (20 - 61)	Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg q24h for 5 days, and following co-administration of DTG 50 mg q24h (and 50 mg q12h if appropriate) with ETR/LPV/RTV 200/400/100 mg	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						once daily + ETR (tablet) DRV (tablet) /RTV (capsule) 200/600/ 100 mg; oral; once daily; 14 days			q12h or ETR/DRV/RTV 200/600/100 mg q12h, each for 14 days	
ING112941 (Drug Interaction) GSK	1 US	Start 23 Jul 2009; Completed 28 Sep 2009; Part 1: 14/14, Part 2: 10/10	To evaluate the effect of a high fat meal and OMP on DTG PK and to evaluate the safety and PK of a 250 mg dose of DTG	Part 1: Randomized, open-label, 2 sequence, 3-treatment crossover Part 2: Randomized, double-blind, single dose PK study	18-65yrs, healthy subjects, male / female	Part 1: DTG 50 mg; tablet; oral; single dose; fasted DTG 50 mg; tablet; oral; single dose; within 30 minutes after the start of a high fat meal DTG 50 mg; tablet; oral; single dose + OMP 40 mg; capsule; oral; once daily;	Part 1: 14 Enrolled, 12 Completed Part 2: 10 Enrolled (includes 2 placebo), 10 Completed	Part 1: 12/2; 40.6yrs (23 - 55) Part 2: 9/1; 38.4yrs (21 - 54)	Plasma DTG following a single dose administration of 50 mg under fasted conditions with and without OMP 40 mg: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, tlag Plasma DTG following a single dose administration of 50 mg under fasted conditions and with a high-	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						5 days Part 2: DTG 250 mg or placebo; oral suspension, single dose; fasted			fat meal: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and tlag Plasma DTG following a single dose administration of 250 mg under fasted conditions: AUC(0-t), AUC(0-∞), Cmax, tmax, C24, and tlag Safety and tolerability parameters following a single supratherapeutic dose of DTG 250 mg	
ING113068 (Drug Interaction) ViiV Healthcare	1 US	Start 09 Sep 2010; Completed 04 Nov 2010; Part A: 12/12, Part B: 15/15	To investigate the effects of fosamprenavir (FPV)/ RTV on the steady-state PK of DTG and to evaluate relative BA of	Part A: Open-label, repeat dose, 2-period, single-sequence Part B: Open-label,	18-65yrs, Healthy subjects, male / female	Part A: DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily +	Part A: 12 Enrolled 12 Completed Part B: 15 Enrolled, 15 Completed	Part A: 10/2; 33.4yrs (24 - 55) Part B: 4/11; 34.7yrs (20 - 60)	Part A: Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg q24h for 5 days and	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			tablets with varying particle size	single dose, randomized, 3-period, cross over study		FPV 700 mg; tablet / RTV 100 mg; capsule; oral; q12h; 10 days Part B: DTG 50 mg using 25 mg tablets with micronized drug substance; oral; single dose DTG 50 mg using 25 mg tablets with unmicronized drug substance; oral; single dose DTG 50 mg using 25 mg tablets with intermediate particle size			following co-administration with FPV/RTV 700/100 mg q12h for 10 days Part B: Plasma DTG AUC(0-∞), AUC(0-t), and Cmax following a single dose of DTG 50 mg	

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						drug substance; oral; single dose				
ING113096 (Drug Interaction) GSK	1 US	Start 15 Feb 2010; Completed 05 Apr 2010; 18/18	To assess the safety, tolerability and PK of repeat dose co-administration of DTG alone, TPV/RTV alone, and DTG in combination with TPV/RTV	Randomized, open-label, repeat dose, 3-period single-sequence, study	18-55yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 5 days TPV / RTV 500/200 mg; capsule; oral; BID; 7 days DTG 50 mg; tablet; oral; once daily and TPV / RTV 500/200 mg; capsule; oral; BID; 5 days	18 Enrolled, 13 Completed	14/4; 29.3yrs (19 - 45)	Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg once daily for 5 days and following co-administration with TPV/RTV 500/200 mg BID for 5 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING114005 (Drug Interaction) ViiV Healthcare	1 US	Start 16 Mar 2010; Completed 26 May 2010; 12/12	To evaluate PK of DTG 100 mg versus 50 mg and the effect of EFV on the PK, safety and tolerability of DTG 50 mg	Open label, repeat dose, 3-period single-sequence	18-65yrs, Healthy subjects, male / female	DTG 100 mg; tablet; oral; single dose DTG 50 mg; tablet; oral; once daily; 5 days DTG 50 mg; tablet; oral; once daily in AM + EFV 600 mg; tablet; oral; once daily in PM; 14 days	12 Enrolled, 12 Completed	12/0; 38.7yrs (2 0- 65)	Plasma DTG AUC(0-24), Cmax, and C24, and dose-normalized AUC(0-24), Cmax, and C24 following single dose administration of 100 mg and 50 mg Plasma DTG steady-state AUC(0-τ), Cmax, C0, Cτ, and Cmin following administration of DTG 50 mg q24h for 5 days and following co-administration with EFV 600 mg q24h for 14 days	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
LAI116181 (Drug Interaction) ViiV Healthcare	1 US	Start 07 Nov 2011; Completed 20 Feb 2012; Cohort 1: 16/16, Cohort 2: 12/12	To assess the potential for a drug interaction between DTG and RPV	Open label, repeat dose, single-sequence, 3-period study	18-55yrs Healthy subjects, male / female	Cohort 1: Treatment A = DTG 50 mg; tablet; oral; q24h; 5 days Treatment B = RPV 25 mg; tablet; oral; q24h; 11 days Treatment C = RPV 25 mg; tablet; oral; q24h + DTG 50 mg; tablet; oral; q24h; 5 days Cohort 2: Treatment D = GSK1265744 30 mg; tablet; oral; q24h;12 days Treatment B = RPV 25 mg; tablet; oral; q24h; 12 days	Cohort 1: 16 Enrolled, 16 Completed Cohort 2: 12 Enrolled, 11 Completed	24/4; 31.4yrs (18 - 50)	Plasma DTG AUC(0-τ), Cmax, and tmax, and Cτ, following 50 mg q24h administration with and without RPV 25 mg q24h Plasma GSK1265744 steady-state AUC(0-τ), Cmax, tmax, and Cτ following GSK1265744 30 mg q24h administration with and without RPV 25 mg q24h Plasma RPV steady-state AUC(0-τ), Cmax, tmax, and Cτ following RPV 25 mg q24h administration	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						Treatment E = RPV 25 mg; tablet; oral; q24h + GSK1265744 30 mg; tablet; oral; q24h; 12 days			with and without DTG 50 mg q24h or GSK1265744 30 mg q24h	
ING116898 (Drug Interaction)/ ViiV Healthcare	1 US	Start 31 Dec 2012; Completed 12 Mar 2013; Cohort 1: 11/12, Cohort 2: 10/12	To evaluate the effect of calcium carbonate and ferrous fumarate on DTG PK	Open label, single dose, 4-period crossover study	Healthy adult subjects	Cohort 1: DTG, 50 mg, tablet, oral, single dose, fasted DTG, 50 mg, tablet, oral single dose, +1200 mg calcium carbonate, oral, fasted DTG, 50 mg, tablet, oral, sinlge dose, + 1200 mg calcium carbonate, oral,	Cohort 1: 12 Enrolled, 11 Completed; Cohort 2: 12 Enrolled, 10 Completed.	Cohort 1: 8/4; 31.4yrs (20 - 59); Cohort 2: 6/6; 34.9yrs (20 - 64)	DTG AUC(0-t), AUC(0-inf), Cmax, C24	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						fed DTG, 50 mg, tablet, oral, single dose, fasted, 2 hours prior to 1200 mg calcium carbonate, oral Cohort 2: DTG, 50 mg, tablet, oral, single dose, fasted DTG, 50 mg, tablet, oral single dose, +324 mg ferrous fumarate, oral, fasted DTG, 50 mg, tablet, oral, sinlge dose, + 324mg ferrous fumarate, oral,				

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						fed DTG, 50 mg, tablet, oral, single dose, fasted, 2 hours prior to 324 mg ferrous fumarate, oral				
200901	1 US	Start 08 Oct 2013; Completed 14 Jan 2014; 16/16	To compare the steady state PK of DTG 50 mg once daily when co-administered with CBZ to those of DTG 50 mg once daily administered alone	Phase I, open-label, 3-period, fixed sequence crossover study	Healthy adult subjects	Period 1: DTG 50 mg, tablet, oral, once daily (Days 1-5) Period 2: CBZ 100 mg, tablet, oral, BID (Days 1-3); CBZ 200 mg, tablet, oral, BID (Days 4-6); CBZ 300 mg, tablet, oral, BID (Days 7-16) Period 3: DTG 50 mg, tablet, oral, once daily + CBZ 300 mg, tablet, oral, BID (Days 1-5)	Period 1: 16 Enrolled, 16 Completed Period 2: 16 Enrolled, 14 Completed Period 3: 14 Enrolled, 14 Completed	14/2; 38.9 yrs (24 - 58)	Steady state $C\tau$, Cmax, AUC(0-τ), CL/F, t½, C0, and Cmin.	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
201102	1 US	Start 18 March 2014; Completed 15 May 2014; 12/12	To describe and compare steady-state plasma DTG PK following administration of DTG 50 mg q24h with and without DCV 60 mg q24h and DCV 60 mg q24h with and without DTG 50 mg q24h	Open-label, 3-period, crossover study	Healthy adult subjects	Treatment A: DTG 50 mg, tablet, oral, once daily x 5 days Treatment B: DCV 60 mg, tablet, oral, once daily x 5 days Treatment C: DCV 60 mg, tablet, oral, once daily + DTG 50 mg, tablet, oral, once daily x 5 days	12 Entered, 12 Completed	9/3; 32.3 yrs (23 - 55)	Plasma DTG steady state AUC(0-τ), Cmax, Cτ, CL/F and t½	Completed CPSR
201167	1 US	Start 19 Feb 2014; Completed 12 May 2014; 15/15	To assess the effect of DTG given once daily or BID on the PK of metformin after repeat dosing	Open label, parallel group, 3-period, fixed sequence study	Healthy adult subjects	**Cohort 1**: Period 1: Metformin IR 500 mg, tablet, oral, BID (Days 1-5) Period 2: Metformin IR 500 mg, tablet, oral, BID + DTG 50 mg, tablet, oral,	**Cohort 1**: Period 1: 15 Enrolled, 15 Completed Period 2: 15 Enrolled, 14 Completed Period 3: 14	Cohort 1: 11/4; 37.7 yrs (21 - 58) Cohort 2: 12/3; 33.9 yrs (21 - 57)	Steady-state plasma metformin PKparameters in Period 2 as compared with those in Period 1 for each cohort: Cmax and AUC(0-τ). Steady-state plasma DTG PK parameters for	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						once daily (Days 1-7) Period 3: Metformin IR 500 mg, tablet, oral, BID (Days 1-10) **Cohort 2**: Period 1: Metformin IR 500 mg, tablet, oral, BID (Days 1-5) Period 2: Metformin IR 500 mg, tablet, oral, BID + DTG 50 mg, tablet, oral, BID (Days 1-7) Period 3: Metformin IR 500 mg, tablet, oral, BID (Days 1-10)	Enrolled, 14 Completed **Cohort 2**: Period 1: Period 1: 15 Enrolled, 15 Completed Period 2: Period 2: 15 Enrolled, 14 Completed Period 3: Period 3: 14 Enrolled, 13 Completed		each cohort: AUC(0-τ), Cmax, C0, Cτ, and CL/F. Steady-state plasma metformin PK parameters in Period 2 as compared with those in Period 1 for each cohort: t½ and CL/F	
ING116265 (PGx) ViiV Healthcare	NA	NA	To evaluate the effects of UGT and CYP polymorphisms on the PK of	Meta-analysis of PGx and PK data from 9 Phase II	Healthy adult subjects	DTG 50 mg; tablet; oral; once daily; 5 days	89 subjects included in the analysis	78/11; 36.9yrs (19 - 64)	NA	Completed: Meta-analysis Report

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			DTG	studies						
Human Pharmacodynamic Studies										
ING111856 (PD) GSK	1 US	Start 28 Sep 2009; Completed 29 Dec 2009; 42/42	To evaluate the effect of DTG on cardiac conduction as assessed by 12-lead electrocardiogram compared with placebo and moxifloxacin (Thorough QTc study of DTG)	Randomized, partial-blind, single dose, 3-period, cross-over study	18-55yrs, Healthy subjects, male / female	DTG 250 mg; oral suspension; single dose Placebo; oral suspension; single dose Moxifloxacin 400 mg; tablet; oral; single dose	42 Enrolled, 38 Completed	17/25; 34.5yrs (18 - 55)	Change from Baseline in QTcF for DTG	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING114819 (PD) ViiV Healthcare	1 US	Start 05 Oct 2010; Completed 03 Dec 2010; 38/36	To evaluate the effect of DTG on GFR as measured by iohexol and to evaluate creatinine clearance, extra-glomerular creatinine excretion, and renal plasma flow	Open-label, randomized, 3-arm, parallel, placebo-controlled	18-65yrs, Healthy subjects, male / female	DTG 50 mg; tablet; oral; once daily; 14 days DTG 50 mg; tablet; oral; q12h; 14 days Placebo; tablet; oral; once daily; 14 days Omnipaque 300 (647 mg/mL of iohexol) 5 mL; solution; IV Amino-hippurate Sodium 2 g/10 mL (20%) of Loading Dose : 8 mg/kg, Maintenance Dose: 12 mg/min; solution; IV	38 Enrolled, 34 Completed	28/10; 31.8yrs (19 - 59)	GFR as measured by iohexol plasma clearance at Days -1, 7, and 14	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
Pharmacokinetic and PK/PD Studies in Target Patient Population										
ING111521 (PK and PK/PD) GSK	14 US	Start 25 Jun 2008; Completed 26 Aug 2008; 35/30	To assess the safety, tolerability and efficacy of repeat dose DTG	Dose-ranging, 10-day, repeat dose, placebo-controlled monotherapy study	18-65yrs, HIV-infected subjects, male/ female	DTG 2, 10, 50 mg tablet; oral; once daily; 10 days; fasted	35 Enrolled (including 7 placebo) 35, Completed	35/0; 38.4yrs (2[redacted] - 5[redacted])	Change from Baseline in plasma HIV-1 RNA to Day 11 DTG following dose administration on Day 1: AUC(0-∞), AUC(0-24), Cmax, tmax, C24, t½, tlag, and CL/F; and following last repeat administration on Day 10: AUC(0-τ), C0, Cτ, Cmin, Cmax, tmax, t½, and CL/F, if data permit Safety and tolerability parameters	Completed CPSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
ING112276 (PK and PK/PD) ViiV Healthcare	34 centres: 6 France, 4 Germany, 3 Russia, 4 Italy, 5 Spain, 12 US	Start 30 Jul 2009; Ongoing; 205/200	To select a once daily oral dose of DTG administered with either ABC/3TC or TDF/ FTC and to evaluate antiviral activity, safety and PK over time	Phase IIb, Randomized, multicentre, parallel group, dose-ranging	≥18yrs, HIV-infected, ARV-naïve subjects, male / female	DTG 10 mg; tablet; oral + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; tablet; oral; once daily; 96 weeks DTG 25 mg; tablet; oral + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; oral; once daily; 96 weeks DTG 50 mg; tablet; oral + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; oral; once daily; 96 weeks	DTG 10 mg: 53 Randomized 47 Completed DTG 25 mg: 51 Randomized 46 Completed DTG 50 mg: 51 Randomized 46 Completed EFV 600 mg: 50 Randomized 39 Completed DTG 50 mg: 138 Enrolled 127 Ongoing	177/28; 37.2yrs (2[redacted] - 7[redacted])	Proportion of subjects with HIV-1 RNA <50 c/mL (c/mL) through Week 16 using the TLOVR algorithm. Dose selection will be based primarily on antiviral activity and tolerability in conjunction with immunologic, safety and PK measures will also be considered	Completed: (Week 16 Synoptic CSR) (Week 24 Full CSR) (Week 48 Abbr. CSR) (Week 96 Full CSR)

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						EFV 600 mg + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/ 200 mg; oral; once daily; 96 weeks				
ING111762 (PK and PK/PD) ViiV Healthcare	185 centres: 4 Belgium, 12 France, 4 Greece, 1 Hungary, 7 Italy, 2 Netherlands, 3 Romania, 24 Spain, 4 UK, 6 Canada, 72 US, 6 Argentina, 2 Australia, 9 Brazil, 5 Chile, 4 Mexico, 12 Russia, 3 South Africa,	Start 26 Oct 2010; Ongoing; 719/688	To evaluate safety and efficacy of DTG 50 mg once daily vs. RAL 400 mg BID, both administered with an investigator-selected background regimen	Phase 3, multicentre randomized, double-blind, active-controlled, parallel group, non-inferiority study	≥18yrs, HIV-infected, ARV-experienced subjects, INSTI-naïve regimen, male / female	DTG 50 mg; tablet; oral; once daily or RAL 400 mg; tablet; oral; BID + Investigator-selected background regimen; 48 weeks	DTG: 354 Randomized 4 Completed, 43 Ongoing RAL: 361 Randomized 236 Completed, 11 Ongoing	487/232; 42.5yrs (1[redacted] - 7[redacted])	The proportion of subjects with HIV-1 RNA <50 c/mL through Week 48 using MSDF algorithm as codified by the FDA's "snapshot algorithm. The proportion of subjects with plasma HIV-1 RNA <50 c/mL will also be assessed at Week 24	Completed: Week 48 Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
	5 Taiwan									
201636 ViiV Healthcare	65 centers: 16 Spain, 14 US, 6 Canada, 5 France, 5 Germany, 5 Russia, 4 Belgium, 4 Italy, 3 Taiwan, 2 Australia, 2 Netherlands, 2 UK, 1 Argentina	Start 14 April 2015; Ongoing; 508/510	To demonstrate the non-inferior antiviral activity of switching to DTG plus RPV once daily compared with continuation of CAR over 48 weeks in HIV-1 infected ARV-therapy-experienced subjects	Randomized open-label, parallel-group, non-inferiority	≥18 yrs HIV-1 infected subjects, male/female	DTG 50 mg tablet; oral; once daily + RPV 25 mg tablet, once daily or continue CAR (2 NRTIs + either an INSTI, an NNRTI, or a PI) up to Week 148 At Week 52, subjects on CAR will switch to DTG 50 mg + RPV 25 mg once daily through Week 148. Subjects on DTG + RPV during the Early Switch Phase will continue on their treatment arm through	DTG + RPV: 252 Randomized 239 Ongoing 48 weeks CAR: 256 Randomized 238 Ongoing 48 weeks	399/109; DTG + RPV: 43.6 (2[redacted] - 7[redacted]) CAR: 43.6 (2[redacted] - 7[redacted])	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48	Week 48 CSR complete Ongoing

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						Week 148.				
201637 ViiV Healthcare	60 Centres: 15 Spain, 13 US, 7 Canada, 5 Germany, 6 France, 4 Russia, 4 Taiwan, 3 Australia, 3 Argentina, 2 Italy, 1 UK	Start 21 April 2015; Ongoing; 516/518	To demonstrate the non-inferior antiviral activity of switching to DTG plus RPV once daily compared with continuation of CAR over 48 weeks in HIV-1 infected ARV-experienced subjects	Randomized open-label, parallel-group, non-inferiority	≥18 yrs HIV-1 infected subjects, male/female	DTG 50 mg tablet; oral; once daily + RPV 25 mg tablet, once daily or continue CAR (2 NRTIs + either an INSTI, an NNRTI, or a PI) up to Week 148 At Week 52, subjects on CAR will switch to DTG 50 mg + RPV 25 mg once daily through Week 148. Subjects on DTG + RPV during the Early Switch Phase will continue on their treatment arm through	DTG + RPV: 261 Randomized 245 Ongoing 48 weeks CAR: 255 Randomized 239 Ongoing 48 weeks	396/119; DTG + RPV: 43.3 (2[redacted] - 7[redacted]) CAR: 43.2 (2[redacted] - 6[redacted])	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48	Week 48 CSR complete Ongoing

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						Week 148.				

a. For ongoing studies, the number of ongoing subjects reported as of data cut off date (~ [redacted] or data cut off date) in respective CSR)

3TC = Lamivudine; ABC = Abacavir; ARV = Antiretroviral; ATV = Atazanavir; BA = Bioavailability ; BCV = Boceprevir; BID = Twice daily; CAR = Current antiretroviral regimen; CPSR = Clinical pharmacology study report ; CSR = Clinical study report; DRV = Darunavir; DTG = Dolutegravir ; EE= Ethinyl Estradiol; EFV = Efavirenz; ETR = Etravirine; FPV = Fosamprenavir; FTC = Emtricitabine; IV = Intravenous; LPV= Lopinavir; NGMN = Norgestimate; OL = Open label ; OMP = Omeprazole ; PD = Pharmacodynamics; PD = Pharmacodynamics; PK = Pharmacokinetics; PK = Pharmacokinetics; QD = Once daily; RAL = Raltegravir; RBT = Rifabutin; RIF = Rifampin; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir; TPV = Tipranavir

Appendix Table 2 Tabular Listing of all Rilpivirine Clinical Pharmacology Studies

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
Pharmacokinetic Studies in Healthy Subjects										
TMC278-C119 (Mass Balance)	1 Belgium	Start: 21-Feb-2005 Completed: 08-Apr-2005 6/6	To characterize excretion and the overall metabolic profile after a single dose of ^{14}C-labeled RPV in humans	Open label, single-dose, mass-balance trial	40-60 yrs Healthy male subjects	Single dose of RPV 150 mg (^{14}C-labeled and unlabeled), oral.	6 Enrolled 6 Completed	6/0 48.0 (4[redacted] - 5[redacted])	AUClast, AUC∞, Cmax, λz, t½,term, and tmax	Completed Full CSR
TMC278-C103 (PK) Janssen	1 Belgium	Start: 25-Aug-2004; Completed: 29-Nov-2004 48/48	To determine single dose and steady-state PK and dose-proportionality of RPV after multiple once daily dosing of a solid oral formulation	Phase I, open label, multiple dose ranging study	18-55 yrs Healthy subjects male / female	Treatment A: RPV 25 mg; tablet; oral; once daily; 14 days. Treatment B: RPV 50 mg; oral; once daily; 14 days. Treatment C: RPV 100 mg; oral; once daily; 14 days. Treatment D: RPV 150 mg; oral; once daily; 14 days	Treatment A: 12 Enrolled 12 Completed Treatment B: 12 Enrolled 12 Completed Treatment C: 12 Enrolled 11 Completed Treatment D: 12 Enrolled 11 Completed	42/6 39yrs (2[redacted] - 5[redacted])	Day 1: Cmax, tmax, AUC24h. Days 7, 10, 12, and 13: C0h. Day 14: C0h, Cmin, tmax, Cmax, AUC24h, λz, t½,term, Css,av, FI, and Accumulation ratio. Accumulation ratio: AUC24h, day14/AUC24h, day 1 for each subject.	Completed Full CSR
TMC278-C104	1	Start: 09-Sep-	To determine	Phase I,	18-55 yrs	Session I: RPV	16 Enrolled	16/0	For RPV and	Completed

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
(PK) Janssen	Netherlands	2004; Completed: 07-Dec-2004 16/16	the effect of steady-state concentrations of RPV on the steady-state PK and urinary excretion of TDF and to determine the effect of steady-state concentrations of TDF on the steady-state PK of RPV	randomized, open-label, 2-sequence, crossover study	Healthy subjects male / female	150 mg once daily on Days 1 to 8 (n=16), oral. Session II: Group 1 (n=8): TDF 300 mg once daily. on Days 1 to 16 + RPV 150 mg once daily on Days 9 to 16, oral. Group 2 (n=8): TDF 300 mg once daily on Days 1 to 16 + RPV 150 mg once daily on Days 1 to 8, oral.	15 Completed	35.0yrs (2[redacted] - 5[redacted])	TDF: AUC24h, AUC24h,test/ref, Cmax, Cmax,test/ref, Cmin, Cmin,test/ref, C0h, C0h,test/ref, Css,av, FI and tmax	Full CSR
TMC278-C106 (PK) Janssen	1 US	Start: 02 June 2005 Completed: 16 December 2005 26/28	To determine the effect of steady-state concentrations of RPV on the steady-state PK of ddI and the effect of steady-state	Phase I, randomized, open-label, 2-sequence, drug interaction study	18-55 yrs Healthy subjects male / female	Session I: RPV 150 mg once daily on Days 1 to 7 (n=16), oral. Session II: Group I (n=12): ddI 400 mg once daily on	Session I: 16 Enrolled 12 Completed Session II: 10 Enrolled 8 Completed	21/5 26.3yrs (1[redacted] - 5[redacted])	C0h, Cmin, Cmax, and AUC12h for RPV, and C0h, Cmin, Cmax, and AUC24h for ddI on the logarithmic scale	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			concentrations of ddI on the steady-state PK of RPV			Days 1-14 + RPV 150 mg once daily on Days 8-14, oral. Group II (n=10): ddI 400 mg once daily on Days 1-14 + RPV 150 mg once daily on Days 1-7, oral.				
TMC278-C105 (PK) Janssen	1 France	Start: 13-Jan-2005 Completed: 04-May-2005 16/16	To determine the potential effect at steady-state of LPV/RTV on the steady-state PK of RPV and the potential effect at steady-state of RPV on the steady-state PK of LPV/RTV	Phase I, randomized, open-label, 2-way crossover, drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: RPV 150 mg oce daily on Days 1-10, oral. Treatment B: LPV/RTV 400/100 mg BID on Days 1 to 20 + RPV 150 mg once daily on Days 11-20, oral.	Treatment A: 8 Enrolled 8 Completed Treatment B: 8 Enrolled 7 Completed	16/0 31.3yrs (1[redacted] - 4[redacted])	For RPV: C0h, C24h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Ratio Cmin, test/ref, Ratio Cmax, test/ref, Ratio AUC24h,test/ref. For LPV/RTV: C0h, C12h, Cmin, tmax, Cmax, AUC12h, Css,av, FI, Ratio Cmin,test/ref, Ratio Cmax,test/ref,	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									Ratio AUC12h,test/ref.	
TMC278-C112 (PK) Janssen	1 Belgium	Start: 19 December 2005 Completed: 10 April 2006 16/16	To determine the effect of steady-state concentrations of DRV/RTV on the steady-state PK of RPV and the effect of steady-state concentrations of RPV on the steady-state PK of DRV and RTV	Phase I, randomized, open-label, 2-way crossover, drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: RPV 150 mg once daily on Days 1-11, oral. Treatment B: DRV/RTV 800/100 mg once daily on Days 1-22 + RPV 150 mg once daily on Days 12-22, oral.	Treatment A: 8 Enrolled 7 Completed Treatment B: 8 Enrolled 6 Completed	13/3 39.1yrs (2[redacted] - 5[redacted])	For RPV: C0h, Cmin, tmax, Cmax, AUC24h, C24h, Css,av, FI, Ratio Cmin,test/ref, Ratio Cmax,test/ref, Ratio AUC24h,test/ref. For DRV: C0h, Cmin, tmax, Cmax, AUC24h, C24h, Css,av, FI%, Ratio Cmin,test/ref, Ratio Cmax,test/ref, Ratio AUC24h,test/ref.	Completed Full CSR
TMC278-TiDP6-C153 (PK) Janssen	1 Poland	Start: 21-Feb-2011 Completed: 16-May-2011 24/24	Effect of steady-state RAL 400 mg BID on the steady-state PK of RPV 25 mg once	Phase I, open-label, 2-way crossover drug interaction study	18-55 yrs Healthy subjects male / female	2 separate sessions of 2 different treatments Treatment 1: RPV 25 mg once daily	Treatment 1: 12/11 Treatment 2: 12 Enrolled 12	24/0 27.0yrs (2[redacted] - 4[redacted])	?	Completed Synopsis Report

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			daily and the effect of steady-state RPV 25 mg once daily. on the steady-state PK of RAL 400 mg BID			Days 1-11 Treatment 2: RAL 400 mg BID Days 1-15 + RPV 25 mg once daily Days 5-15	Completed			
R278474-C108 (PK) Janssen`	1 Belgium	Start: 25-May-2004 Completed: 20-Sep-2004 16/12	Effect of steady-state RIF on the steady-state PK of RPV, and the effect of steady-state RPV on the steady-state PK of RIF and its active metabolite 25-desacetylrifampin	Phase I, randomized, open-label, 3-way crossover, drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: RPV 150 mg once daily for 7 days, oral. Treatment B: RIF 600 mg once daily for 7 days, oral. Treatment C: RPV 150 mg once daily + RIF 600 mg once daily for 7 days, oral.	Treatment A: 6 Enrolled 6 Completed Treatment B: 5 Enrolled 4 Completed Treatment C: 5 Enrolled 5 Completed	10/6 40.6yrs (1[redacted] - 5[redacted])	For RPV: AUC24h, AUC24h,with/ without, Cmax, Cmax,with/ without, Cmin, Cmin,with/without , tmax, C0h,with/without. C0h For RIF and 25-desacetylrifampin : AUC24h, AUC24h,with/ without, Cmax, Cmax,with/ without, Cmin, Cmin,with/without , tmax, C0h,with/without, AUC24h,RFB-	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									desacetyl/RFB and AUC24h,RIF-desacetyl/RIF, with/without	
TMC278-C125 (PK) Janssen	1 Belgium	Start: 18-Nov-2005 Completed: 16-Mar-2006 18/18	To determine the effect of steady-state RPV on the steady-state PK of RBT and its active metabolite 25-O-desacetyl-RBT, and the effect of steady-state RBT on the steady-state PK of RPV	Phase I, randomized, open-label, 3-way crossover, drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: RPV 150 mg once daily for 11 days, oral. Treatment B: RBT 300 mg once daily for 11 days, oral. Treatment C: RPV 150 mg once daily + RBT 300 mg once daily for 11 days, oral.	Treatment A: 6 Enrolled 6 Completed Treatment B: 6 Enrolled 5 Completed Treatment C: 6 Enrolled 5Completed	16/2 41.4yrs (2[redacted] - 5[redacted])	RPV (Treatment A and C):C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Ratio C0h,test/ref, Ratio Cmin,test/ref, Ratio Cmax,test/ref, Ratio AUC24h,test/ref. RBT and 25-O-desacetyl-RBT: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Ratio C0h,test/ref, Ratio Cmin,test/ref, Ratio Cmax,test/ref, Ratio AUC24h,test/ref.	Completed Full CSR
TMC278-C127 (PK)	1 France	Start: 04-Jul-2005	To investigate the effect of	Phase I, randomized,	18-45 yrs Healthy	Treatment A: RPV 150 mg	Treatment A: 8 Enrolled	16/0 26.1yrs	For RPV: C0h, Cmin, tmax,	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
Janssen		Completed: 19-Oct-2005 16/16	steady-state KTZ on the steady-state PK of RPV and the effect of steady-state RPV on the steady-state PK of KTZ	open-label, 2-way crossover, drug interaction study	subjects male / female	once daily on Days 1 to 11, oral. Treatment B: KTZ 400 mg once daily on Days 1 to 22 + RPV 150 mg once daily on Days 12 to 22, oral.	6 Completed Treatment B: 8 Enrolled 8 Completed	(1[redacted] - 3[redacted])	Cmax, AUC24h, Css,av, FI, Ratio C0h,test/ref, Ratio Cmin,test/ref, Ratio Cmax,test/ref, Ratio AUC24h,test/ref. For KTZ: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Ratio C0h,Day 22/ Day 11, Ratio Cmin,Day 22/ Day 11, Ratio Cmax,Day 22/ Day 11, Ratio AUC24h,Day 22/ Day 11.	
TMC278-TiDP6-C123 (PK) Janssen	1 US	Start: 16-Oct-2007 Completed: 15-Jan-2008 16/16	To investigate the effect of steady-state RPV on the single-dose PK of sildenafil and its active	Phase I, randomized, open-label, 2-way crossover, drug interaction	19-55 yrs Healthy subjects male	Treatment A: Single dose of sildenafil 50 mg on Day 1, oral. Treatment B: RPV 75 mg once daily on	Treatment A: 8 Enrolled 8 Completed Treatment B: 8 Enrolled 7 Completed	16/0 38.0yrs (2[redacted] - 5[redacted])	For RPV: C0h, Cmin, Cmax, tmax, AUC24h, Css,av, FI, Ratio Cmin, test/ref, Ratio	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			metabolite N-desmethyl sildenafil and the effect of single-dose sildenafil on the steady-state PK of RPV	study		Days 1-12 + single dose of sildenafil 50 mg on Day 12, oral.			Cmax, test/ref, Ratio AUC24h, test/ref. For sildenafil: C0h, Cmax, tmax, AUClast, AUC∞, λz, t1/2term, Ratio Cmax, test/ref, Ratio AUC∞, test/ref, Ratio AUClast, test/ref. For N-desmethyl sildenafil: Cmax, tmax, AUClast, AUC∞, λz, t1/2term, Cmax, N-desmethyl sildenafil/sildenafil, AUClast, N-desmethyl sildenafil/ sildenafil,	
TMC278-C116 (PK) Janssen	1 Germany	Start: 28-Oct-2005 Completed: 25-Jan-2006 16/16	To investigate the effect of steady-state atorvastatin on the steady-state PK of RPV and the	Phase I, randomized, open-label, 2-way crossover, drug interaction	18-45 yrs Healthy subjects male / female	Treatment A: Atorvastatin 40 mg once daily on Days 1-4, oral. Treatment B: RPV 150 mg	Treatment A: 8 Enrolled 8 Completed Treatment B: 8 Enrolled 8 Completed	16/0 30.0yrs (1[redacted] - 4[redacted])	For RPV: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Ratio C0h,test/ref, Ratio Cmin,test/ref,	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			effect of steady-state RPV on the steady-state PK of atorvastatin, atorvastatin lactone, and the active metabolites 2-OH-atorvastatin and 4-OH-atorvastatin.	study		once daily on Days 1-15 + atorvastatin 40 mg once daily on Days 12-15, oral.			Ratio Cmax,test/ref, Ratio AUC24h,test/ref. For atorvastatin, atorvastatin lactone, 2-OH-atorvastatin, and 4-OH-atorvastatin: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, λz, t1/2term, Ratio C0h,test/ref, Ratio Cmin,test/ref, Ratio Cmax,test/ref, and Ratio AUC24h,test/ref.	
TMC278-C120 (PK) Janssen	1 UK	Start: 20-Jul-2005 Completed: 01-Dec-2005 16/16	To determine the effect of steady-state concentrations of RPV on the steady-state PK of EE, and on the steady-	Phase I, open-label, single-sequence, drug interaction study	18-45 yrs Healthy subjects female	Treatment A: EE/ norethindrone 0.035 mg/1 mg once daily on Days 1-21, no trial drug on Days 22-28,	Treatment A: 16 Enrolled 15 Completed Treatment B: 15 Enrolled 15 Completed	0/16 27.1yrs (2[redacted] - 4[redacted])	For RPV: C0h, C24h, Cmax, Cmin, Css,av, tmax, AUC24h, FI. For EE and norethindrone: C0h, C24h, Cmax, Cmin,	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			state PK of norethindrone.			oral. Treatment B: EE/ norethindrone 0.035 mg/1 mg once daily on Days 29-49 + RPV 150 mg once daily on Days 29-43, no trial drug on Days 50-56, oral.			Css,av, tmax, AUC24h, FI, Ratio Cmax,Y/X, Ratio AUC24h,Y/X, Ratio Cmin,Y/X.	
TMC278-TiDP6-C136 (PK) Janssen	1 UK	Start: 28-Jul-2008 Completed: 02-Dec-2008 18/18	To determine the effect of steady-state concentrations of RPV 25 mg once daily on the steady-state PK of EE 35 μg once daily and the effect of steady-state concentrations of RPV 25 mg once daily on the steady-state PK of	Phase I, open-label, single-sequence, drug interaction study	18-45 yrs Healthy subjects female	Treatment A: EE/ norethindrone 0.035 mg/1 mg once daily on Days 1-21, no trial drug on Days 22-28, oral. Treatment B: EEl/ norethindrone 0.035 mg/1 mg once daily on Days 29-49 + RPV 25 mg once daily on	Treatment A: 18 Enrolled 16 Completed Treatment B: 16 Enrolled 15 Completed	0/18 26.9yrs (2[redacted] - 3[redacted])	For RPV: C0h, C24h, Cmin, Cmax, Css,av, tmax, AUC24h, FI. For EE and norethindrone: C0h, C24h, Cmin, Cmax, Css,av, tmax, AUC24h, FI, Ratio Cmin,test/ref, Ratio Cmax,test/ref, Ratio AUC24h,test/ref	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			norethindrone 1 mg once daily			Days 29-43, no trial drug on Days 50-56, oral.				
TMC278-TiDP6-C121 (PK) Janssen	1 The Netherlands	Start: 31-Oct-2008 Completed: 15-Jun-2009 13/16	To evaluate the effect of steady-state RPV 25 mg once daily on the steady-state PK of R- and S-methadone	Phase I, open-label, single-sequence, drug interaction study	18-55 yrs Healthy subjects male / female	Methadone individualized maintenance therapy 60 to 100 mg once daily on Days -14 to 12 + RPV 25 mg once daily on Days 1-11.	13 Enrolled 12 Completed	13/0 41.0yrs (3[redacted] - 5[redacted])	For RPV: C0h, Cmin, tmax, Cmax, AUC24h, Css,av and FI. For R- and S-methadone: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Ratio Cmin,test/ref , Ratio Cmax,test/ref, Ratio AUC24h,test/ref.	Completed Full CSR
TMC278-C114 (PK) Janssen	1 Belgium	Start: 12-Jul-2005 Completed: 03-Nov-2005 16/16	To investigate the effect of steady-state OMP on the single-dose and steady-state PK of RPV and the effect of single-dose and steady-state RPV on	Phase I, randomized, open-label, 2-way crossover, drug interaction study	18-45 yrs Healthy subjects male / female	Treatment A: RPV 150 mg once daily on Days 1-11, oral. Treatment B: OMP 20 mg once daily on Days 1-22 + RPV 150 mg once daily on Days 12-22,	Treatment A: 8 Enrolled 7 Completed Treatment B: 8 Enrolled 8 Completed	13/3 34.1yrs (2[redacted] - 4[redacted])	For RPV: C0h, Cmin, tmax, Cmax, AUC24h, Ratio Cmax,test/ref, Ratio AUC24h,test/ref, Css,av, FI, Ratio C0h,test/ref, Ratio Cmin,test/ref. For OMP, 5-	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			the steady-state PK of OMP and its metabolites 5-hydroxyomeprazole and OMP sulfone			oral.			hydroxyOMP, and OMP sulfone: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, λz, t1/2, Ratio C0h,Day 22/ Day 11, Ratio Cmin,Day 22/ Day 11, Ratio Cmax,Day 22/ Day 11, Ratio AUC24h,Day 22/ Day 11, Ratio C0h,Day 12/ Day 11, Ratio Cmin,Day 12/ Day 11, Ratio Cmax,Day 12/ Day 11, Ratio AUC24h,Day 12/ Day 11, Ratio AUC24h-5-hydroxyOMP/ OMP,Day 12/ Day 11, Ratio AUC24h 5-hydroxyOMP/ OMP,Day 22/	

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									Day 11, Ratio AUC24h OMP sulfone/OMP, Day 12/Day 11, and Ratio AUC24h OMP sulfone/OMP, Day 22/Day 11.	
TMC278-C140 PK) Janssen	1 France	Start: 13-Mar-2006 Completed: 03-Jul-2006 24/24	To investigate the effect of single-dose famotidine on the single-dose PK of RPV in 3 different dosing regimens and to investigate the relationship between intragastric pH and the PK of RPV	Phase I, randomized, open-label, 4-way crossover, drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: Single dose of RPV 150 mg, oral. Treatment B: Single dose of famotidine 40 mg + single dose of RPV 150 mg 2 hours later (positive control), oral. Treatment C: Single dose of RPV 150 mg + single dose of famotidine 40 mg 4 hours later, oral. Treatment D: Single dose of	Treatment A: 6 Enrolled 6 Completed Treatment B: 6 Enrolled 6 Completed Treatment C: 6 Enrolled 5 Completed Treatment D: 6 Enrolled 6 Completed	24/0 30.5yrs (2[redacted] - 5[redacted])	For RPV: tmax, Cmax, AUClast, AUC∞, λz, t1/2term, Ratio Cmax,test/ref, Ratio AUClast,test/ref, and Ratio AUC∞,test/ref. For famotidine: tmax, Cmax, AUClast, AUC∞, λz, t1/2term.	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						famotidine 40 mg (in evening) + single dose of RPV 150 mg 12 hours later, oral.				
TMC278-C109 (PK) Janssen	1 Belgium	Start: 14-Feb-2005 Completed: 03-May-2005 16/16	To determine the effect of paracetamol on the steady-state PK of RPV in healthy volunteers and to establish the effect of steady-state RPV on the PK of paracetamol.	Phase I, randomized, open-label, 2-way crossover, drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: Single dose of paracetamol 500 mg on Day 1, oral. Treatment B: RPV 150 mg once daily on Days 1-11 + single dose of paracetamol 500 mg on Day 11, oral.	Treatment A: 8 Enrolled 8 Completed Treatment B: 8 Enrolled 8 Completed	9/7 40.9yrs (1[redacted] - 5[redacted])	For RPV: Days 10 and 11: AUC24h, Ratio AUC24h,test/ref, Cmax, Ratio Cmax,test/ref, Cmin, Ratio Cmin,test/ref, C0h, Ratio C0h,test/ref, tmax, Css,av, and FI. For paracetamol: Days 1 and 11: AUC∞, Ratio AUC∞,test/ref, AUClast, Ratio AUClast,test/ref, Cmax, Ratio Cmax,test/ref, tmax, t1/2term, and λz.	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
TMC278-C139 (PK) Janssen	1 US	Start: 19-Sep-2005 Completed: 17-Mar-2006 25/25	To investigate the effect of single dose and steady-state RPV on the PK of chlorzoxazone and 6-hydroxy-chlorzoxazone after a single dose of chlorzoxazone and the effect of a single dose of chlorzoxazone on the steady-state PK of RPV	Phase I, open-label, drug interaction study	18-55 yrs Healthy subjects male / female	Single doses of chlorzoxazone 500 mg on Days 1, 4, and 19 + RPV150 mg once daily on Days 4 to 19, oral.	25 Enrolled 19 Completed	13/12 43.4yrs (2[redacted] - 5[redacted])	For RPV: C0h, tmax, Cmax, Cmin, AUC24, Css,av, FI, Ratio C0h, Day 15/ Day 14, Ratio Cmin, Day 15/ Day 14, Ratio Cmax, Day 15/ Day 14, Ratio AUC24h, Day 15/Day 14, Ratio C0h, Day 19/Day 18, Ratio Cmin, Day 19/Day 18, Ratio Cmax, Day 19/Day 18, Ratio AUC24h, Day 19/Day 18. For chlorzoxazone and 6-hydroxy-chlorzoxazone: tmax, Cmax, AUClast, AUC∞, λz, t½ term, Ratio Cmax, Day 4/ Day 1, Ratio	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
									AUClast, Day 4/Day 1, Ratio AUC∞, Day 4/Day 1, Ratio Cmax, Day 15/Day 1, Ratio AUClast, Day 15/Day 1, Ratio AUC∞, Day 15/Day 1, Ratio Cmax, Day 4/Day 1, Ratio AUClast, Day 4/Day 1, Ratio AUC∞, Day 4/Day 1, Ratio Cmax, Day 19/Day 1, Ratio AUClast, Day 19/Day 1, Ratio AUC∞, Day 19/Day 1.	
TMC278IFD1001 (PK) Janssen	1 Belgium	Start: 31-Jan-2012 Completed: 05-Apr-2012 22/22	To investigate the effect of steady-state RPV on the single dose PK of digoxin	Phase I, open-label, 2-way crossover drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: Digoxin 0.5 mg single dose Day 1 Treatment 2: RPV 25 mg once daily Days 1-16 +	Treatment A: 11 Enrolled 11 Completed Treatment B: 11 Enrolled 10	11/11 45.5yrs (3[redacted] – 5[redacted])	For RPV: C0h, Cmin, Cmax, tmax, AUC0-24h, Css,av and FI. For digoxin: C0h, Cmax, tmax, AUClast, AUC∞,	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
						digoxin 0.5 mg single dose Day 11	Completed		AUC0-4h, λz, t1/2term, CL/F, Ratio Cmax RPV+digoxin/ digoxin, Ratio AUC0-4h RPV+digoxin/ digoxin, Ratio AUClast RPV+digoxin/ digoxin and Ratio AUC∞ RPV+digoxin/ digoxin	

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
TMC278IFD 1003 (PK) Janssen	1 Belgium	Start: 02-May-2012 Completed: 17-Oct-2012 20/20	To assess the PK of RPV 50 mg once daily and at another dosing regimen in combination with RBT 300 mg once daily compared with the PK of RPV 25 mg once daily alone in healthy adult subjects	Phase I, open-label, 2-sequence drug interaction study	18-55 yrs Healthy subjects male / female	Treatment A: RPV 25 mg once daily Days 1-11 Treatment B: RBT 300 mg once daily Days 1-17 + RPV 50 mg once daily Days 1-11 Treatment C: RBT 300 mg once daily Days 1-17 + RPV 25 mg once daily Days 1-11	Treatment A: 10 Enrolled 4 Completed Treatment B: 10 Enrolled 6 Completed	12/8 43.0yrs ([redacted])	On Days 1, 8, 9, and 10 of Treatments A, B, and C: C0h On Day 11 of Treatments A, B and C: C0h, Cmin, Cmax, tmax, C_T, AUC_T, Clast, tlast, Cavg, Fl, λz, t1/2term, AUClast, and AUC_∞. For each test/reference comparison: Ratio Cmin,test/ref[b], Ratio Cmax,test/ref[b], and Ratio AUC_T,test/ref[b].	Completed Full CSR
TMC278IFD 1004	1 US	Start: 30-Oct-2012 Completed: 9-Jan-2013 20/20	To assess the effect of steady-state RPV 25 mg once daily on the PK of a single dose of	Phase 1, open-label, sequential study	18-55 yrs Healthy subjects male / female	Treatment A: Metformin 850 mg single dose; Day 1 Treatment B: RPV 25 mg once daily;	Treatment A: 20 Enrolled 20 Completed Treatment B: 20 Enrolled	20/0 28.4yrs ([redacted])	AUClast, AUC_∞, and Cmax	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			metformin in healthy adult subjects			Day 5 - 17 + Metformin 850 mg single dose; Day 15	20 Completed			
TMC278-TiDP6-C130	2 Germany	Start: 18-Jun-2008 Completed: 16-Nov-2009 32/32	To assess the single-dose and steady-state PK of RPV in subjects with mild or moderate hepatic impairment compared to matched healthy control subjects	Open-label, parallel, controlled, sequential study	Subjects with mild or moderate hepatic impairment and matched; healthy control subjects with normal hepatic function	RPV 25 mg once daily; oral; 11 days	Panel A1, Healthy: 8 Enrolled 8 Completed Panel A2, Mild hepatic impairment: 8 Enrolled 8 Completed Panel B1, Healthy: 8 Enrolled 8 Completed Panel B2, Moderate hepatic impairment: 8 Enrolled 8 Completed	20/12 Panel A1, 48.0 (3[redacted] - 6[redacted]) Panel A2, 47.5 (4[redacted] - 5[redacted]) Panel B1, 52.0 (4[redacted] - 6[redacted]) Panel B2, 53.0 (4[redacted] - 6[redacted])	Cmax and AUC24h for Day 1, and C24h, Cmax, and AUC24h for Day 11,	Completed Full CSR
TMC114HIV 3015	4 US	Start: 01 Nov-2011 Completed: 23-Jun-2016 19/12	The primary objective of the RPV arm of the study was to assess the influence of pregnancy on	Phase 3b, multicenter, open-label study	18 years or older Pregnant females (18-26 weeks of gestation), HIV-1	RPV 25 mg once daily; oral; fed	19 Enrolled 12 Completed	0/19; 27.16yrs (2[redacted] - 3[redacted])	Cmax, tmax, C0h, Cmin, AUC24h, Css,avg, FI, CL/F	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
			the plasma PK of RPV during the 2nd and 3rd trimesters of gestation, as well as postpartum		infected					
Pharmacokinetic Studies in HIV-1-infected Subjects										
R278474-C101 (PK) Janssen	1 UK	Start: 27-Nov-2003 Completed: 01-Mar-2004 15/16	To determine the single dose PK of RPV in HIV-1 infected subjects taking at least 2 NRTIs and EFV or NVP	Phase I, open-label, parallel group, add-on single dose study	18-55 yrs Male subjects taking at least 2 N(t)RTIs and EFV or NVP	Group 1: At least 2 N(t)RTIs and EFV 600 mg once daily + RPV 50 mg single dose (n=7), oral. Group 2: At least 2 N(t)RTIs and NVP 200 mg BID. + RPV 50 mg single dose (n=8), oral.	Group 1: 7 Enrolled 6 Completed Group 2: 8 Enrolled 8 Completed	15/0 45.7yrs (3[redacted] - 6[redacted])	For RPV: AUC∞, AUClast, Cmax, λz, t1/2term, and tmax For EFV and NVP: C0h For EFV: C12h	Completed Full CSR
Phase III Trials in HIV-1-infected Subjects										
TMC278-TiDP6-C209 (Efficacy & Safety) Janssen	112 Centers 34 US, 7 France, 7 South Africa,	Start: 21-Apr-2008 Week 48 Data cutoff: [redacted];	To demonstrate non-inferiority of treatment with RPV	Phase III, multi-national, randomized, double-blind,	18yrs or older treatment-naïve HIV-1 infected	RPV 25 mg + EFV placebo once daily + fixed background	RPV: 346 Enrolled 296 Completed	543/147; 36.0[c] (1[redacted] - 7[redacted])	Demonstrate non-inferiority of RPVcompared with EFV with a maximum	Completed 48-Week CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
	5 Australia, 5 Argentina, 5 Brazil, 5 Portugal, 4 Canada, 4 Italy, 4 Spain, 4 Taiwan, 4 Thailand, 4 UK, 3 Denmark, 3 Russia, 3 Romania, 2 Austria, 2 Mexico, 2 Sweden, 1 Netherlands ,1 Puerto Rico	690/680	when administered as 25 mg once daily compared with the control (EFV) group in regard to the proportion of virologic responders (plasma viral load < 50 copies/mL, according to the TLOVR algorithm) at 48 weeks in treatment-naïve HIV-1 infected adult subjects, with a maximum allowable difference of 12%	double-dummy, active-controlled trial	subjects	regimen (TDF 300 mg/FTC 200 mg once daily) from for 96 weeks, oral Or EFV 600 mg + RPV placebo once daily + fixed background regimen (TDF 300 mg/FTC 200 mg once daily) from for 96 weeks, oral	Week 48 EFV: 344 Enrolled 288 Completed Week 48		allowable difference of 10% at 48 weeks	
TMC278-TiDP6-C215 (Efficacy & Safety) Janssen	98 Centers 29 US, 7 Canada, 7 Germany, 6 South	Start: 22-May-2008 Week 48 Data cutoff: [redacted]	To demonstrate non-inferiority of treatment with RPV	Phase III, international, randomized, double-blind, double-	18yrs or older treatment-naïve HIV-1 infected	RPV 25 mg + EFV placebo once daily + fixed background	RPV: 340 Enrolled 296 Completed	494/184; 36.0yrs[c] (1[redacted] - 6[redacted])	Demonstrate non-inferiority of RPV compared with EFV with a maximum	Completed 48-Week CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
	Africa, 5 Belgium, 4 Brazil, 4 Spain, 3 Australia, 3 Chile, 3 China, 3 Italy, 3 France, 3 Russia, 3 UK, 2 Costa Rica, 2 India, 2 Mexico, 2 Panama, 2 Thailand, 1 Portugal, 1 Puerto Rico,		when administered as 25 mg once daily compared to the control (EFV) group in regard to the proportion of virologic responders (plasma viral load <50 copies/mL, according to TLOVR algorithm) at 48 weeks in treatment-naïve HIV-infected adult subjects, with a maximum allowable difference of 12%.	dummy, active-controlled trial	subjects	regimen containing ABC 600 mg/3TC 300 mg, AZT 300 mg/3TC 300 mg BID, or TDF 300 mg/FTC 200 mg once daily for 96 weeks, oral. Or EFV 600 mg + RPV placebo once daily + fixed background regimen containing ABC 600 mg/3TC 300 mg, AZT 300 mg/3TC 300 mg BID, or TDF 300 mg/FTC 200 mg once daily for 96 weeks, oral.	Week 48 EFV: 340 Enrolled 282 Completed Week 48		allowable difference of 10% at 48 weeks	
Human Pharmacodynamic Studies										
TMC278-	1 Belgium	Start:	To evaluate the	Double-	18-55 yrs	Treatment A:	Treatment A:	19/22	For RPV: On Day	Completed

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
TiDP6-C131 (PK) Janssen		20-Apr-2007 Completed: 24-Sep-2007 41/42	effect of single dose and steady-state administration of RPV vs. placebo on the QT/QTc interval with 2 dose regimens, 75 mg once daily and 300 mg once daily	blind, double-dummy, randomized, placebo-and active-controlled, 3-period crossover trial	Healthy subjects male / female	RPV 75 mg on Days 1-11 + RPV placebo on Days 1-11 + moxifloxacin placebo on Day 12, oral. Treatment B: RPV 300 mg on Days 1-11 + moxifloxacin placebo on Day 12, oral. Treatment C: RPV placebo on Days 1-11 + 400 mg moxifloxacin on Day 12, oral.	41 Enrolled 38 Completed Treatment B: 41 Enrolled 39 Completed Treatment C: 41 Enrolled 39 Completed	40.0yrs (2[redacted] - 5[redacted])	1 of Treatments A and B: tmax, Cmax, AUC24h. On Days 9 and 10 of Treatments A and B: C0h. On Day 11 of Treatments A and B: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI, Accumulation ratio. For moxafloxacin: On Day 12 of Treatment C: tmax, Cmax, AUC24h, λz, t1/2term, AUC∞	Full CSR
TMC278-TiDP6-C152 (PK) Janssen	1 US	Start: 03-Sep-2008 Completed: 03-Mar-2009 120/120	To evaluate the effect of RPV 25 mg once daily at steady-state on the QT/QTc interval in healthy subjects	Double-blind, double-dummy, randomized, placebo-and active-controlled, 3-period crossover	18-55 yrs Healthy subjects male / female	RPV Treatment A: RPV 25 mg once daily on Days 1 to 11 + moxifloxacin placebo once daily on Day 11. Treatment B:	Treatment A: 60 Enrolled 57 Completed Treatment B: 60 Enrolled 58 Completed	68/52 30.8yrs (1[redacted] - 5[redacted])	For RPV: C0h, Cmin, tmax, Cmax, AUC24h, Css,av, FI. For moxafloxicin: C0h, tmax, Cmax, AUClast, AUC∞, λz, t1/2term For EFV: C0h,	Completed Full CSR

Protocol No. (Study Type) Sponsor	No. Study Centres Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed[a]	Gender M/F; Mean Age (Range)	Primary Endpoint(s)	Study Reporting Status (Type of Report)
				trial to evaluate the effect of RPV on the QT/QTc interval, and a double-blind, randomized, placebo-controlled, 2-period crossover trial to evaluate the effect of EFV on the QT/QTc interval.		RPV placebo once daily on Days 1 to 11 + moxifloxacin placebo once daily on Day 11. Treatment C: RPV placebo once dailyon Days 1 to 11 + moxifloxacin 400 mg once daily on Day 11. EFV Treatment D: EFV 600 mg once daily for 11 days Treatment E: EFV placebo once daily for 11 days	Treatment C: 60 Enrolled 56 Completed Treatment D: 60 Enrolled 50 Completed Treatment E: 60 Enrolled 52 Completed		Cmin, tmax, Cmax, AUC24h, Css,av, FI.	

a. For ongoing studies, the number of ongoing subjects reported as of data cut-off date (~Month Year or data cut off date) in the respective CSR
b. Test = Treatments B and C; Reference = Treatment A; τ = dosing interval: 24 hours for Treatment A, Treatment B and Treatment C.
c. Median age is presented

RPV = Rilpivirine; ddI = Didanosine; LPV = Lopinavir; RTV = Ritonavir; PK = Pharmacokinetics; DRV = Darunavir; EFV = Efavirenz; NVP = Nevirapine; RAL = Raltegravir; RIF = Rifampin; RBT = Rifabutin; KTZ = Ketoconazole; EE = Ethinylestradiol; FI = Fluctuation Index; OMP = Omeprazole;

Appendix Table 3 Summary of Single Dose Pharmacokinetic Parameters

Appendix Table 3.1 Summary of Single Dose Dolutegravir Pharmacokinetic Parameters

Study	Population/ No. of Subjects completed	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter[a]				
				Cmax (μg/mL)	tmax (h)	AUC (0-∞) (μg.h/mL)	T1/2 (h)	C24 (μg/mL)
ING111207	Healthy adult/ 13	Oral Suspension	2 mg/ 8	0.23 (20)	0.63 (0.25-1.00)	2.78 (26)	12.7 (20)	0.038 (41)
			5 mg/ 7	0.66 (20)	0.5 (0.50-1.50)	8.87 (27)	14.3 (25)	0.126 (28)
			10 mg/ 8	1.23 (9)	0.63 (0.25-1.50)	14.6 (21)	12.7 (9)	0.196 (34)
			25 mg/ 8	2.76 (12)	0.75 (0.50-1.50)	35.1 (30)	12.7 (21)	0.469 (41)
			50 mg/ 6	4.56 (21)	1.25 (0.50-3.00)	73.2 (19)	14.2 (19)	1.06 (27)
			100 mg/ 5	8.14 (12)	1.00 (0.75-3.00)	136 (24)	14.7 (23)	1.80 (33)
ING111322	Healthy adult/32	Oral Suspension	10 mg/ 8	1.24 (12)	0.50 (0.50-1.00)	15.8(12)	11.8 (19)	0.23 (19)
			25 mg/ 10	2.66 (21)	1.00 (0.50-2.00)	43.1(28)	12.6 (17)	0.65 (33)
			50 mg/ 8	4.52 (20)	0.75 (0.50-1.00)	75.8(28)	12.6 (14)	1.18 (32)
ING111521	HIV-infected/ 35	Oral Tablet	2 mg (fasted)/ 9	0.18 (35)	1.5 (0.5-3.0)	2.63 (39)	10.7 (30)	0.03 (49)
			10 mg (fasted)/ 7	0.57 (28)	2.0(1.0-6.0)	10.1 (26)	11.8 (22)	0.15 (30)
			50 mg (fasted)/ 10	2.46 (32)	2.1 (1.0-3.97)	40.5 (33)	11.2 (29)	0.59 (31)
ING111602	Healthy adult/ 16	Oral Tablet	50 mg (alone)/ 16	2.03 (25)	2.5 (0.5-8.0)	35.6 (33)	NR	0.51 (38)
			50 mg (+ multi-vitamin)/ 16	1.31 (25)	2.5 (0.5-8.0)	23.74 (30)	NR	0.34 (33)
			50 mg (+ Maalox)/ 16	0.56 (29)	2.5 (0.5-8.0)	9.40 (36)	NR	0.13 (41)
			50 mg (+ Maalox 2 hrs post dose)/ 16	1.67 (51)	2.5 (0.5-8.0)	26.33 (45)	NR	0.36 (42)
ING111853	Healthy adult/ 6	Oral Suspension	20 mg (fasted)/ 6	2.57 (24)	0.50 (0.50-2.00)	35.9 (12)	15.6 (16)	N/A
ING111856	Healthy adult/ 42	Oral Suspension	250 mg (fasted)/ 41	12.4 (27)	3.08 (1.52-6.05)	167 (33)	NR	3.86 (48)
ING112941	Healthy adult/ 14	Oral Tablet	50 mg (fasted)/ 12	1.84 (44)	4.00 (1.00-5.00)	34.7 (57)	14.4 (21)	0.56 (63)
			50 mg (fasted + OMP)/ 12	1.69 (19)	3.00 (1.00-5.03)	34.8 (26)	16.3 (20)	0.53 (27)
		Oral Suspension	250 mg/ 8	14.1 (10)	2.50 (1.50-4.00)	278 (15)	14.5 (10)	4.08 (17)
ING113097	Healthy and moderate hepatic	Oral Tablet	50 mg (fasted)/ 8 healthy matches	1.80 (49)	3.0 (1.0-4.0)	37.3 (47)	14.9 (24)	0.57 (44)

Study	Population/ No. of Subjects completed	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter[a]				
				Cmax (μg/mL)	tmax (h)	AUC (0-∞) (μg.h/mL)	T1/2 (h)	C24 (μg/mL)
	impairment adult/ 16		50 mg (fasted)/ 8 with moderate hepatic impairment	1.78 (17)	4.0 (2.0-5.0)	38.5 (30)	15.5 (19)	0.59 (36)
ING113125	Healthy and severe renal impairment adult/ 16	Oral Tablet	50 mg (fasted)/ 8 healthy matches	1.86 (45)	2.00 (1.0, 4.0)	37.1 (58)	15.4 (15)	NR
			50 mg (fasted)/ 8 with severe renal impairment	1.50 (34)	2.00 (1.0, 3.0)	23.5 (48)	12.7 (31)	NR
ING114005	Healthy adult/ 12	Oral Tablet	50 mg (fasted)/ 12	1.83 (35)	2 (1-4)	24.3 (44)[b]	13.6 (24)	0.53 (59)
			100 mg (fasted)/ 12	2.77 (35)	2 (1-4)	34.3 (41)	NR	0.80 (53)
ING115381	Healthy adult (Japanese)/ 10	Oral Tablet	50 mg(fasted)/ 10	2.14 (47)	NR(2.0-4.0)	43.4 (46)	14.6 (10)	0.67 (45)
ING116898	Healthy adult/12 (Cohort 1)	Oral Tablet	50 mg (fasted)/12	1.98 (46)	3 (0.5-6.0)	35.6 (62)	12.2 (28)	0.542 (66)
			50 mg (fasted, +Calcium Carbonate)/12	1.25 (45)	2 (0.5-12)	21.8 (66)	12.7 (24)	0.332 (74)
			50 mg (fed, Calcium Carbonate)/11	2.13 (30)	3 (1.0-6.02)	39.2 (47)	12.3 (25)	0.588 (54)
			50 mg (2hrs prior to Calcium Carbonate)/11	1.98 (46)	3 (1.0-4.0)	33.8 (57)	12.4 (24)	0.492 (58)
	Healthy adult/11 (Cohort 2)	Oral Tablet	50 mg (fasted)/11	1.77 (41)	3 (1.0-6.0)	33.6 (40)	13.2 (16)	0.528 (41)
			50 mg (fasted, +Ferrous Fumarate)/11	0.742 (56)	4 (2.0-6.0)	15.1 (53)	14.3 (23)	0.227 (56)
			50 mg (fed, Ferrous Fumarate)/10	1.90 (25)	3.5 (1.0-8.0)	34.1 (33)	12.8 (20)	0.540 (42)
			50 mg (2hrs prior to Ferrous Fumarate)/10	1.79 (52)	2 (0.5-6.0)	32.3 (47)	13.7 (25)	0.489 (48)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) are presented.
b. AUC(0-24) is reported.
NR = Not reported; N/A = Not available

Appendix Table 3.2 Summary of Single Dose Rilpivirine Pharmacokinetic Parameters

Study	Population/ No. of Subjects completed	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Parameter[a]				
				tmax (h)	Cmax (ng/mL)	AUClast (ng.h/mL)	AUC∞ (ng.h/mL)	t1/2,term
TMC278-TiDP6-C137	Healthy adults/18	Phase IIb Oral Tablet	75 mg/19	5.0	296	10340 (168h)	11450	48.0
TMC278-C114	Healthy adults/15	Phase IIb Oral Tablet	150 mg/16	3.5	683	7711 (24h)	NA	NA
TMC278-C119	Healthy adults/6	Oral Solution	150 mg/6	3.5	602.8	16240	18520	56.56
TMC278-TiDP6-C130	Healthy adults/8	Phase III Oral Tablet	25 mg/8	5.0	144.3	2152[b]	NA	60.6
	Mild hepatic impairment/8		25 mg/8	5.0	187	3206[b]	NA	80.8
	Healthy/8		25 mg/8	5.0	146.8	2318[b]	NA	56.0
	Moderate hepatic impairment/8		25 mg/8	20.0	143.5	2525[b]	NA	90.56
TMC278-C140	Healthy adults/24	Phase IIb Oral Tablet	150 mg/23	5.0	564	19920	21630	41.0
			150 mg/ (+40 mg famotidine 2h before RPV)23	5.0	108	4819	5349	44.5
			150 mg/ (+40 mg famotidine 4h after RPV)24	4.0	665	20790	22660	40.6
			150 mg/ (+40 mg famotidine 12h before RPV)24	5.0	552.8	17200	18470	39.04
TMC278-TiDP6-C131	Healthy adults/41	Phase III Oral Tablet	300 mg/39	4.5	838	9119 (24h)	NA	NA
R278474-C101	HIV-1 infected adults/15	Oral Solution	50 mg (+600 mg EFV)/7	4.0	176	2179	2246	19.4
			50 mg (+200 mg NFV)/8	4.0	222	6402	7144	40.1

a. Data presented are least squares mean except for tmax where median is presented.
b. AUC24h is reported
NA = Not available

Appendix Table 4 Summary of Repeat Dose Pharmacokinetic Parameters

Appendix Table 4.1 Summary of Repeat Dose DTG/RPV FDC Pharmacokinetic Parameters: Pre-dose Plasma Dolutegravir Concentrations

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	t1/2 (h)	Cτ (μg.mL)
201636	HIV-1 infected subjects/508	Oral Tablet	50 mg (+RPV 25 mg)/ 239 (average)	QD	NR	NR	NR	NR	1.58 (61)[b]
			50 mg (+RPV 25 mg)/ 130 (wk 4)	QD	NR	NR	NR	NR	1.25 (84)[c]
			50 mg (+RPV 25 mg)/ 210 (wk 24)	QD	NR	NR	NR	NR	1.52 (70)[c]
			50 mg (+RPV 25 mg)/ 215 (wk 48)	QD	NR	NR	NR	NR	1.55 (76)[c]
201637	HIV-1 infected subjects/516	Oral Tablet	50 mg (+RPV 25 mg)/ 242 (average)	QD	NR	NR	NR	NR	1.27 (57)[b]
			50 mg (+RPV 25 mg)/ 176 (wk 4)	QD	NR	NR	NR	NR	1.27 (73)[c]
			50 mg (+RPV 25 mg)/ 207 (wk 24)	QD	NR	NR	NR	NR	1.22 (70)[c]
			50 mg (+RPV 25 mg)/ 215 (wk 48)	QD	NR	NR	NR	NR	1.16 (65)[c]

a. Data presented are geometric mean (%CVb) except for tmax where median (range) are presented
b. Data presented as C0avg (average predose concentration across Weeks 4, 24, 48)
c. Data presented as C0
NR = Not reported; QD = Once daily;

Appendix Table 4.2 Summary of Repeat Dose DTG/RPV FDC Pharmacokinetic Parameters: Pre-dose Plasma Rilpivirine Concentrations

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]						
					tmax (h)	C0h (ng/mL)	Cmin (ng/mL)	Cmax (ng/mL)	Css,av (ng/mL)	AUC24h (ng.h/mL)	t1/2 (h)
201636	HIV-1 infected subjects/508	Oral Tablet	25 mg (+DTG 50 mg)/233 (average)	QD	NR	81.8 (47)[b]	NR	NR	NR	NR	NR
			25 mg (+DTG 50 mg)/130 (wk 4)	QD	NR	71.9 (66)	NR	NR	NR	NR	NR
			25 mg (+DTG 50 mg)/210 (wk 24)	QD	NR	80.0 (46)	NR	NR	NR	NR	NR
			25 mg (+DTG 50 mg)/211 (wk 48)	QD	NR	84.5 (53)	NR	NR	NR	NR	NR
201637	HIV-1 infected subjects/508	Oral Tablet	25 mg (+DTG 50 mg)/242 (average)	QD	NR	79.2 (47)[b]	NR	NR	NR	NR	NR
			25 mg (+DTG 50 mg)/175 (wk 4)	QD	NR	71.8 (51)	NR	NR	NR	NR	NR
			25 mg (+DTG 50 mg)/207 (wk 24)	QD	NR	79.7 (55)	NR	NR	NR	NR	NR
			25 mg (+DTG 50 mg)/215 (wk 48)	QD	NR	81.3 (53)	NR	NR	NR	NR	NR

a. Data presented are least squares mean except for tmax where median is presented.
b. Data presented as C0avg (average predose concentration across Weeks 4, 24, 48)
NR = Not reported; QD = Once daily

Appendix Table 4.3 Summary of Repeat Dose Dolutegravir Pharmacokinetic Parameters

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING111322	Healthy adult/ 32	Oral Suspension	10 mg/ 8	QD x 10 days	1.47 (24)	0.50 (0.25-2.00)	16.7 (15)	13.7 (15)	0.35 (20)
			25 mg (+MDZ)/ 10		3.09 (26)	1.00 (0.50-2.00)	38.4 (23)	15.0 (16)	0.84 (33)
			50 mg/ 8		6.16 (15)	1.00 (0.50-2.00)	76.8 (19)	15.3 (8)	1.64 (25)
ING111405	Healthy adult/ 31	Oral Tablet	30 mg/ 30	QD x 5 days	2.80 (15)	NR	36.9 (19)	12.1 (15)	0.77 (29)
			30 mg (+LPV/RTV 400/100 mg)/ 15	QD (+LPV/RTV q12h) x 14 days	2.94 (21)	NR	38.0 (25)	12.2 (22)	0.77 (36)
			30 mg (+DRV/RTV 600/100 mg)/ 15	QD (+DRV/RTV q12h) x 14 days	2.38 (20)	NR	27.3 (23)	9.78 (17)	0.45 (37)
ING111521	HIV-infected adult/ 35	Oral Tablet	2 mg/ 9	QD x 10 days	0.22 (25)	1.00 (0.42-3.00)	2.56 (29)	11.1 (24)	0.04 (50)
			10 mg/ 7	QD x 10 days	0.80 (23)	1.48 (0.50-3.00)	10.1 (20)	11.6 (21)	0.19 (25)
			50 mg/ 10	QD x 10 days	3.34 (16)	2.00 (0.97-4.00)	43.4 (20)	12.0 (22)	0.83 (26)
ING111603	Healthy adult/ 16	Oral Tablet	50 mg/ 15	QD x 5 days	4.34 (19)	3.00 (1.00-4.07)	60.4 (22)	12.4 (21)	1.29 (29)
			50 mg (+ETR 200 mg)/ 15	QD (+ETR q12h) x 14 days	2.10 (24)	2.00 (1.00-3.00)	17.8 (39)	6.39 (22)	0.16 (84)
ING111604	Healthy adult/ 16	Oral Tablet	50 mg/ 15	QD x 5 days	3.45 (30)	3.00 (1.00-4.00)	46.6 (32)	N/A	1.08 (39)
			50 mg (+300 mg TDF)/ 15	QD x 5 days	3.34 (26)	3.00 (1.00-4.03)	46.9 (28)	N/A	0.99 (32)
ING111762	HIV-infected adult/ 354	Oral Tablet	50 mg/337 (average)	QD	NR	NR	NR	NR	0.856 (140)[b]
			50 mg/329 (Wk 4)		NR	NR	NR	NR	0.786 (143)[c]
			50 mg/262 (Wk 24)		NR	NR	NR	NR	0.956 (129)[c]
			50 mg/106 (Wk 48)		NR	NR	NR	NR	0.907 (147)[c]
ING111854	Healthy adult/ 24	Oral Tablet	30 mg/ 12	QD x 5 days	3.21 (19)	3.00 (1.00-4.00)	45.3 (21)	13.3 (19)	1.00 (30)
			30 mg (+ATV/RTV 300/100 mg)/ 12	QD x 14 days	4.29 (19)	4.00 (2.00-4.00)	73.3 (16)	24.1 (11)	2.21 (16)
			30 mg/ 12	QD x 5 days	3.42 (13)	4.00 (1.00-4.00)	45.8 (17)	12.6 (20)	0.95 (29)
			30 mg (+ATV 400 mg)/ 12	QD x 14 days	5.11 (20)	4.00 (2.00-4.00)	87.4 (17)	23.8 (21)	2.67 (21)
ING111855	Healthy adult female/ 16	Oral Tablet	50 mg (+OC)/ 15	BID (+ OC QD) x 10 days	7.77 (23)	1.00 (1.0-6.0)	68.6 (27)	NR	4.00 (36)

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING112276	HIV-infected adult/ 155	Oral Tablet	10 mg/ 15	QD x 10 days	1.10 (37)	2.0 (2.0-4.0)	16.0 (40)	NR	0.30 (71)
			25 mg/ 15	QD x 10 days	1.71 (43)	2.0 (2.0-8.0)	23.1 (48)	NR	0.54 (67)
			50 mg/ 15	QD x 10 days	3.40 (27)	2.0 (2.0-4.0)	48.1 (40)	NR	1.20 (62)
ING112934	Healthy adult/ 17	Oral Tablet	50 mg/ 8 (Cohort 1)	QD x 5 days	3.52 (12)	3.50 (2.00-4.00)	47.8 (19)	11.3 (18)	0.97 (33)
			50 mg/ 8 (Cohort 2)	QD x 5 days	3.38 (26)	3.02 (1.00-12.00)	45.2 (22)	10.4 (17)	0.94 (40)
			50 mg (+ ETR 200 mg and LPV/RTV 400/100 mg)/ 8	QD (+ETR and LPV/RTV q12h) x 14 days	3.78 (12)	3.50 (1.00-4.00)	52.8 (18)	15.4 (25)	1.23 (32)
			50 mg (+ ETR 200 mg and DRV/RTV 600/100 mg)/ 9	QD (+ETR and DRV/RTV q12h) x 14 days	2.98 (18)	4.00 (1.00-4.00)	33.9 (22)	10.2 (16)	0.59 (33)
ING113068	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	2.38 (38)	2.0 (1.0-4.0)	30.6 (39)	12.1 (19)	0.61 (45)
			50 mg (+FPV/RTV 700/100 mg BID)/ 12	QD x 10 days	1.82 (57)	2.0 (1.0-4.0)	19.9 (57)	9.54 (26)	0.31 (64)
ING113096	Healthy adult/ 18	Oral Tablet	50 mg/ 14	QD x 5 days	4.53 (23)	3.00 (2.00-3.00)	64.5 (28)	14.8 (22)	1.48 (40)
			50 mg (+TPV/RTV 500/200 mg)/ 14	QD (+TPV/RTV BID) x 5 days	2.42 (23)	4.00 (1.00-4.00)	26.4 (30)	7.88 (20)	0.35 (54)
ING113099	Healthy adult/ 27	Oral Tablet	50 mg/ 20	QD x 7 days	2.78 (34)	2.0 (1.0-5.1)	35.1 (42)	11.2 (30)	0.63 (72)
			50 mg/ 11	BID x 7 days	5.55 (49)	1.0 (1.0-4.0)	46.3 (55)	9.54 (48)	2.41 (77)
			50 mg (+ RIF 600 mg)/ 11	BID (+RIF QD) x 14 days	3.13 (25)	2.0 (1.0-5.0)	42.6 (31)	4.24 (23)	0.67 (55)
			50 mg (+ RBT 300 mg)/ 9	QD x 14 days	3.41 (23)	3.0 (1.0-4.0)	37.0 (32)	8.64 (22)	0.53 (56)
ING114005	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	3.08 (30)	2.0 (1.0-4.0)	42.3 (39)	13.9 (23)	0.91 (53)
			50 mg (+EFV 600 mg QD)/ 12	QD x 14 days	1.87 (42)	1.0 (1.0-4.0)	18.2 (50)	7.82 (21)	0.22 (76)
ING114819	Healthy adult/ 38	Oral Tablet	50 mg (+iohexol and PAH infusion)/ 11	QD x 14 days	2.83 (27)	NR	39.1 (38)	NR	0.84 (61)
			50 mg (+iohexol and PAH infusion)/ 11	BID x 14 days	5.50 (34)	NR	51.6 (36)	NR	3.02 (40)

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING115696	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	4.27 (25)	4.0 (1.0-4.0)	58.6 (32)	13.8 (21)	1.32 (40)
			50 mg (+prednisone)/ 12	QD x 10 days (Day 5)	4.47 (31)	3.5 (1.0-4.0)	65.9 (37)	15.2 (17)	1.59 (47)
			50 mg (+prednisone)/ 12	QD x 10 days (Day 10)	4.54 (29)	3.5 (1.0-4.0)	65.0 (37)	14.6 (24)	1.53 (50)
ING115697	Healthy adult/ 32	Oral Tablet	50 mg/ 16 (Cohort 1)	QD x 5 days	4.62 (21)	2.50 (1.0, 4.0)	61.5 (27)	13.2 (18)	1.31 (38)
			50 mg/ 16 (Cohort 2)	QD x 5 days	4.99 (23)	3.00 (1.0, 4.0)	68.9 (25)	14.5 (19)	1.59 (35)
			50 mg (+BCV 800 mg)/ 13	QD (+q8h BCV) x 10 days	4.82 (17)	3.00 (1.0, 4.0)	65.3 (22)	13.8 (19)	1.40 (36)
			50 mg (+TVR 750 mg)/ 15	QD (+ q8h TVR) x 10 days	5.81 (15)	4.00 (1.1, 4.0)	84.2 (21)	16.7 (18)[d]	2.09 (28)
ING115698	Healthy adult/ 11	Oral Tablet	50 mg (+methadone)/ 11	BID x 5 days	4.88 (35)	NR	44.3 (37)	NR	2.63 (41)
LAI116181	Healthy adult/ 28	Oral Tablet	50 mg/ 16	QD x 5 days	3.46 (30)	3.50 (1.0-4.0)	48.8 (35)	NR	1.07 (45)
			50 mg (+RPV 25 mg)/ 16	QD x 5 days	3.90 (25)	3.50 (1.0-4.0)	54.7 (33)	NR	1.31 (46)
200901	Healthy adult/ 16	Oral Tablet	50 mg/ 16	QD x 5 days	4.16 (14.4)	3.01 (2.00-6.00)	53.8 (21.4)	12.9 (23.8)	1.20 (39.1)
			50 mg (+ CBZ 300 mg/ 14	QD (+ CBZ BID) x 5 days	2.77 (25.0)	2.50 (1.00-6.00)	27.4 (22.1)	7.31 (16.9)	0.325 (45.9)
201102	Healthy adult/ 12	Oral Tablet	50 mg/ 12	QD x 5 days	2.65 (32.0)	2.00 (1.00, 4.00)	35.7 (34.7)	13.9 (32.8)	0.771 (41.3)
			50 mg (+ DCV 60 mg/ 12	QD x 5 days	3.43 (24.5)	2.00 (1.00,3.00)	47.3 (26.3)	16.2 (32.6)	1.11 (36.6)
201167	Healthy adult/ 15	Oral Tablet	50 mg (+ Metformin 500 mg/ 14	QD (+ Metformin BID) x 7 days	3.81 (27.7)	4.00 (1.00, 11.9)	54.6 (25.7)[e]	NR	1.25 (33.7)
			50 mg (+ Metformin 500 mg/ 14	BID x 7 days	6.81 (19.3)	2.50 (1.00, 4.00)	65.6 (23.8)	NR	4.37 (31.0)

a. Data presented are geometric mean (%CVb) except for tmax where median (range) are presented
b. Data presented as C0avg
c. Data presented as C0
d. N = 14
e. For 1 subject, AUClast with last observed concentration at 11.93 hr post-dose was used as AUC(0-τ)as there were not enough data points in the terminal phase to estimate AUC(0-τ).

ATV = Atazanavir; BCV = Boceprevir; BID = Twice Daily; CBZ = Carbamazepine; DCV = Daclatasvir; DRV = Darunavir; ETR = Etravirine; FPV = Fosamprenavir; LPV = Lopinavir; MDZ = Midazolam; N/A = Not applicable; NR = Not reported; OC = Oral contraceptive; PAH = Para-aminohippurate; QD = Once daily; RBT = Rifabutin; RIF = Rifampin; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir; TPV = Tipranavir

Appendix Table 4.4 Summary of Repeat Dose Rilpivirine Pharmacokinetic Parameters

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]						
					tmax (h)	C0h (ng/mL)	Cmin (ng/mL)	Cmax (ng/mL)	Css,av (ng/mL)	AUC24h (ng.h/mL)	t1/2 (h)
TMC278-C103	Healthy adults/48	Phase IIb Oral Tablet	25 mg/12	QD × 1 day	4.0	NA	NA	90	NA	1072	NA
				QD × 14 days	4.0	90	67	204	108	2589	51
			50 mg/12	QD × 1 day	4.0	NA	NA	138	NA	1551	NA
				QD × 14 days	4.0	158	116	299	172	4139	49
			100 mg/12[b]	QD × 1 day	4.0	NA	NA	398	NA	4464	NA
				QD × 14 days	4.0	348	249	685	387	9278	46
			150 mg/12[c]	QD × 1 day	4.0	NA	NA	524	NA	5608	NA
				QD × 14 days	4.0	505	362	1019	566	13581	45
TMC278-C104	Healthy adults/16	Phase IIb Oral Tablet	150 mg/16	QD × 7 days	4.0	500	409	1005	617	14805	NA
			150 mg (+TDF 300 mg)/16	QD (+TDF 300 QD) × 16 days	4.0	467	391	921	600	14404	NA
TMC278-C106	Healthy adults/26	Phase IIb Oral Tablet	150 mg/14	QD × 7 days	4.0[d]	542	491	1366[d]	762	18286	NA
			150 mg (+ddI 400 mg)/21	QD (+ddI QD) × 14 days	4.0	644	527	1379	768	18429	NA
TMC278-C105	Healthy adults/16	Phase IIb Oral Tablet	150 mg/15	QD × 10 days	5.0	507	479	1265	824	19770	NA
			150 mg (+LPV/RTV 400/100 mg)/15	QD (+LPV/RTV 400/100 BID) × 20 days	4.0	972	809	1619	1250	29990	NA
TMC278-C112	Healthy adults/16	Phase IIb Oral Tablet	150 mg/14	QD × 11 days	4.0	416	360	991	531	12740	NA
			150 mg (+ DRV/RTV 800/100 mg)/14	QD (+DRV/RTV QD) × 22 days	4.0	1233	1013	1860	1276	30630	NA
R278474-C108	Healthy adults/16	Oral Solution	150 mg/15	QD × 7 days	4.0	545	478	1123	669	16051	NA
			150 mg (+RIF 600 mg)/16	QD (+RIF QD) × 7 days	4.0	56.7	53	356	134	3218	NA
TMC278-C125	Healthy adults/18	Phase IIb Oral Tablet	150 mg/14	QD × 11 days	5.0	434	364	992	633	15184	NA
			150 mg (+ RBT 300 mg)/16	QD (+RBT QD) × 11 days	5.0	229	187	683	362	8692	NA

Study	Population/ No. of Subjects	Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a]						
					tmax (h)	C0h (ng/mL)	Cmin (ng/mL)	Cmax (ng/mL)	Css,av (ng/mL)	AUC24h (ng.h/mL)	t1/2 (h)
TMC278-C127	Healthy adults/16	Phase IIb Oral Tablet	150 mg/15	QD × 11 days	5.0	462	379	1015	623	14960	NA
			150 mg (+ KTZ 400 mg)/14	QD (+KTZ QD) × 22 days	7.0	844	674	1385	983	23590	NA
TMC278-TiDP6-C123	Healthy adults/16	Phase III Oral Tablet	75 mg/16	QD × 12 days	5.0	202	177	460	272	6517	NA
			75 mg (+ sildenafil 50 mg)/16	QD (+sildenafil SD) × 12 days	4.0	210	187	428	271	6504	NA
TMC278-C116	Healthy adults/16	Phase IIb Oral Tablet	150 mg/16	QD × 15 days	4.0	452	382	887	589	14130	NA
			150 mg (+atorvastatin 40 mg)/16	QD (+atorvastatin QD) × 4 days	5.0	430	346	844	546	13110	NA
TMC278-C114	Healthy adults/16	Phase IIb Oral Tablet	150 mg/16	QD × 11 days	4.0	621	507	1205	781	18730	NA
			150 mg (+ OMP 20 mg)/15	QD (+OMP QD) × 22 days	4.0	431	347	779	497	11920	NA
TMC278-C109	Healthy adults/16	Phase IIb Oral Tablet	150 mg/16	QD × 11 days	4.0	390	323	937	533	12799	NA
			150 mg (+paracetamol 500 mg)/16	QD (+paracetamol SD) × 1 day	3.0	461	403	1015	612	14679	NA
TMC278-TiDP6-C152	Healthy adults/60	Phase III Oral Tablet	25 mg/57	QD × 11 days	5.0	132	95	247	139	3324[e]	NA
TMC278IFD1003	Healthy adults/20	Phase III Oral Tablet	25 mg/18	QD × 11 days	4.0	113	88	211	135	3249	55
			50 mg (+RBT 300 mg)17	QD (RBT QD × 17 days) × 11 days	4.0	109	86	303	158	3781	30
			25 mg (+RBT 300 mg)17	QD (RBT QD × 17 days) × 11 days	5.0	59	49	148	82	1965	40
TMC278IFD1004	Healthy adults/20	Phase III Oral Tablet	25 mg/	QD (+metformin SD Day 1) × 12 days	4.0	84	63	155	92	2203	NA

a. Data presented are least squares mean except for tmax where median is presented.
b. For the parameters of Day 10 until Day 14: n=11
c. For the parameters of Day 7 until Day 14: n=11
d. For Cmax and tmax, n =15
e. n = 56

ddI = Didanosine; DRV = Darunavir; KTZ = Ketoconazole; LPV= Lopinavir; NA = Not available; OMP = Omeprazole; QD = Once daily; RBT = Rifabutin; RIF = Rifampin; RTV = Ritonavir; SD = Single dose; TDF = Tenofovir disoproxil fumarate

Appendix Table 5 Summary of Pharmacokinetic Parameters of Co-administered Drugs

Appendix Table 5.1 Summary of Pharmacokinetic Parameters of Co-administered Drugs with Dolutegravir

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING111322	Healthy adult/ 32	MDZ/ Oral Tablet	3 mg/ 10	Single dose	NR	NR	0.0163 (23)[b]	NR	NR
			3 mg (+25 mg DTG)/ 10	Single dose (DTG once daily x 10 days)	NR	NR	0.0154 (41)[b]	NR	NR
ING111405	Healthy adult/ 31	LPV/ Oral Tablet	400 mg (+100 mg RTV + 30 mg DTG)/ 15	BID (RTV BID, DTG once daily) x 14 days	11.5 (22)	NR	95.8 (25)	NR	4.52 (43)
		DRV/ Oral Tablet	600 mg (+100 mg RTV + 30 mg DTG)/ 15	BID (RTV BID, DTG once daily) x 14 days	5.811 (23)	NR	46.5 (29)	NR	2.190 (47)
		RTV/ Oral Tablet	100 mg (+400 mg LPV + 30 mg DTG)/ 15	BID (LPV BID, DTG once daily) x 14 days	0.884 (36)	NR	4.59 (33)	NR	0.115 (50)
		RTV/ Oral Tablet	100 mg (+600 mg DRV + 30 mg DTG)/ 15	BID (DRV BID, DTG (once daily) x 14 days	0.815 (32)	NR	5.42 (25)	NR	0.202 (34)
ING111603	Healthy adult/ 16	ETR/Oral Tablet	200 mg (+50 mg DTG)/ 15	BID (DTG once daily) x 14 days	1.12 (28)	NR	10.3 (24)	NR	0.638 (24)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING111604	Healthy adult/ 16	TDF/Oral Tablet	300 mg/ 15	Once daily x 7 days	0.274 (34)	1.00 (1.00-2.00)	2.45 (41)	NR	0.0472 (49)
			300 mg (+DTG 50 mg)/ 15	Once daily x 5 days	0.300 (34)	1.00 (1.00-4.03)	2.74 (39)	NR	0.0560 (46)
ING111854	Healthy adult/ 24	ATV/Oral Tablet	400 mg (+100 mg RTV + 30 mg DTG)/ 12	Once daily x 14 days	5.39 (26)	NR	53.08 (31)	NR	1.08 (42)
			400 mg (+ 30 mg DTG)/ 12	Once daily x 14 days	4.85 (42)	NR	27.49 (45)	NR	0.19 (84)
ING111855	Healthy adult female/ 16	NGMN (as Ortho-Cyclen)/ Oral Tablet	0.25 mg (+ 0.035 mg EE +50 mg DTG)/ 15 Analyte: NGMN	Once daily (DTG BID) x 10 days	0.00142 (18)	1.50 (1.0-2.5)	0.0138 (16)	22.02 (19)	NR
		NGMN (as Ortho-Cyclen)/ Oral Tablet	0.25 mg (+ 0.035 mg EE)/ 15 Analyte: NGMN	Once daily x 10 days	0.00159 (30)	1.00 (1.0-3.0)	0.0141 (25)	22.29 (32)	NR
		EE (as Ortho-Cyclen)/ Oral Tablet	0.035 mg (+0.25 mg NGMN +50 mg DTG)/ 15	Once daily (DTG BID) x 10 days	0.000100 (22)	1.00 (0.5-2.5)	0.000952 (19)[c]	14.39 (19)[c]	NR
		EE (as Ortho-Cyclen)/ Oral Tablet	0.035 mg (+0.25 mg NGMN)/ 15	Once daily x 10 days	0.000101 (25)	1.00 (0.5-2.0)	0.000916 (27)	13.60 (24)	NR

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING112934	Healthy adult/ 17	ETR/Oral Tablet	200 mg (+400 mg LPV +100 mg RTV + 50 mg DTG)/ 8	BID (LPV, RTV BID; DTG once daily) x 14 days	0.974 (73)	4.00 (2.00-4.00)	8.834 (79)	NR	0.585 (93)
			200 mg (+ 600 mg DRV +100 mg RTV + 50 mg DTG)/ 9	BID (DRV, RTV BID; DTG once daily) x 14 days	0.886 (32)	4.00 (3.00-4.00)	7.691 (34)	NR	0.495 (42)
ING113068	Healthy adult/ 12	FPV/Oral Tablet	700 mg (+100 mg RTV +50 mg DTG)/ 12 Analyte: amprenavir	BID (RTV BID, DTG QD) x 10 days	6.34 (28.1)	1.00 (0.50-2.00)	40.9 (35.8)	8.35 (45.9)	1.91 (59.4)
ING114005	Healthy adult/ 12	EFV/Oral Tablet	600 mg (+50 mg DTG)/ 12	Once daily x 14 days	6.02 (40)	NR	84.18 (62)	22.17 (54)	2.41 (80)
			600 mg (+50 mg DTG; CYP2B6*6 subjects)/ 3	Once daily x 14 days	9.50 (27)	NR	173.78 (26)	39.09 (34)	5.85 (25)
			600 mg (+50 mg DTG; CYP2B6*1/*6 subjects)/ 6	Once daily x 14 days	4.52 (17)	NR	55.69 (28)	15.61 (24)	1.45 (40)
ING115697	Healthy adult/ 32	TVR/Oral Tablet	750 mg (+50 mg DTG)/ 15 (except n=10 for T1/2)	q8h (DTG once daily) x 10 days	3.21 (17)	3.00 (2.0-4.0)	19.22 (19)	5.14 (27)	1.75 (26)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
ING115698	Healthy adult/ 11	Methadone/Oral Tablet	Individualized doses/ 11 Analyte: R-methadone	Once daily x 3 days	0.150 (81.4)	NR	2.51 (77.9)	NR	0.082 (79.9)
			Individualized doses (+50 mg DTG) / 11 Analyte: R-methadone	Once daily (DTG BID) x 5 days	0.145 (78.5)	NR	2.39 (77.7)	NR	0.078 (80.6)
			Individualized doses/ 11 Analyte: S-methadone	Once daily x 3 days	0.188 (91.4)	NR	2.79 (90.3)	NR	0.0838 (97.3)
			Individualized doses (+50 mg DTG) / 11 Analyte: S-methadone	Once daily (DTG BID) x 5 days	0.195 (82.3)	NR	2.81 (85.4)	NR	0.0847 (92.7)
			Individualized doses/ 11 Analyte: total methadone	Once daily x 3 days	0.337 (86.5)	NR	5.32 (83.2)	NR	0.166 (86.9)
			Individualized doses (+50 mg DTG) / 11 Analyte: total methadone	Once daily (DTG BID) x 5 days	0.337 (80.1)	NR	5.23 (80.6)	NR	0.164 (84.9)
LAI116181	Healthy adult/ 28	RPV/Oral Tablet	25 mg/ 16 (Cohort 1, Period 2)	Once daily x 11 days	0.148 (29)	4.00 (4.0-6.0)	2.23 (33)	NR	0.0745 (41)
			25 mg (+50 mg DTG)/ 16 (Cohort 1, Period 3)	Once daily x 5 days	0.164 (36)	4.00 (2.0-5.0)	2.37 (34)	NR	0.0905 (48)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug				
					Cmax (μg/mL)	tmax (h)	AUC (0-τ) (μg.h/mL)	T1/2 (h)	Cτ (μg.mL)
201102	Healthy adult/ 12	DCV/Oral Tablet	60 mg/ 12	QD x 5 days	1.19 (42.6)	1.01 (1.00, 6.00)	11.4 (47.9)	8.58 (23.2)	0.166 (69.3)
			60 mg (+ DTG 50 mg/ 12	QD x 5 days	1.22 (42.2)	1.00 (0.50, 4.00)	11.2 (41.6)	8.42 (29.4)	0.176 (53.8)
201167	Healthy adult/ 15	Metformin/Oral Tablet	500 mg/ 15 (Cohort 1, Period 1)	BID x 5 days	0.932 (26.2)	4.00 (1.00, 6.00)	6.82 (26.5)	3.97 (18.2)	NR
			500 g/ 14 (+50 mg DTG) (Cohort 1, Period 2)	BID (DTG QD) x 7 days	1.55 (22.6)	4.00 (1.00, 6.03)	12.2 (23.1)	4.33 (24.0)	NR
			500 mg/ 14 (Cohort 1, Period 3)	BID x 10 days	0.979 (31.1)	4.00 (1.00, 6.00)	7.55 (28.1)	4.60 (35.8)	NR
			500 mg/ 15 (Cohort 2, Period 1)	BID x 5 days	0.875 (24.3)	4.00 (1.50, 8.00)	6.49 (16.0)[d]	4.27 (26.5)c	NR
			500 mg/ 14 (+50 mg DTG) (Cohort 1, Period 2)	BID (DTG QD) x 7 days	1.85 (13.1)	4.00 (1.00, 6.00)	15.9 (15.9)	4.89 (19.6)	NR
			500 mg/ 13 (Cohort 1, Period 3)	BID x 10 days	0.872 (14.8)	4.00 (2.00, 8.00)	6.69 (16.4)	4.48 (24.3)[e]	NR

a. Data presented are geometric mean (%CVb) except for tmax where median (range) is presented.
b. Presented as AUC(0-t).
c. N = 14
d. For 1 subject, AUClast with last observed concentration at 11.93 hr post-dose was used as AUC(0-τ)as there were not enough data points in the terminal phase to estimate AUC(0-τ).
e. PK Parameter could not be calculated for 1 subject

ATV = Atazanavir; BID = Twice daily; DRV = Darunavir; EE = Ethinyl estradiol; EFV = Efavirenz; ETR = Etravirine; FPV=Fosamprenavir; LPV= Lopinavir; NGMN = Norelgestromin/ Norgestimate; MDZ = Midazolam; NR = Not reported; OC = Oral contraceptive; PAH = Para-aminohippurate; Q8h = Dosed every 8 hours (three times daily); QD = Once daily; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir; TPV = Tipranavir.

Appendix Table 5.2 Summary of Pharmacokinetic Parameters of Co-administered Drugs with Rilpivirine

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug			
					Cmax (ng/mL)	tmax (h)	AUC24h (ng.h/mL)	Cmin (ng/mL)
R278474-C101	HIV-1 infected adults/15	EFV/Oral Tablet	600 mg (+50 mg RPV)/7	Once daily (RPV SD) × 6 days	172 (21)	4.0 (4.0 - 4.0)	2150 (34)[b]	NA
		NVP/Oral Tablet	200 mg (+50 mg RPV)/8	Once daily (RPV SD) × 6 days	219 (18)	4.0 (4.0 - 8.0)	6949 (24)[b]	NA
TMC278-C104	Healthy adults/16	TDF/Oral Tablet	300 mg (+150 mg RPV)/15	Once daily (RPV once daily) × 16 days	347 (18)	2.50 (1.0 - 4.0)	3519 (22)	65 (29)
TMC278-C106	Healthy adults/26	ddI/Oral Capsule	400 mg (+150 mg RPV)/13	Once daily (RPV once daily) × 14 days	1197 (34)	2.00 (1.00 - 3.00)	3989 (28)	NQ
TMC278-C105	Healthy adults/26	LPV/Oral Capsule	400 mg (+150 mg RPV)/15	BID (RPV once daily) × 20 days	12990 (23)	4.0 (1.0 - 5.0)	109800 (29)[c]	5011 (45)
		RTV/Oral Capsule	100 mg (+150 mg RPV)/15		978 (39)	4.0 (3.0 - 5.0)	5459 (40)[c]	148 (56)
TMC278-C112	Healthy adults/16	DRV/Oral Capsule	800 mg (+150 mg RPV)/14	Once daily (RPV once daily) × 22 days	6537 (21)	3.0 (1.0 - 4.0)	68820 (30)	1257 (44)
		RTV/ Oral Capsule	100 mg (+150 mg RPV)/14		510 (50)	4.5 (2.0 - 6.0)	3811 (38)	24 (51)
R278474-C108	Healthy adults/16	RIF/Capsule	600 mg (+150 mg RPV)/16	Once daily (RPV once daily) × 7 days	8.7[d] (36)	3.0 (2.0 - 6.0)	41[e] (42)	NA
		25-desacetyl-RIF/ Capsule			0.71[d] (50)	3.5 (2.0 - 6.0)	3.6[e] (56)	NA
TMC278-C125	Healthy adults/16	RBT/ Oral Capsule	300 mg (+150 mg RPV)/16	Once daily (RPV once daily) ×	401 (26)	4.5 (2.0 - 6.0)	3990 (26)	60 (39)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug			
					Cmax (ng/mL)	tmax (h)	AUC24h (ng.h/mL)	Cmin (ng/mL)
		25-*O*-desacetyl-RBT/Oral Capsule		11 days	30 (43)	5.0 (3.0 - 5.0)	286 (55)	3.65 (47)
TMC278-C127	Healthy adults/16	KTZ/Oral Tablet	400 mg (+150 mg RPV)/14	Once daily (RPV once daily) × 22 days	7.5[d] (16)	4.0 (3.0 - 12.0)	62[e] (20)	0.11[f] (66)
TMC278-TiDP6-C123	Healthy adults/16	Sildenafil/Oral Tablet	50 mg (+75 mg RPV)/16	SD (RPV once daily × 12 days)	125 (31.23)	2.0 (0.5 - 3.0)	508.1[g] (30.06)	NA
		N-desmethyl Sildenafil/Oral Tablet			79.60 (50.02)	2.0 (0.5 - 3.0)	297.7[g] (47.77)	NA
TMC278-C116	Healthy adults/16	Atorvastatin/ Oral Tablet	40 mg (+150 mg RPV)/16	Once daily (RPV once daily) × 4 days	16 (52)	3.0 (0.5 - 5.0)	92 (60)	0.84 (68)
		Atorvastatin lactone/ Oral Tablet			6.7 (65)	5.0 (1.0 - 5.0)	66 (61)	0.74 (62)
		2-hydroxy-atorvastatin/Oral Tablet			11.5 (43)	5.0 (0.5 - 6.0)	103 (47)	1.22 (45)
		4-hydroxy-atorvastatin/Oral Tablet			0.87 (54)	5.0 (0.5 - 16.0)	11.4 (49)	0.26 (77)
		Total HMG CoA reductase activity/Oral Tablet			27 (45)	NR	209 (51)	2.43 (56)
TMV278-C120	Healthy adults/15	EE/Oral Tablet	35 μg (+150 mg RPV)/15	Once daily (RPV once daily) ×	93[h] (33)	4.0 (1.0 - 6.0)	1179[j] (27)	22[j] (36)

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug			
					Cmax (ng/mL)	tmax (h)	AUC24h (ng.h/mL)	Cmin (ng/mL)
		Norethindrone/ Oral Tablet	1 mg (+150 mg RPV)/15	21 days	9.4 (32)	2.0 (1.0 - 4.0)	100 (29)	1.6 (42)
TMC278-TiDP6-C136	Healthy adults/18	EE/Oral Tablet	35 μg (+25 mg RPV)/15	Once daily (RPV once daily) × 21 days	90.15[h] (29.96)	1.5 (1.0-4.0)	1063[i] (24.86)	22.77[j] (30.88)
		Norethindrone/ Oral Tablet	1 mg (+25 mg RPV)/15		12630[h] (30.74)	1.5 (1.0 - 4.0)	122700[i] (31.26)	1716[j] (52.76)
TMC278-TiDP6-C121	Healthy subjects/13	R-Methadone/ Oral Tablet	Individualized dose 60-100 mg (+25 mg RPV)/12	Once daily (RPV once daily) Day -14 to 12	258.9 (39.09)	2.5 (1.15 - 6.0)	4398 (43.78)	142.2 (50.96)
		S-Methadone/ Oral Tablet			293.8 (38.99)	2.5 (1.2 - 6.0)	4364 (47.25)	126.7 (58.18)
TMC278-C114	Healthy subjects/16	OMP/Oral Tablet	20 mg (+150 mg RPV)/15	Once daily (RPV SD) × 11 days	346 (63)	4.0 (1.0 - 6.0)	956 (85)	0
		5-hydroxy-OMP/ Oral Tablet			175 (39)	5.0 (1.0 - 6.0)	612 (28)	0
		OMP sulfone/ Oral Tablet			79 (59)	5.0 (2.0 - 9.0)	568 (99)	2.00 (169)
		OMP/Oral Tablet	20 mg (+150 mg RPV)/15	Once daily (RPV once daily) × 22 days	314 (62)	4.0 (2.0 - 6.0)	824 (93)	0
		5-hydroxy-OMP/ Oral Tablet			180 (40)	4.0 (2.0 - 6.0)	630 (28)	0
		OMP sulfone/ Oral Tablet			74 (70)	5.0 (3.0 - 6.0)	458 (111)	0
TMC278-C109	Healthy adults/16	Paracetamol/ Oral Tablet	500 mg (+150 mg RPV)/16	SD (RPV once daily × 11 days)	5.48[d] (36)	1.0 (0.3 - 2.0)	20.16[b,e] (22)	NR
		Paracetamol glucuronide/ Oral Tablet			8.22 (20)	3.0 (2.0 - 4.0)	60 (21)	NR

Study	Population/ No. of Subjects	Co-administered Drug/Route of Administration/ Dosage Form	Dose/ No. of Subjects	Regimen	Parameter[a] of Co-administered Drug			
					Cmax (ng/mL)	tmax (h)	AUC24h (ng.h/mL)	Cmin (ng/mL)
		Paracetamol sulfate/ Oral Tablet			3.22[d] (22)	2.0 (1.0 - 3.0)	18[b, e] (23)	NR
TMC278-C139	Healthy adults/25	Chlorzoxazone/ Oral Caplet	500 mg (+150 mg RPV)/9	SD (RPV SD)	14[d] (32)	1.5 (1.0 - 3.0)	34[b, e] (27)	NR
		6-hydroxy-chlorzoxazone/ Oral Caplet			0.29[d] (31)	2.0 (1.0 - 3.0)	1.00[b,e]. (34)	NR
		Chlorzoxazone/ Oral Caplet	500 mg (+150 mg RPV)/16	SD (RPV once daily × 16 days)	14[d] (19)	1.5 (0.5 - 3.0)	36[b, e] (17)	NR
		6-hydroxy-chlorzoxazone/ Oral Caplet			0.28[d] (29)	1.75 (0.5 - 3.0)	1.03[b, e] (31)	NR
TMC278-TiDP6-C153	Healthy adults/24	RAL/Oral Tablet	400 mg (+ 25 mg RPV)/23	BID (RPV once daily) × 15 days	1248 (94.52)	3.0 (1.0 - 12.0)	4736[c] (76.79)	56.36 (95.59)
TMC278IFD1001	Healthy adults/22	Digoxin/Oral Tablet	0.5 mg (+ 25 mg RPV)/22	SD (RPV once daily × 16 days)	1.93 (33.1)	1.74 (0.65 - 3.02)	4736 (76.79)	NA
TMC278IFD1004	Healthy adults/20	Metformin/ Oral Tablet	850 mg (25 mg RPV)/20	SD (RPV once daily × 12 days)	1285 (20)	3.0 (1.0 -5.0)	8793[g] (19)	NA

a. Data presented are geometric mean (%CVb) except for tmax where median (range) is presented
b. AUC = AUC∞
c. AUC = AUC12h
d. Cmax presented as μg/mL
e. AUC presented as μg.h/mL
f. Cmin presented as μg/mL
g. AUC = AUClast
h. Cmax presented as pg/mL
i. AUC presented as pg.h/mL
j. Cmin presented as pg/mL

ATV = Atazanavir; BID = Twice daily; DRV = Darunavir; EE = Ethinyl estradiol; EFV = Efavirenz; ETR = Etravirine; FPV=Fosamprenavir; LPV= Lopinavir; MDZ = Midazolam; NGMN = Norelgestromin/Norgestimate; NA = Not available; NQ = Not quantifiable; NR = Not reported; OC = Oral contraceptive; PAH = Para-aminohippurate; q8h = Dosed every 8 hours (three times daily); RAL = Raltegravir ; RPV = Rilpivirine; RTV = Ritonavir; TDF = Tenofovir disoproxil fumarate; TVR = Telaprevir; TPV = Tipranavir.

Module 2.7.2.4

Special Studies

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ABBREVIATIONS

AAG	α_1-acid glycoprotein
ABC	Abacavir
ADA	HIV strain
AIDS	Acquired immunodeficiency syndrome
APV	Amprenavir
AVR	Antiviral
ARV	Antiretroviral
AZT	Azidothymidine
BID	Twice daily (bis in die)
BL	Baseline
BVDV	Bovine Viral Diarrhea Virus
CAR	Current Antiretroviral Regimen
CBMC	Umbilical cord blood mononuclear cells
CC50	Cell cytotoxicity 50%
CCR5	Chemokine receptor 5
CDC	Centers for Disease and Prevention Control
CI	Confidence Interval
CIP4	Cell line derived from 293T cells
c/mL	Copies per milliliters
CSR	Clinical study report
CVW	Confirmed Virologic Withdrawal
D4T	Stavudine
DBF	Database freeze
DDI	Dideoxyinosine
DNA	Deoxyribonucleic acid
DRV/r	Darunavir + ritonavir
DTG	Dolutegravir
EC50	Effective Dose 50
EFV	Efavirenz
ETR	Etravirine
EVG	Elvitegravir
FC	Fold Change
FDA	Food and Drug Administration
FPV	Fosamprenavir
FTC	Emtricitabine
g	Gram
GLP	Good Laboratory Practice
GSK	GlaxoSmithKline
GSS	Genotypic susceptibility score
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCMV	Human Cytomegalovirus
HeLa CD4	Human cell line
HIV-1	Human Immunodeficiency Virus type 1

HSV	Herpes simplex virus
IAS	International AIDS Society
IC50	50% Inhibitory Concentration
ICH	International Conference on Harmonisation
IDV	Indinavir
IN	Integrase
INI	Integrase Inhibitor
INSTI	INtegrase Strand Transfer Inhibitor
IP	Investigational product
IQR	Interquartile range
ITT-E	Intent to treat exposed
LPV	Lopinavir
Magi CCR5	Cells obtained through the NIH AIDS Research and Reference Reagent Program
[redacted]	[redacted]
mg	Milligrams
mL	Millilitre
MOI	Multiplicity of infection
Molt-4	Human T cell lymphocytic leukemia cell line
MT-2	Human T cell lymphocytic leukemia cell line
MT4	Human T cell lymphocytic leukemia cell line
MVC	Maraviroc
M8166	Human T cell lymphocytic leukemia cell line
NIH	National Institutes of Health
nM	Nano molar
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
N(t)RTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
PBMC	Peripheral Blood Mononuclear Cells
PDVF	Protocol Defined Virologic Failure
PHA	Phytohemagglutinin
PHIV	Pseudotyped HIV
PI	Protease Inhibitor
pPVW	Potential Precautionary Virologic Withdrawal
PRO	Protease
PSS	Phenotypic susceptibility score
PSSf	PSS with full sensitivity only
PVW	Precautionary Virologic Withdrawal
RAP	Reporting and analysis plan
RAL	Raltegravir
RAM	Resistance Associated Mutation
RNA	Ribonucleic acid
RPV	Rilpivirine
RT	Reverse Transcriptase
RTV, /r	Ritonavir

SDM	Site Directed Mutant
SE	Single Entity
[redacted]	[redacted]
[redacted]	[redacted]
SQV	Saquinavir
SVW	Suspected Virologic Withdrawal
T-20	Enfuvirtide
TDF	Tenofovir disoproxil fumarate
TFV	Tenofovir
TLOVR	Time to Loss of Virological Response
TPV	Tipranavir
TZM-bl	Cells obtained through the NIH AIDS Research and Reference Reagent Program
USA	United States of America
VF	Virologic Failure
VFres	Virologic Failure, rebounjder
VFss	Virologic Fairlure Snapshot
VL	Viral Load
VZV	Varicella Zoster Virus
µg	Microgram
3TC	Lamivudine

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1. BACKGROUND AND OVERVIEW OF CLINICAL PHARMACOLOGY

This section is not applicable.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

This section is not applicable.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS

This section is not applicable.

4. SPECIAL STUDIES

Where no studies have been performed with dolutegravir (DTG) and rilpivirine (RPV), summaries of previously submitted non-clinical and clinical virology studies from DTG or RPV single entity (SE) development programs support this application and are categorized as "key" studies or "supportive" studies. Virology data from these key or supportive studies are incorporated via cross reference to the previously approved DTG and RPV SE marketing applications (m1.4.4).

4.1. Nonclinical Virology - Dolutegravir

Dolutegravir (DTG) inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral DNA integration which is essential for the HIV replication cycle.

Dolutegravir has low nM activity against wild type human immunodeficiency virus type 1 (HIV-1) and HIV-2 in a variety of cell lines, regardless of subtype. DTG has little activity against non-HIV viruses. Human serum causes approximately 75-fold increase in DTG 50% inhibitory concentration (IC_{50}) against HIV-1. DTG is additive or synergistic when assayed in combination with other antiretroviral agents.

When HIV-1 Strain IIIB was passaged in the presence of DTG for 112 days, viruses with a 4.1-fold maximum increase in IC_{50} and S153Y or S153F substitutions in the integrase gene were observed. Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM DTG selected for E92Q [Fold Change (FC)=3.1] and G193E (FC=3.2) substitutions in the integrase (IN) region on Day 56. Passage of HIV-1 NL432 with Q148H, Q148K, or Q148R raltegravir (RAL) resistant mutations resulted in selection of additional mutations and an increase in DTG FC relative to wild type. Passage of HIV-1 NL432 with E92Q, Y143C, Y143R or N155H RAL resistant mutations did not lead to additional substitutions. Passage of HIV-1 subtypes B, and A/G in TZM-bl cells selected for integrase mutation R263K. The single R263K substitution did not alter susceptibility to integrase inhibitors, giving a FC of 1.5, 0.81 and 1.3 for DTG, RAL and elvitegravir (EVG), respectively.

Comparative susceptibilities to DTG and RAL were obtained from 60 RAL resistant site directed HIV-1 mutants and 6 site directed HIV-2 mutants. DTG retained activity against a vast majority of these mutants, and had similar activity for equivalent mutants for both HIV-1 and HIV-2. Additionally, susceptibilities to DTG and RAL were determined for over 700 RAL resistant clinical isolates, with DTG retaining activity <10 FC against >90% of them. Dolutegravir has a <10 FC against 67 (73%) of the 92 clinical isolates with Q148 + ≥2 integrase strand transfer inhibitor (INSTI)-resistance substitutions and 168 (91%) of the 184 isolates with Q148 + 1 INSTI resistance substitutions.

Evaluation of ~1000 RAL- resistant isolates from [redacted] clinical isolate library collected from [redacted] to [redacted] demonstrated a decreasing proportion of Q148+≥2 pathway isolates over time. Of 104 RAL-resistant isolates in the Q148+≥2 pathway (using the original broad listing of secondary RAL-resistance mutations), just 62 (59.6%) harboured two of the key secondary resistance mutations L74I, E138A/K/T, G140A/C/S associated with decreased response in ING112574.

The dissociation of DTG, RAL, and EVG from wild type and mutant IN proteins complexed with DNA was investigated to obtain a better understanding of integrase inhibitor (INI) dissociation kinetics. DTG demonstrated slower dissociation from all IN-DNA complexes tested, including those with single, double, and up to four residues clinically relevant IN substitutions; these studies provide a mechanism-based explanation for differences in the in vitro and clinical profiles of DTG versus RAL and EVG.

Clonal analyses of isolates from Viking 3 (ING112574) provided information that the INI-associated resistance mutations reside on the same subset of viral genomes and that this accumulation of INI-associated resistance mutations results in the reduction of DTG susceptibility. Emergent integrase substitutions between Day 1 and Day 11 have been observed in subjects in the placebo arm of a 10 day DTG monotherapy study; these substitutions typically were mixture changes at a given position each present once across five of six placebo subjects, and two placebo subjects had emergent substitutions at position 196 in the integrase open reading frame. This is indicative of the high variability in HIV-1 genotype even in the absence of INI selective pressure over time. Polymorphisms at the most variable positions in wild type IN do not reduce susceptibility to DTG.

A series of in vitro studies have been conducted to investigate the virology of DTG. A listing of these studies is provided in Table 1.

Table 1 List of Virology (Primary Pharmacodynamic) Non-Clinical Studies Performed with DTG

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility
Antiviral mechanistic study using quantitative PCR GSK Document Number RH2010/00018/00 Complete	MT-4 cells	In vitro	B	No	[redacted]
Anti-HIV activity in peripheral blood mononuclear cells (PBMCs) GSK Document Number RH2007/00071/00 GSK Document Number RH2007/00116/00	Human PBMCs	In vitro	B	No	GSK and [redacted]
Antiviral activity in tissue culture cells GSK Document Number RH2007/00071/00 GSK Document Number RH2007/00116/00	Human MT-4 and CIP-4 cells	In vitro	B	No	GSK and [redacted]
Integrase inhibition in strand transfer assays GSK Document Number RH2007/00071/00 and GSK Document Number RH2007/00116/00	Recombinant HIV integrase	In vitro	B	No	GSK and [redacted]
Anti-HIV activity in the presence of human serum and purified human serum proteins GSK Document Number RH2007/00071/00 GSK Document Number RH2007/00116/00 Completed	Human MT-4 and CIP-4 cells	In vitro	B	No	GSK and [redacted]
Anti-HIV activity in combination with other antiviral agents[a] GSK Document Number RH2009/00002/00 Completed	MT-4 cells	In vitro	A	No	GSK

Module 2.7.2.4 Special Studies

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility
Anti-HIV activity in combination with maraviroc GSK Document Number RH2009/00009/00 Completed	Magi-CCR5 cells	In vitro	A	No	[redacted]
Evaluation of cytotoxicity in antiviral assays GSK Document Number RH2007/00071/00 GSK Document Number RH2007/00116/00 Completed	Human MT-4 and CIP-4 cells	In vitro	B	No	GSK and [redacted]
Evaluation of cytotoxicity in human cell lines and peripheral blood lymphocytes (PBMCs) GSK Document Number RH2007/00036/00 Completed	Human leukemic B- and T-cells lines and PBMCs	In vitro	B	No	GSK
Testing of GSK1349572A Against a Range of Viruses GSK Document Number 2011N113854_00 Completed		In vitro	A	No	[redacted]
Dissociation from integrase-DNA complexes GSK Document Number 2011N114191_00 Completed	Wildtype and mutant integrase protein	In vitro	B	No	GSK
Integrase inhibitor susceptibility of multiple clinical isolates of HIV-1 GSK Document Number RH2007/00090/00 Completed	293 cells	In vitro	A	No	[redacted]
Anti-HIV activity against a panel of HIV-1 and HIV-2 isolates GSK Document Number RH2008/00134/00 Completed	Human PBMC and MDM cells	In vitro	A	No	[redacted]

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility
Anti-HIV activity against protease inhibitor (PRI)-resistant strains GSK Document Number RH2008/00141/00 Completed	MT-4 cells	In vitro	A	No	[redacted]
Anti-HIV activity against reverse transcriptase inhibitor (RTI)-resistant strains GSK Document Number RH2008/00142/00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Anti-HIV activity against integrase inhibitor resistant HIV-1 strains GSK Document Number RH2007/00115/00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Anti-HIV activity of RSC-364735 against integrase inhibitor resistant HIV-1 strains GSK Document Number RH2005/00088/00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Anti-HIV activity against raltegravir-resistant strains GSK Document Number RH2008/00143/00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Anti-HIV activity against raltegravir-resistant HIV-2 strains GSK Document Number 2012N141511_00 Completed	M8166	In vitro	A	No	[redacted]
Anti-HIV activity against integrase site directed mutant strains and resistant clinical isolates GSK Document Number RH2009/00010/00 Completed	293 cells	In vitro	A	No	[redacted]

Module 2.7.2.4 Special Studies

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility
Isolation of GSK1349572-resistant HIV-1 mutants GSK Document Number RH2007/00119/00 Completed	MT-2 cells	In vitro	A	No	[redacted]
Isolation of GSK1349572-resistant mutants from integrase inhibitor resistant HIV-1 strains GSK Document Number RH2008/00144/00 Completed	MT-2 cells	In vitro	A	No	[redacted]
Anti-HIV activity against integrase site directed mutant s from GSK1349572-passage studies GSK Document Number RH2010/00017/00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Activity against 700 raltegravir resistant clinical isolates GSK Document Number 2012N146158_00 Completed	293 cells	In vitro	A	No	[redacted]
Characterization of DTG resistance in the raltegravir resistance clinical isolation population GSK Document Number 2012N152930_00	293 cells	In vitro	A	No	[redacted]
Dissociation from integrase-DNA complexes with various substitutions including combinations observed during Viking (ING112961) GSK Document Number 2012N145179_00 Completed	Wildtype and mutant integrase protein	In vitro	B	No	GSK

Module 2.7.2.4 Special Studies

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility
Minority species analysis of samples from antiretroviral experienced, raltegravir resistant subjects in ING112961 GSK Document Number 2012N151522_00 Completed	Ultradeep pyrosequencing, clonal analysis	In vitro		No	GSK
Isolation of GSK1349572 Resistant Mutants from Integrase Inhibitor-Resistant HIV-1 Strains (2) GSK Document Number 2012N141510_00 Completed	MT-2 cells	In vitro	A	No	[redacted]
Antiviral activity of DTG by Baseline Resistance in ING112574 GSK Document Number 2012N148111_00 Completed	293 Cells	In vitro	A	No	[redacted]
Anti-HIV activity against integrase inhibitor resistant HIV-1 strains of interest GSK Document Number 2013N167276_00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Anti-HIVI activity against additional mutant strains, including R263K GSK Document Number 2013N182814_00 Completed	HeLa-CD4 cells	In vitro	A	No	[redacted]
Dissociation from integrase-DNA complexes with various substitutions including combinations observed during ING111762 GSK Document Number 2013N181427_00 Ongoing	Wildtype and mutant integrase protein	In vitro	A	No	GSK

Type of Study Document Number Status	Species (Strain)/ Test System	Method of Administration	Form	GLP	Testing Facility
Activity in combination with rilpivirine GlaxoSmithKline Document Number 201N229965_00	CEM-SS cells and HIV-1 IIIB	In vitro	A	No	[redacted]

Key:

a. Other antiviral agents including anti- hepatitis B virus (HBV) and anti- hepatitis C virus (HCV) drugs.

A = GSK1349572A (sodium salt of dolutegravir). B = GSK1349572B (dolutegravir parent form). HeLa-CD4 = Human epithelial cell line expressing CD4. MDM = Monocyte-derived macrophage cells. MT-4 = Human T-cell lymphotropic virus transformed cell line. PBMC = Peripheral blood mononuclear cells. Magi- chemokine receptor 5 (CCR5) cells = human cell line (HeLa CD4) LTR β-gal cells expressing high levels of CD4 and CCR5, [redacted] - [redacted], GSK - GlaxoSmithKline

Testing Facility:

GSK = GlaxoSmithKline.

[redacted] = [redacted]

[redacted] = [redacted]

[redacted] = [redacted]

4.1.1. Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral Deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle.

The antiviral mechanism of DTG on HIV replication was investigated [GlaxoSmithKline Document Number RH2010/00018/00, GlaxoSmithKline Document Number RH2007/00119/00, GlaxoSmithKline Document Number RH2010/00017/00, GlaxoSmithKline Document Number 2011N114191_00] using quantitative PCR, in vitro passage, and direct binding dissociation studies. A dose dependent decrease in integrated HIV-1 DNA (Alu PCR) and an increase of 2 LTR circles was observed with DTG treatment suggesting that the antiviral activity is a direct consequence of its effect on viral integration. Dolutegravir demonstrated equivalent potency against two nonnucleoside inhibitor resistant, three nucleoside inhibitor resistant and two protease inhibitor resistant HIV-1 mutant clones (one with three and one with six mutations) compared with the wild type strain [GlaxoSmithKline Document Number RH2008/00141/00, GlaxoSmithKline Document Number RH2008/00142/00]. In addition, passage studies with DTG selected mutations within the integrase enzyme; some of those mutations recreated as site-direct mutant HIV virus conferred moderate but greater than wild-type levels of DTG resistance. Direct and prolonged DTG binding to integrase protein was demonstrated with purified integrase in DNA:Mg2+ complexes in bead based assays. These data are also consistent with direct targeting of the HIV-1 integrase in cells.

4.1.2. Cell Based Antiviral Assays

Dolutegravir activity against Ba-L HIV-1 in peripheral blood mononuclear cells (PBMCs), HIV-1 strain IIIB in MT4 cells and pseudotyped HIV-1 in cell line derived from 293T cells (CIP4) cells was examined [GlaxoSmithKline Document Number RH2007/00071/00, GlaxoSmithKline Document Number RH2007/00116/00].

For PBMC assays, cells were stimulated with phytohemagglutinin and interleukin-2 and infected with HIV-1 strain BaL or HIV-1 strain NL432. Following incubation with DTG for 4 or 7 days, the antiviral activity was assayed by reverse transcriptase (RT) activity resulting in effective dose 50 (EC_{50}s) of 0.51 nM (BaL) and 0.53 nM (NL432). For MT-4 assays, cells were infected with HIV-1 strain IIIB and incubated with DTG for 4 or 5 days followed by cell viability analyses with CellTiter-Glo or MTT resulting in EC_{50}s of 0.71 and 2.1 nM, respectively (Table 2). For pseudotyped HIV (PHIV) assays, the infected cells were incubated with DTG for 2 days and when assayed for cell viability by Steady Glo gave an EC_{50} of 2.2 nM. In vitro strand transfer biochemical assays using purified HIV-1 integrase, which measure the inhibition of the amount of donor DNA covalently attached to target DNA by DTG using either [^{3}H] target DNA or a sandwich ELISA resulted in IC_{50}s of 2.7 nM and 12.6 nM, respectively.

Table 2 Antiviral Activity of DTG in PBMC, MT4, or CIP4 cells

Cells/Cell lines	Virus	DTG Geometric mean EC_{50} (nM)	95% CI	N
PBMC	Ba-L	0.51	0.34-0.77	12
PBMC	NL432	0.53	SD = 0.21	5
MT4	HIV-1^{IIIB}	0.71	0.40-1.3	9
MT4	HIV-1^{IIIB}	2.1	SD = 0.82	3
CIP4	PHIV vector	2.2	0.96-5.2	2

Data Source: RH2007/00071/00 Table 1, Table 2, and Table3; RH2007/00116/00 Table 1 and Table 2
CI - Confidence Interval

4.1.3. Effect of Human Serum and Serum Proteins

The effect of human serum albumin (HSA)(20 or 40 mg/mL), α_1-acid glycoprotein (AAG) (2 mg/mL) (Table 3) and human serum (extrapolated up to 100%) on the antiviral activity of DTG was evaluated in the PHIV or MT-4 assay systems. HSA was the predominant DTG binding component compared with AAG. Maximum fold shift observed with MT-4 assays performed at GSK [GlaxoSmithKline Document Number RH2007/00071/00] and [redacted] [GlaxoSmithKline Document Number RH2007/00116/00] and extrapolated to 100% human serum provided a mean consensus 75-fold shift in the EC_{50} values for DTG and a resulting PA-EC_{50} of 38 nM for PBMCs in 100% serum [Kobayashi, 2011].

Table 3 The Effect of Serum Proteins on Antiviral Activity of DTG in HIV-1 IIIB-Infected MT4 Cells

Serum Protein	Geometric Mean EC_{50}	95% Confidence Interval	Potency Shift	N
40 mg/mL HSA	25 nM	12 – 52 nM	11-fold	10
2 mg/mL AAG	4.6 nM	1.4 – 15 nM	2.1-fold	4

Data Source: RH2007/00071/00 Table 4 and Table 5

4.1.4. Antiviral Activity in Combination with other Antiviral Agents

Dolutegravir was tested for antiviral activity in combination with currently approved antiviral drugs [GlaxoSmithKline Document Number RH2009/00002/00, GlaxoSmithKline Document Number RH2009/00009/00, GlaxoSmithKline Document Number 2015N229965]. The greatest value of the in vitro combination studies is to identify antagonism of antiviral activity indicating that certain drugs should not be used clinically in combination. In this regard, the in vitro combination data support the conclusion that the antiviral activity of DTG is compatible with other approved antiretrovirals.

Combination testing is included as part of pre-clinical early development of a new anti-HIV agent, and is carried out in cell culture. Testing is carried out against two representatives of each drug class to assess whether antagonism of antiviral activity is present. Cell line and HIV strain characteristics may determine their use in combination

studies - for example the MT-4 and CEM-SS cell lines are broadly used for HIV-1 cell culture analyses including combination studies, but they do not express the CCR-5 receptor and so are not used for cell receptor inhibitor maraviroc testing. Instead, the MAGI-CCR5 cell line is used with maraviroc as it expresses the CCR-5 receptor with which maraviroc interacts and inhibits. Similarly, HIV-1Ba-L is a CCR-5 tropic virus and would be used for maraviroc testing while the HIV-1 strain HIV-1 IIIB is CXCR4-tropic and would not be used for maraviroc testing.

It is important to include a positive control for antagonism to show that the assay being used is able to measure antagonism. The combination of RBV and d4T was used as the positive control for antagonism for the early DTG and RPV combination studies with other drug classes, as well as in the more recent study with DTG + RPV.

The in vitro anti-HIV-1 activity of DTG was studied in checkerboard format in combination with representative anti-HIV drugs (stavudine, abacavir, efavirenz, nevirapine, lopinavir, amprenavir, enfuvirtide, and RAL) and anti-HBV (adefovir) and anti-HCV (ribavirin) drugs in MT-4 cells with HIV-1 strain IIIB (Table 4), and in combination with the anti-HIV drug maraviroc in cells obtained through the NIH Acquired immunodeficiency syndrome (AIDS) Research and Reference Reagent Program (Magi-CCR5 cell line) with HIV-1 strain BaL (Table 5), and in combination with the non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine in CEM-SS cells with HIV-1 strain IIIB (Table 6). All drugs with inherent anti-HIV activity were additive or synergistic with DTG, or if without inherent anti-HIV activity (ribavirin) had no apparent effect on DTG activity.

Table 4 Inhibition of HIV-1_{IIIB} by DTG in Combination with Other Marketed Anti-HIV Agents in MT-4 cells

Compound	Deviation from Additivity			Interaction with DTG
	Average	S.E.	p-value	
DTG	0.031	0.151	0.423	Additive
D4T	-0.473	0.083	0.001	Synergy
ABC	-0.605	0.150	0.002	Synergy
EFV	-0.356	0.102	0.005	Synergy
NVP	-0.246	0.087	0.015	Synergy
LPV	-0.310	0.082	0.005	Synergy
APV	-0.332	0.085	0.003	Synergy
T-20	-0.245	0.110	0.034	Synergy
PMEA	-0.179	0.168	0.168	Additive
RAL	-0.05	0.16	0.39	Additive

Data Source: RH2009/00002/00 Table 2

D4T – Stavudine, ABC – Abacavir, EFV – Efavirenz, NVP – Nevirapine, LPV – Lopinavir, APV – Amprenavir, T-20 – Enfuvirtide, PMEA - 9-(2-phosphonylmethoxyethyl)adenine, RAL - Raltegravir

Table 5 Antiviral Efficacy and Cytotoxicity Results for DTG in Combination with Maraviroc vs HIV-1 BA-L in MAGI-CCR5 Cells

Setup	Antiviral	Cytotoxicity	Interpretation
1	44.6 / -0.08	3.41 / -2.15	Antiviral: Additive (Nonantagonistic) Cytotoxicity: Additive to Slightly Antagonistic
2	38.7 / -0.73	0 / -93.8	
3A	28.4 / 0	0 / -132	
3B	33.4 / -0.08	2.52 / -35.7	
Mean	**36.3 / -0.21**	**0.18 / -64.6**	

Data Source:RH2009/00009/00 Table 2

Table 6 Antiviral Efficacy and Cytotoxicity Results for DTG in Combination with Rilpivirine vs HIV-1 IIIB in CEM-SS Cells

Setup	Antiviral	Cytotoxicity	Interpretation
1	1.31 / -4.99	3.44 / 0	Antiviral: Additive (Nonantagonistic) Cytotoxicity: Additive (Nonantagonistic)
2	37.1 / -4.70	0 / -35.8	
3	0 / -7.65	0 / -0.46	
4	0 / -6.15	0 / -6.42	
Mean	**8.99 / -5.25**	**0 / -9.85**	

Data Source:2015N229965 Table 2

4.1.5. Evaluation of Cytotoxicity in Antiviral Assays

Cytotoxicity assays with DTG were conducted in parallel with the antiviral assays [GlaxoSmithKline Document Number RH2007/00071/00, GlaxoSmithKline Document Number RH2007/00116/00]. Overall the cytotoxicities measured in these assays were distinct from the antiviral potencies and provided selectivity ratios from >350-fold to 6800-fold indicating that the observed antiviral activity of DTG was not due to cytotoxicity.

4.1.6. Evaluation of Cytotoxicity in Human Cell Lines and Peripheral Blood Mononuclear Cells

Cytotoxicity assays were conducted in proliferating human leukemic and lymphomic cell lines and PHA stimulated and unstimulated human PBMCs from the same donors, with resulting cell cytotoxicity (CC) IC_{50}s for DTG in proliferating IM-9, U-937, MT-4 and Molt-4 cells of 4.8, 7.0, 14 and 15 μM, respectively and in unstimulated and stimulated PBMCs of 189 μM and 52 μM, respectively [GlaxoSmithKline Document Number RH2007/00036/00] (Table 7). When compared to the antiviral activity of DTG IC_{50} of 0.51 nM in PBMCs the selectivity index for antiviral activity was >9400.

Table 7 Cytotoxicity Assay Results in PBMCs and B and T Cells

Cells/Cell lines	DTG CC_{50} (μM)	95% CI	Flavopiridol CC_{50} (μM)	95% CI
IM-9 (n=4)	4.8	3.0-7.7	0.019	0.012-0.030
U-937 (n=4)	7.0	4.8-10	0.035	0.024-0.050
MT-4 (n=4)	14	7.0-29	0.13	0.062-0.26
Molt-4 (n=4)	15	12-19	0.16	0.13-0.21
Stimulated PBMCs (n=8)	52	36-76	0.36	0.25-0.53
Unstimulated PBMCs (n=8)	189	58-620	0.29	0.15-0.56

Data Source:RH2007/00036/00 Table 1

4.1.7. Susceptibility of Multiple Subtype B Clinical Isolates of HIV-1

Dolutegravir activity against site directed mutant strains and clinical isolates with integrase resistance mutations was evaluated at [redacted] using the Integrase PhenoSense assay [GlaxoSmithKline Document Number RH2007/00090/00].

The susceptibility of 13 clinically diverse HIV-1 subtype B isolates to integrase inhibition by DTG was tested with [redacted]'s PhenoSense assay. The mean IC_{50} for viral replication of the clinical isolate based viruses was 0.52 nM (range 0.41 to 0.60 nM) (Table 8).

Table 8 Activity of DTG against a Panel of HIV-1 Clinical Isolates

Virus	EC_{50} (nM)
ASJM 108	0.54
ASM 34	0.54
ASM 42	0.59
NIH 57	0.60
NIH 660	0.41
NIH 657	0.54
NIH 714	0.54
NIH 727	0.50
CV 110	0.49
CV 154	0.49
CV 163	0.55
CV 243	0.43
CV 281	0.49
HIV-1 IIIB	0.46
HXB2	0.65
NL4-3	0.60
Isolate mean	0.52
Isolate Median	0.54
Isolate standard deviation	0.06
Isolate range	0.41 - 0.60
Laboratory virus mean	0.57
Laboratory virus median	0.60
Laboratory virus standard deviation	0.10
Laboratory virus range	0.46 - 0.65

Data Source: RH2007/00090/00 Table 1

4.1.8. Susceptibility of a Panel of HIV-1 and HIV-2 Isolates in PBMCs and Monocyte Derived Macrophages

The antiviral activity of DTG was tested against a panel of HIV-1 isolates (3 in each group of M subtypes A, B, C, D, E, F and G, and 3 group O isolates) (Table 9) and 3 HIV-2 isolates, in PBMC assays [GlaxoSmithKline Document Number RH2008/00134/00] (Table 10). The antiviral activity of DTG against four subtypes of B HIV-1 isolates was also evaluated in cell based monocyte-derived macrophage assays (Table 11). DTG was highly active with broad activity against all HIV-1 (geometric mean EC_{50} of 0.20 nM and range of 0.02 to 2.14 nM) and HIV-2 (geometric mean EC_{50} of 0.18 nM and range of 0.09 to 0.61 nM) isolates tested. In the monocyte-derived macrophage assays using 4 subtype B isolates, the geometric mean EC_{50} was 0.87 nM and values ranged from 0.37 to 1.98 nM. Mean EC_{50}s for each of these categories are listed in Table 12.

Table 9 Activity of DTG against HIV-1 in PBMCs

HIV-1 Isolate	Envelope Subtype	EC_{50} (nM)
92RW009	A	0.18
92UG037	A	0.09
92UG029	A	0.50
92BR014	B	2.14
JR-CSF	B	0.05
92TH026	B	0.08
Ba-L	B	<0.10
Ba-L	B	0.20
92BR025	C	0.14
93IN101	C	<0.10
93IN101	C	0.51
93MW959	C	0.05
92UG001	D	0.17
92UG024	D	0.35
92UG046	D	0.16
93TH073	E	0.09
CMU08	E	0.24
CMU06	E	0.32
93BR019	F	0.44
93BR020	F	0.23
93BR029	F	<0.10
93BR029	F	0.07
JV1083	G	0.87
RU132	G	0.20
G3	G	0.02
BCF01	O	0.41
BCF02	O	0.42
BCF03	O	1.79

Data Source:RH2008/00134/00 Table 3

Table 10 Activity of DTG against HIV-2 Isolates in PBMCs

HIV-2 Isolate	EC_{50} (nM)
CDC 310319	0.61
CDC 310342	<0.10
CEC 310342	0.18
CBL 20	0.09

Data Source:RH2008/00134/00 Table 4
CDC - Centers for Disease and Prevention Control

Table 11 Activity of DTG against Subtype B Isolates in Macrophages

HIV-1 Isolate	EC_{50} (nM)
Ada	1.33
Ba-L	1.98
92BR014	0.58
92TH026	0.37

Data Source: RH2008/00134/00 Table 5

Table 12 Mean Activity of DTG against Broad Subtypes and HIV-2 in PBMCs, and Subtype B Isolates in Macrophages

Virus	Mean EC_{50} (nM)
Subtype A	0.26
Subtype B	0.62
Subtype C	0.23
Subtype D	0.23
Subtype E	0.22
Subtype F	0.25
Subtype G	0.36
Group O	0.87
HIV-2	0.29
Subtype B in Macrophages	1.07

Data Source: RH2008/00134/00 Table 3, Table 4, and Table 5

4.1.9. Activity against non-HIV Viruses

Dolutegravir was evaluated for antiviral activity against a panel of 19 non-HIV viruses. In general, DTG did not exhibit significant antiviral activity in this panel [GlaxoSmithKline Document Number 2011N113854_00]. Some activity was observed against bovine viral diarrhea virus (BVDV) (EC_{50} = 66 μM), dengue virus (DENV) (IC_{50} = 69.5 μM), measles virus (EC_{50} = 30.3 μM), HCV (EC_{50} = 11.2 μM), and varicella zoster virus (VZV) (EC_{50} = 88.1μM) (Table 13, Table 14, Table 15). DTG displayed the highest antiviral activity against HCV. DTG caused a mild cytotoxic effect at the high test concentration.

Table 13 Activity of DTG against a Range of Viruses in Cytoprotection Assays

Virus	High Concentration (μM)	EC_{50} (μM)	TC_{50} (μM)
Adenovirus	100	>100	>100
Bovine Viral Diarrhea Virus	100	66	>100
Dengue Virus (serotype 2)	100	69.5	>100
Yellow Fever Virus	100	>100	>100
HSV-1	100	>100	>100
HSV-2	100	>100	>100
Influenza A	100	>100	64.9
Influenza B	100	>100	75.7
Human Parainfluenza	100	>100	>100
Measles Virus (Morilli virus)	100	30.3	>100
Respiratory Syncytial Virus	100	>100	>100
Coxsackie A Virus	100	>100	97.6
Coxsackie B Virus	100	>100	>100
Enterovirus	100	>100	>100
Polio Virus	100	>100	>100
Rhinovirus	100	>100	>100

Data Source:2011N113854_00 Table 3

Table 14 Activity of DTG against Hepatitis C Virus (Replicon Assay)

Virus	High Concentration (μM)	EC_{50} (μM)	TC_{50} (μM)
HCV	100	11.2	96.7

Data Source: 2011N113854_00 Table 4

Table 15 Activity of DTG in a Plaque Reduction Assay

Virus	High Concentration (μM)	EC_{50} (μM)	TC_{50} (μM)
HCMV	100	>100	>100
VZV	100	88.1	>100

Data Source: 2011N113854_00 Table 5
HCMV - Human Cytomegalovirus

4.1.10. Isolation of DTG Resistant HIV-1 Mutants

Selection of resistant mutants during in vitro passage of virus in the presence of drug may provide insight into the resistance mutations selected in vivo. Resistant mutants were isolated during passage of wild type virus, virus with RAL resistant mutants, and during simultaneous passage of HIV-1 subtypes B, A/G, and C.

4.1.10.1. Isolation from Wild type HIV-1 Strain IIIB

Virus cultures were derived by co-culturing MT-2 cells with Molt-4 cells persistently infected with HIV-1 strain IIIB [GlaxoSmithKline Document Number RH2007/00119/00]. This strain has ~40% T124A polymorphism in integrase in viral stocks used for passage [Kobayashi, 2011]. The culture media from the co-cultures including resuspended co-cultured cells was used for initiating passage of resistant variants. Every 3 or 4 days the cells were examined for apparent cytopathic effects and supernatants were used to infect new MT-2 cells in the presence of increasing DTG concentrations (up to 5-fold). Infected cell DNA was prepared and HIV proviral DNA sequence was determined.

At selected intervals (14, 28, 42, 56, 70, 84, 98 and 112 days), susceptibility to DTG was measured using the supernatant from passaged cells (briefly expanded in fresh M8166 cells) in assays using HeLa-CD4 cells carrying a reporter β-galactosidase gene. Viruses highly resistant to DTG were not observed during the 112 day passage, with a 4.1-fold maximum fold resistance observed for the passaged resistant virus with substitutions at the conserved IN positions S153Y and S153F. As noted above the detection of T124A is selection of a pre-existing minority variant that does not have differential susceptibility DTG. These data are consistent with direct targeting of the HIV-1 integrase in cells and provide a relative fold resistance level for virus with these substitutions (Table 16).

Table 16 Passage with HIV IIIB

Days of Culture	Amino Acid Substitution	DTG Fold Change
14	T124A	1.2-2.5
28	T124A	0.57-1.0
	T124A, S153F	1.9
42	T124A	0.48-1.7
	T124A, S153F	1.7
56	T124A	0.95-2.9
	T124A, S153F	2.7
70	T124A	1.1-3.1
	T124A, S153Y	2.9
	L101I, T124A, S153F	2.4
84	T124A	0.82-3.1
	S153Y	3.7
	T124A, S153Y	3.3
	L101I, T124A, S153F	2.4
98	T124A	1.3-3.1
	T124A, S153Y	4.1
	L101I, T124A, S153F	3.0
112	T124A	1.2-4.1
	S153Y	2.1
	T124A, S153Y	1.8-2.6
	L101I, T124A/, 153F	2.0

Data Source: RH2007/0019/00 Table 1

4.1.10.2. Isolation from Wild Type and Site Directed Mutant INI Resistant HIV-1 Strain NL432

Wild type HIV-1 NL432 and molecular clones with single amino acid substitutions (E92Q, Q148H, Q148K, Q148R, and N155H) within the IN open reading frame were passaged sequentially under increasing concentration of DTG for up to 56 days [GlaxoSmithKline Document Number RH2008/00144/00]. Passaged virus populations were analyzed for genotypic changes on Days 14, 28, 42 and 56, and for phenotypic fold change (FC) on Day 56 samples (Table 17).

Table 17 Passage of NL-432 and Single Mutants with DTG

Initial Virus	DTG Initial Conc. / Final Conc (nM)	Days of Culture	Amino Acid Substitution	DTG Fold Change of Passaged Virus Pools
NL-432	6.4 / 6.4	56	E92Q	3.1
			G193E	3.2
Q148K	6.4 / 32	14	E138K, Q148K	-
		28	E138K, Q148K	-
		42	E138K, Q148K	-
		56	E138K, Q148K	47 - 190
Q148R	6.4 / 6.4 or 32	14	Q148R	-
		28	G140S, Q148R	-
		42	G140S, Q148R	-
		56	G140S, Q148R	16 (6.4 final conc.)
			G140S, Q148R, V201I	39 (32 final conc.)
Q148R	6.4 / 6.4	14	E138K, Q148R	-
		28	E138K, Q148R	-
		42	E138K, Q148R	-
		56	E138K, G140S, Q148R	13
Q148H	6.4 / 6.4 or 32	14	G140S, Q148H	-
		28	G140S, Q148H	-
		42	G140S, Q148H	-
		56	G140S, Q148H	4.8 – 8.0 (6.4 final conc.)
			T97A, G140S, Q148H	44 (32 final conc)
			V75I, E138K, G140S, Q148H, M154I	46 (32 final conc)
N155H	6.4 / 32	14	N155H	-
		28	N155H	-
		42	N155H	-
		56	N155H	2.0 – 3.9
E92Q	6.4 / 6.4	14	E92Q	-
		28	E92Q	-
		42	E92Q	-
		56	E92Q	2.9 – 4.1

Data Source: RH2008/00144/00 Table 1

Passage of the wild type HIV-1 NL432 in the presence of 6.4 nM DTG selected for E92Q (FC=3.1) and G193E (FC=3.2) substitutions in the IN region on Day 56. Passage of the Q148K mutant selected E138K/Q148K (FC=47 to190) on Day 14 and was present throughout the remaining passages up to 32 nM DTG with no additional substitutions selected up to Day 56. Passage of the Q148R mutant selected E138K/Q148R and G140S/Q148R (FC=16) on Days 14 and 28, respectively, in the presence of 6.4 nM DTG. Further passage at ≤32 nM DTG selected E138K/G140S/Q148R (FC=13) and G140S/Q148R/V201I (FC=39) by Day 56. Passage of Q148H selected G140S/Q148H

(FC=4.8 to 8) on Day 14 in the presence of 6.4 nM DTG, and selected T97A/G140S/Q148H (FC=44) and V75I/E138K/G140S/Q148H/M154I (FC=46) on Day 56 in the presence of 32 nM DTG. Passage of the E92Q or N155H mutant viruses in the presence of DTG did not lead to additional substitutions. Passage of site directed mutant virus with polymorphic substitutions L101I, L101I/T124A, and RAL resistance mutations Y143C and Y143R in the presence of DTG did not lead to additional substitutions [GlaxoSmithKline Document Number 2012N141510_00]

Passage of site direct double mutant virus G140S/Q148R at 6.4 nM selected V113L at Day 56 (FC not determined). Passage of G140S/Q148H at 6.4 nM dolutegravir selected the addition of N155H at Day 28 (FC = 85 to >120) and E92Q (FC >120), and of E92Q/E138K by Day 56 (FC >120). Passage at 32 nM DTG selected for addition of F139S at day 28 (FC not determined), L74M at Day 42 (FC = 15 to 95), or L74M/T112S/V113L (FC >120). All FCs were determined at Day 56 (Table 18).

Table 18 Passage of Double Mutants with DTG

Initial Virus	DTG Initial Conc. (nM)	Days of Culture	Amino Acid Substitution Added	DTG Fold Change of Passaged Virus Pools
G140S/Q148R	6.4	56	V113L	
G140S, Q148H	6.4	28	N155H	-
		42	N155H	-
		56	N155H	85 - >120
G140S, Q148H	6.4	28	E92Q	-
		42	E92Q	-
		56	E92Q E92Q/E138K	>120 >120
G140S, Q148H	32	28	F139S	-
		42	F139S	-
		56	F139S	-
G140S, Q148H	32	42	L74M	-
		56	L74M	15 - 95
		56	L74M, T112S, V113L	>120

Data Source: RH2008/00144/00 Table 1- Table 2

4.1.10.3. Selection of R263K in Passage Experiments using HIV-1 with Subtype B, C, and A/G

Serial passage experiments were performed with DTG using healthy donor primary human cord blood mononuclear cells (CBMCs) infected with various subtype B, C, and A/G viruses [Quashie, 2012]. After 20 weeks, the R263K mutation was observed in all five subtype B selections and one of two subtype A/G selections. During the selections, neither L101I nor T124A appeared. However, the S153Y substitution was observed in combination with R263K for one subtype B virus and S153T was partially detected in one subtype C virus. Importantly, the only subtype B or A/G virus that did not bear the R263K mutation carried the G118R mutation, which was characterized as a resistance mutation to MK-2048, another second generation integrase inhibitor. The same mutation (G118R) was observed in one subtype C virus. The R263K mutation was detected alone

or in combination with other substitutions that varied among virus strains. R263K emerged early in culture in both subtype B and A/G viruses (Table 19).

Table 19 Serial Passage Experiments with CBMCs infected with Subtype B, A/G, and C HIV-1 Viruses in the Presence of Increasing Concentrations of DTG

		Week 20		Week 37	
Subtype	Virus	DTG Concentration (μM)	Acquired Mutations	DTG Concentration (μM)	Acquired Mutations
B	5331	0.05	R263K		
B	BK-132	0.05	R263K, W243G/W	0.05	R263K, E138E/K
B	5326	0.05	R263K/R, S153Y, R166K/R	0.05	S153Y
B	PNL4.3	0.05	R263K, M50I/M, V151I	0.05	R263K, M50I, V151I
B	12197 RAL TI	0.01	R263K, D288E	0.025	R263K, D288E (Week 34)
A/G	6399	0.025	G118R, E69E/K	0.05	G118R
A/G	96USSN20	0.1	R263K	0.1	R263K, H51H/Y
C	4742	0.05	G118R	0.05	G118R, H51Y
C	96USNG31	0.01	S153S/T	0.025	H51Y, G193E/G

Data Source: Quashie, 2012 ,Table 1

4.1.11. Assessment of Resistance

Comparative susceptibilities to DTG and RAL were obtained from 60 RAL resistant site directed HIV-1 mutants and 6 site directed HIV-2 mutants.

4.1.11.1. Sixty-two Integrase Inhibitor Resistant HIV-1 Strains

HIV-1 viruses (30 with single mutations, Table 20) and 32 with two or more mutations, (Table 21) were produced from wildtype virus NL-432 using site directed mutagenesis DTG and other INI susceptibilities were tested in HeLa-CD4 cell assay carrying a reporter β-galactosidase gene driven by HIV-1 LTR [GlaxoSmithKline Document Number RH2005/00088/00, GlaxoSmithKline Document Number RH2007/00115/00, GlaxoSmithKline Document Number RH2008/00143/00, GlaxoSmithKline Document Number RH2010/00017/00, GlaxoSmithKline Document 2013N167276_00). DTG showed anti-HIV activity (susceptibility) with fold change (FC) <5 against 29 of 30 INI-resistant mutant viruses with single mutations including T66A/I/K, E92Q/V, Y143C/H/R, Q148H/K/R, Q148R, and N155H, while for RAL there were 19/30 mutant viruses with

FC <5. EVG (compound 3927 in [GlaxoSmithKline Document Number RH2005/00088/00]) FC was obtained for 23 of these 30 viruses; 13 of 23 had FC <5. In addition, of the 32 INI-resistant mutant viruses with two or more mutations, 23 of 32 showed FC <5 to DTG compared with FC < 5 for 4 of 32 for RAL. EVG FC was obtained for 25 of these 32 viruses; 2 of 25 had FC <5.

Overall against the 62 site directed mutant viruses (single and ≥2 mutations), DTG showed a fold change (FC) of <2 for 41 of 62, while RAL showed a FC of <2 for 18 of 60. DTG showed a FC of ≥10 for 6 of 60, while RAL showed a FC of ≥10 for 31 of 62. Of the 48 mutant viruses with data for EVG, 9 of 48 showed a FC of <2, and 30 of 48 showed a FC of ≥10.

The resistance profile for Q148 pathway RAL-resistant HIV-1 is relatively complex due to the large number of potential substitutions which may be present in subjects failing RAL therapy. The in vitro data against site directed mutant HIV-1 with lab strain NL432 reflects this: virus with G140S/Q148H, G140S/Q148K, and G140S/Q148R had respective DTG FCs of 2.6, 1.5, and 8.4. The rank order and relative FC ranges shifted however with E138K in combination with Q148, with FCs for E138K/Q148H = 0.89, E138K/Q148K = 19, and E138K/Q148R = 4.0.

Table 20 Fold Change (FC) of DTG and RAL against INI-Resistance Single Mutant Viruses by HeLa-CD4 Assay

Virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
Wild type (NL432)	1.0 (IC_{50}=2.1 nM, SD=0.36)	1.0 (IC_{50}=6.1 nM, SD=0.89)	-
Wild type (NL432)	1.0 (IC_{50}=2.0 nM, SD=0.34)	1.0 (IC_{50}=8.6 nM, SD=1.3)	1.0 (IC_{50}=1.3 nM, SD=0.24)
T66A	0.26 (0.01)	0.61 (0.09)	-
T66I	0.26 (0.09)	0.51 (0.10	8 (1.7)
T66K	2.3 (0.35)	9.6 (1.3)	84 (29)
E92I	1.5 (0.19)	2.1 (0.62)	-
E92Q	1.6 (0.12)	3.5 (1.4)	19 (8.1)
E92V	1.3 (0.20)	1.4 (0.18)	-
G118R	10 (4.7)	7.2 (1.5)	-
G118S	1.1 (0.21)	1.2 (0.30)	-
F121Y	0.81 (0.12)	6.1 (1.3)	36 (23)
T124A	0.95 (0.19)	0.82 (0.08)	1.2 (0.29)
E138K	0.97(0.029)	1.0 (0.30)	0.93 (0.12)
G140S	0.86 (0.30)	1.1 (0.22)	2.7 (0.63)
Y143C	0.95 (0.26	3.2 (0.57)	1.5 (0.46)
Y143R	1.4 (0.29)	16 (3.9)	1.8 (0.16)
Y143H	0.89 (0.11)	1.8 (0.38)	1.5 (0.047)
P145S	0.49 (0.08)	0.87 (0.20)	>345
Q146R	1.6 (0.17)	1.2 (0.26)	2.8 (0.72)
Q148H	0.97 (0.67)	13 (5.0)	7.3 (2.3)
Q148K	1.1 (0.19)	83 (6.6)	>1726
Q148R	1.2 (0.21)	47 (9.3)	244 (91)
I151L	3.6 (3.6)	8.4 (4.7)	-
S153F	1.6 (0.20)	1.3 (0.14)	2.8 (0.93)
S153Y	2.5 (1.1)	1.3 (0.19)	2.3 (0.49)
M154I	0.93 (0.27)	0.82 (0.18)	1.1 (0.18)
N155H	0.99 (0.094)	8.4 (1.8)	25 (7.8)

Virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
N155S	1.4 (0.36)	6.2 (1.9)	68 (2.6)
N155T	1.9 (0.32)	5.2 (2.0)	-
E157Q	0.85 (0.21)	0.92 (0.34)	1.1 (0.62)
G193E	1.3 (0.25)	1.3 (0.35)	1.3 (0.40)
R263K	1.5 (0.39)	0.81 (0.18)	1.3 (0.76)

Data Source:RH2010/00017/00 Table 1; 2013N167276_00 Table 1; RH2007/00115/00 Table 1, Table 2; RH2008/00143/00 Table 1

Table 21 Fold Change (FC) of DTG and RAL against INI-Resistance Multiple Mutant Viruses by HeLa-CD4 Assay

virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
Wild type (NL432)	1.0 (IC_{50}=2.1 nM, SD=0.36)	1.0 (IC_{50}=6.1 nM, SD=0.89)	-
Wild type (NL432)	1.0 (IC_{50}=2.0 nM, SD=0.34)	1.0 (IC_{50}=8.6 nM, SD=1.3	1.0 (IC_{50}=1.3 nM, SD=0.24)
T66I, I74M	0.35 (0.08)	2.0 (0.81)	-
T66I, E92Q	1.2 (0.19)	18 (3.6)	185 (103)
T66K, L74M	3.5 (0.94)	40 (13)	117 (33)
V72I, F121Y, T125K	1.3 (0.54)	13 (7.1)	-
V72I, F121Y, T125K, I151V	1.2 (0.32)	7.0 (2.8)	-
L74M, N155H	0.91 (0.17)	28 (12)	42 (8.6)
V75I, E138K, G140S, Q148H, M154I	21 (6.6)	>660	2600 (450)
E92Q, N155H	2.5 (1.2)	>130	320 (39)
T97A, N155H	1.1 (0.46)	26 (7.9)	37 (6.9)
T97A, G140S, Q148H	13 (2.1)	>660	3900 (630)
L101I, S153F	2.0 (0.11)	1.3 (0.54)	2.6 (0.23)
L101I, T124A, S153F	1.9 (0.24)	1.4 (0.14)	2.0 (0.40)
F121Y, T125K	0.98 (0.35)	11 (0.49)	-
E138K, Q148H	0.89 (0.24)	17 (5.9)	6.7 (1.5)
E138K, Q148K	19 (8.0)	330 (75)	-
E138K, Q148R	4.0 (1.1)	110 (37)	461 (229)
E138A, Q148R	2.6 (0.47)	110	260 (12)
E138K, G140S, Q148H	4.5 (1.1)	500 (210)	1600 (370)
E138K, G140S, Q148R	8.3 (1.1)	>660	190 (43)
E138K, G140S, Q148H, M154I	8.4 (1.5)	>660	2400 (670)
E138A, S147G, Q148R	1.9 (0.89)	27 (3.7)	130 (8.8)
G140C, Q148R	4.9 (1.8)	200 (42)	-
G140S, Q148H	2.6 (1.4)	>130	>890
G140S, Q148K	1.5 (0.10)	3.7 (1.3)	94 (53)

virus	DTG FC (SD)	RAL FC (SD)	EVG FC (SD)
G140S, Q148R	8.4 (4.0)	200 (5.3)	-
G140S, Q148H, M154I	7.0 (0.98)	>660	3000 (780)
G140S, Q148R, V201I	10 (3.0)	>660	420 (80)
Y143H, N155H	1.7 (0.27)	38	16 (4.6)
Q148R, N155H	10 (1.4)	>140	390
N155H, G163R	1.1 (0.18)	17 (5.9)	35 (12)
N155H, G163K	1.4 (0.40)	23 (7.2)	35 (4.4)
N155H, D232N	1.4 (0.25)	20 (3.9)	36 (7.1)

Data Source: RH2010/00017/00 Table 1 and Table 2; RH2007/00088/00 Table 1, Table 2; RH2008/00143/00, Table 1

4.2. Nonclinical Virology – Rilpivirine

Table 22 Listing of Non-clinical virology Rilpivirine Studies

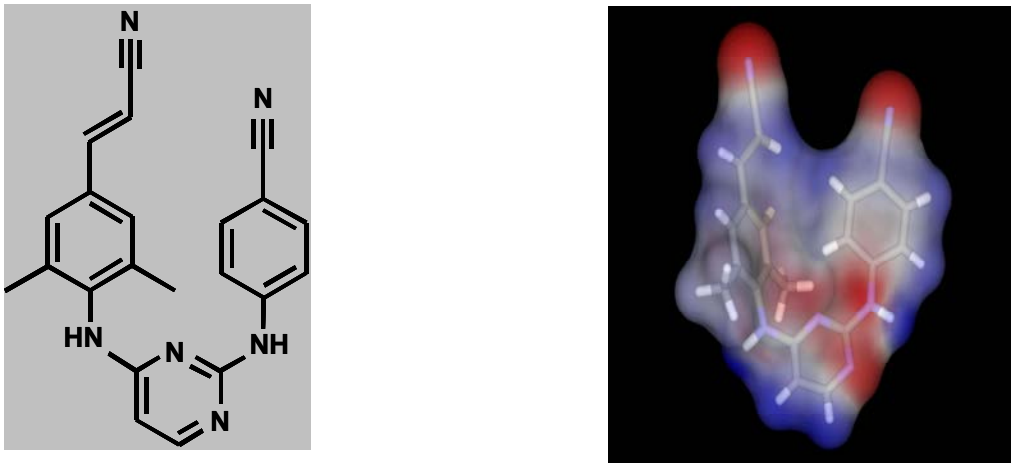
Report Number	Title
TMC278-IV1-AVMR	Mechanism of action and in-vitro antiviral activity of TMC278 against wild type and NNRTI-resistant HIV
TMC278-IV1-AVMR-RD	Raw data for TMC278-IV1-AVMR
TMC278-IV2-AVMR	Mechanism of action and in-vitro antiviral activity of TMC278 against wild type and NNRTI-resistant HIV
TMC278-IV2-AVMR-RD	Raw data for TMC278-IV2-AVMR

4.2.1. Mechanism of Drug Action

4.2.1.1. Inhibition of HIV-1 Reverse Transcriptase

The inhibitory effect of RPV (chemical structure shown in Figure 1) on HIV-1 reverse transcriptase (RT) activity was determined by an enzymatic assay. The median inhibitory activity of HIV-1 RT for RPV (IC_{50}) was 42 nM, with an interquartile range (IQR) ranging from 31 to 44 nM (TMC278-IV1-AVMR).

Figure 1 Chemical Structure and 3-dimensional Model of RPV



Description: The chemical structure of RPV, C22H18N6, or 4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2-pyrimidinyl]amino]benzonitrile, is shown. Red represents CN groups or the nitrogen of the pyrimidine and the nitrogen of the aniline (highest density of charge in the structure), and blue represents the aromatic group (no charge).

4.2.1.2. Structural Modelling of RPV and HIV-1 Reverse Transcriptase

Crystal structures of the binding site between RPV and the HIV-1 RT complex revealed that RPV, similarly to other members of the diarylpyrimidine (DAPY) family of inhibitors, binds to the HIV-1 RT and adapts to the conformational changes in the NNRTI-binding pocket [Das, 2004; Das, 2008; Landsdon, 2010; Fang, 2008].

In a first study, the structure of wild-type HIV-1 RT in complex with RPV was determined at 1.8 Å resolution [Das 2008]. RPV makes important contacts with a number of key amino acids in the NNRTI-binding pocket, for example the second linker nitrogen in a water-mediated hydrogen bond network with the main-chain carbonyl group of E138 of the p51 subunit and the positioning of the cyanovinyl group of RPV in a hydrophobic tunnel connecting the NNRTI-binding pocket to the nucleic acid-binding cleft.

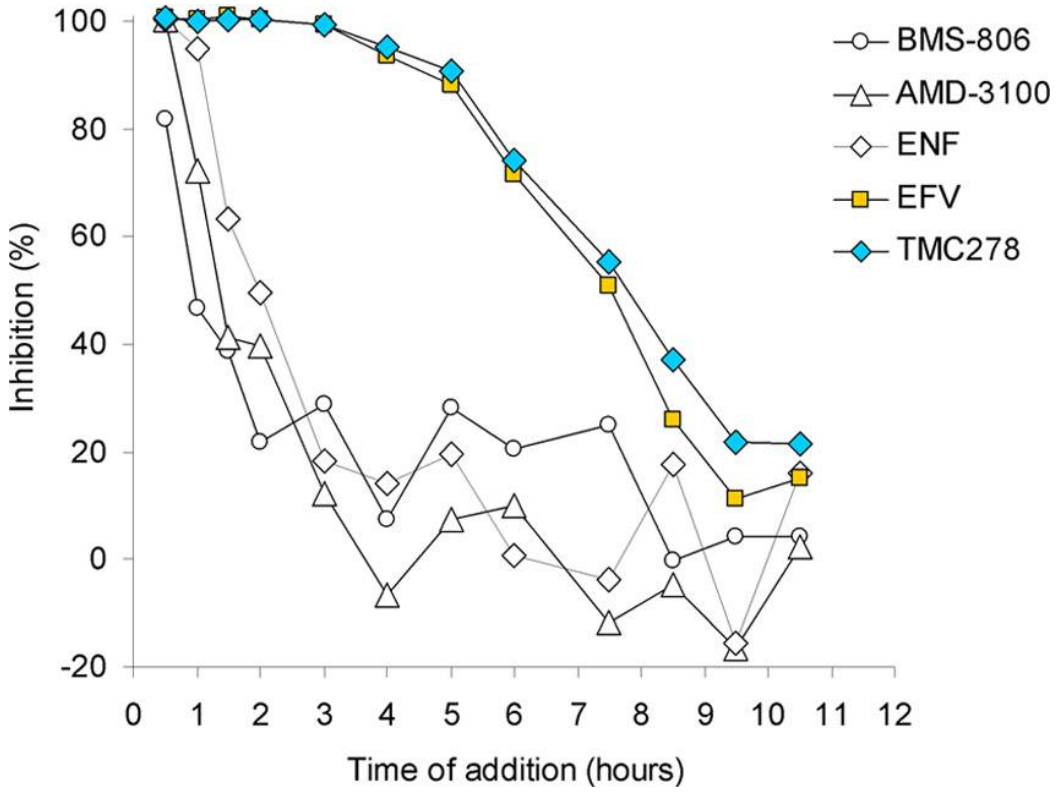
The crystal structures of RPV in complexes with the double mutant RT enzymes with K103N/Y181C (at 2.1 Å resolution) and L100I/K103N (at 2.9 Å resolution) demonstrated that RPV can adapt to bind mutant RTs. The flexible binding pocket acted as a molecular ‘‘shrink wrap’’ that made a shape complementary to the optimized RPV in wild-type and drug-resistant forms of HIV-1 RT. These crystal structures provided a better understanding of how the flexibility of an inhibitor could compensate for drug-resistance mutations.

Another study reported data on the crystal structures of wild-type and K103N HIV-1 RT in complexes with etravirine (ETR) and RPV (Landsdon, 2010). RPV was positioned in a similar fashion as ETR in the NNRTI binding pocket, adopting the expected horseshoe type shape. RPV was also cocrystallized with K103N RT to gain insight into the nature of retained activity against this important resistance mutation. The position of RPV in the pocket revealed no evidence of shifting in response to the K103N mutation.

4.2.1.3. Time of Addition

A time of addition assay was conducted in order to evaluate the stage at which RPV acts in the HIV-1 replication cycle (TMC278-IV1-AVMR). The antiviral activity of RPV, enfuvirtide (fusion inhibitor), AMD-3100 (CXCR4 entry inhibitor), BMS-806 (CD4/HIV-1 gp120 attachment inhibitor), and EFV were studied at different times of addition of the drugs to the infected HIV-1/IIIB cell culture. The data presented in Figure 2 show that the activity profile of RPV was similar to that of EFV. Both RPV and EFV inhibited virus replication by at least 50% up to 8 hours after initiation of infection. This confirmed a similar mode of action for EFV and RPV, i.e., inhibition of the HIV-1 RT.

Figure 2 Effect of the Time of Addition of Compound on the Antiviral Activity of RPV



Data Source: TMC278-IV1-AVMR, Figure 2

4.2.1.4. In Vitro Antiviral Activity against Wild-type HIV-1, HIV-2, and SIV in Human Cell Lines

The antiviral activities of RPV against HIV-1 IIIB and HIV-2 ROD were compared with those of other NNRTIs, EFV, ETR, and NVP. The median EC_{50} value for RPV against HIV-1/IIIB observed in the MT4 T-cell line is in the subnanomolar range (0.73 nM). This median EC_{50} value was lower than that obtained for EFV, ETR, and NVP by a factor of 2.4, 3.7, and 46.7, respectively (TMC278-IV1-AVMR). The antiviral activity of RPV against HIV-2 ROD and SIV/mac251 was compared with that of EFV, ETR, and NVP in MT4-LTR-eGFP cells (Refer to Module 5.3.5.4/TMC278-IV2-AVMR). The median EC_{50} values for RPV against HIV-2 ROD and SIV/mac251 observed in the MT4-LTR-eGFP cell line were 5.22 µM and 8.55µM, respectively. The median EC_{50} value for HIV-2 ROD was lower than that obtained for EFV and NVP and similar to that obtained for ETR.

4.2.1.5. In Vitro Antiviral Activity against Wild-type HIV-1 in Human Primary Cells

The in vitro antiviral activity of RPV, EFV and ETR, and the control NRTI AZT was determined against HIV-1/Ba-L and HIV-1/ADA in monocyte-derived macrophages (MDMs) (TMC278-IV2-AVMR). The data presented in Table 23 show EC_{50} values of

0.18 and 0.22 nM (0.07 to 0.08 ng/mL) for RPV and for HIV-1/BaL and HIV-1/ADA, respectively.

Table 23 In Vitro Antiviral Activity of RPV, EFV and ETR against HIV-1/BaL and HIV-1/ADA

HIV-1 Primary Isolate	Antiviral Activity (nM)							
	RPV		EFV		ETR		Control (AZT)	
	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}	EC_{50}	EC_{90}
Ba-L	0.18	1.28	1.15	7.85	0.65	4.44	2.44	29.4
ADA	0.22	1.07	0.64	5.67	0.40	2.52	5.74	35.5

Data Source: TMC278-IV2-AVMR, Table 2
Reported values are the result of one experiment run in triplicate. For the method refer to Report from [redacted], TMC278-IV2-AVMR-RD.

4.2.1.6. Antiviral Activity against Wild-type HIV-1 Group M and Group O Primary Isolates

RPV was determined to be active against HIV-1 Group M primary isolates from diverse origins with EC_{50} values ranging from 0.07 to 1.01 nM for Group M and EC_{50} values ranging from 2.88 to 8.45 nM for Group O. These values were similar to those observed in MT4 cells with HIV-1 IIIB, HIV-2 ROD, and SIV/mac 251 (Refer to TMC278-IV1-AVMR-RD and TMC278-IV2-AVMR). The median EC_{50} of RPV against all the HIV-1 primary clinical isolates tested in PBMC cultures was 0.26 nM (IQR: 0.15 - 0.52 nM). There was no apparent difference in the antiviral activity of RPV based on virus tropism.

Compared to the HIV-1 Group M primary isolates, similar results were obtained testing the antiviral activity of RPV against a panel of nine Group M recombinant HIV-1 clinical isolates of subtypes A1, AE, AG, BG, C, D, F1, G, and H (Refer to TMC278-IV1-AVMR).

4.2.1.7. In Vitro Antiviral Activity against Other Viruses in Various Cell Lines

No antiviral activity of RPV (EC_{50} values >10 μM) was observed against human hepatitis B virus, herpes simplex virus 2, human corona virus, influenza A virus, and vaccinia virus (Refer to TMC278-IV2-AVMR).

4.2.1.8. Multiplicity of Infection

The antiviral activity of RPV against HIV-1/IIIB was studied at 3 multiplicities of infection (MOIs); (0.25, 0.0025, and 0.00025); (Refer to TMC278-IV2-AVMR). Comparable EC_{50} values were obtained at the 3 MOIs for RPV, EFV, and ETR. EC_{50} values clearly increased with increasing MOI for NVP and the NRTI control AZT.

4.2.1.9. Effect of Serum Proteins on in Vitro Antiviral Activity

The antiviral activity of RPV was compared to those of other NNRTIs in the presence or absence of human serum proteins (Refer to TMC278-IV1-AVMR). The data show a reduction in the antiviral activity of RPV in the presence of 1 mg/mL AAG, 45 mg/ml

HSA, and 50% human serum as demonstrated by median EC_{50} ratios of 1.8, 39.2, and 18.5, respectively. Comparable results were obtained for EFV.

4.2.1.10. In Vitro Cytotoxicity and Selectivity Index

The in vitro effects of RPV on the cell proliferation and the viability of HeLa (epithelial cervix, adenocarcinoma), Hep G2 (epithelial liver, hepatoblastoma), HEp-2 (epithelial cervix adenocarcinoma), MRC-5 (normal fetal lung fibroblast), and A549 (epithelial lung carcinoma) cells were investigated (Refer to TMC278-IV2-AVMR). EFV, ETR, and NVP were tested in the same assays.

The CC50 value (as a measure of inhibition of cell proliferation) was determined as the concentration of a compound that resulted in a drop of 50% cell growth compared to the control. The median CC50 values of RPV, EFV, ETR, and NVP on the different cells were measured at Day 3 and Day 5. The data show that the median CC50 values for RPV range between 17.34 to 34.51 μM (6.35 to 12.65 μg/mL) and between 16.90 to 35.59 μM (6.19 to 13.04 μg/mL) at Day 3 and Day 5, respectively. Median CC_{50} values for EFV, ETR, and NVP are all > 40 μM, except for NVP on MRC-5 cells.

The TC_{50} value (as a measure of inhibition of cell viability) was defined as the concentration of a compound that resulted in a 50% reduction in cell growth on Day 3 or Day 5 compared to Day 0. Median TC_{50} values of RPV, EFV, ETR, and NVP on the different cells were determined at Day 3 and Day 5. The data show that the median TC_{50} values for RPV range between 33.94 to > 40.00 μM (12.44 to >14.66 μg/mL) and between 31.93 to > 40.00 μM (11.70 to >14.66 μg/mL) at Day 3 and Day 5, respectively. Median TC_{50} values for EFV, ETR, and NVP at Day 3 and Day 5 are all > 40 μM.

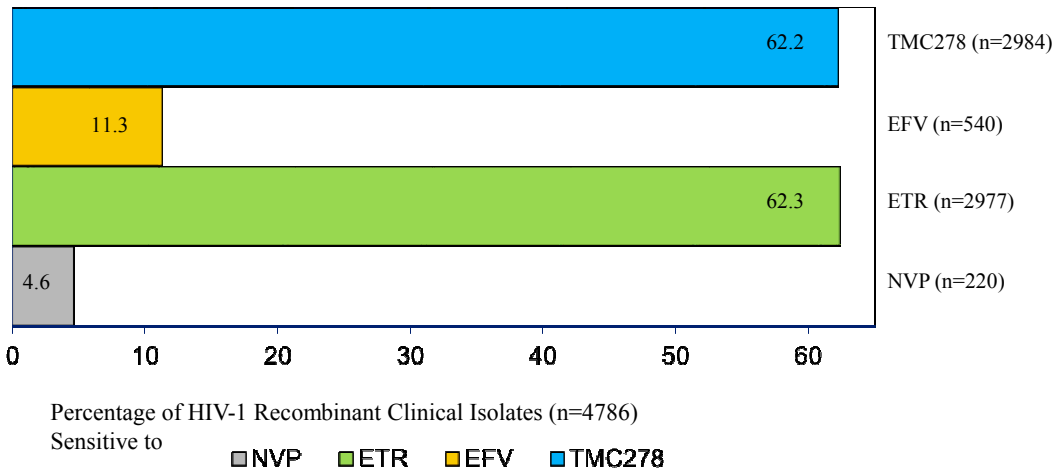
Median CC_{50} values for RPV, EFV, ETR, and NVP on MT4-LTR-eGFP cells were measured at Day 3. The median CC_{50} for RPV was 5.91 μM, whereas it was > 32 μM for EFV, ETR, and NVP.

4.2.2. In Vitro Drug Resistance

4.2.2.1. Antiviral Activity of RPV against HIV-1 NNRTI-Resistant Recombinant Clinical Isolates

A large-scale evaluation of the antiviral activity of RPV was done on a panel of 4,786 HIV-1 recombinant clinical isolates chosen from a library of 10,990 on the basis of resistance to a first-generation NNRTI (i.e., FC>biological cutoff [BCO] for either or both EFV and NVP) (TMC278-IV1-AVMR). The percentages of HIV-1 recombinant clinical isolates with sensitivity (i.e., FC≤BCO) to RPV, EFV, ETR, and NVP are presented in Figure 3. The data show that, in vitro, 62% of these HIV-1 recombinant clinical isolates, resistant to at least one first-generation NNRTI, retained sensitivity to RPV or ETR, as compared with 11.3% to EFV, and 4.6% to NVP.

Figure 3 Analysis of the Prevalence of HIV-1 Recombinant Clinical Isolates Sensitive to RPV, ETR, EFV, or NVP Among Those Resistant to at Least one First-Generation NNRTI (n = 4,786)



Data Source: TMC278-IV1-AVMR, Figure 3

4.2.2.2. Mechanism of Drug Resistance

In vitro selection experiments starting from WT HIV-1 or from HIV-1 harboring mutations in the RT were performed to determine the rate of emergence of resistant viruses as well as the mutations associated with decreased susceptibility to RPV upon drug selective pressure (Refer to TMC278-IV1-AVMR).

Two methods were used to isolate viruses under the selective pressure of RPV:

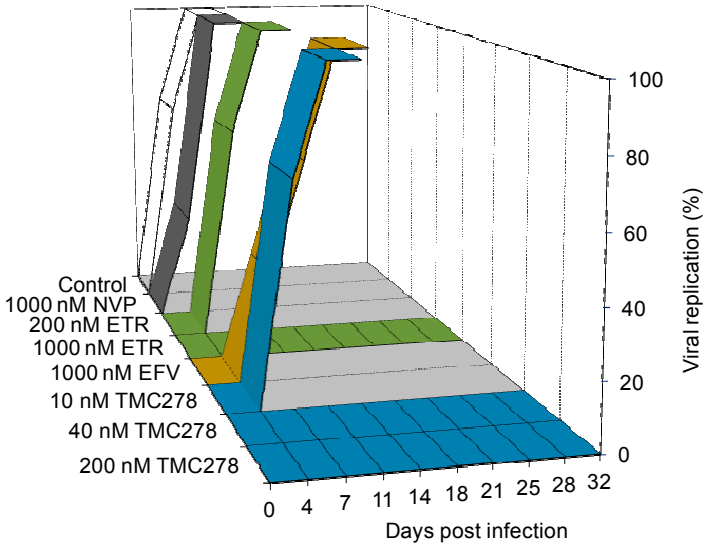
- high MOI selection experiments, where a high initial virus inoculum was propagated for several passages at a fixed drug concentration, were performed. This methodology was used to determine the rate of emergence of resistant viruses under selective pressure of RPV, allowing for a standardized comparison with other NNRTIs;
- low MOI selection experiments, where a low virus inoculum was propagated in the presence of increasing drug concentrations, were performed. This methodology was used to determine the mutations that were associated with decreased susceptibility to RPV in vitro.

In Vitro Selection from Wild-type and mutant HIV-1 at High MOI at Fixed Drug Concentrations

The phenotype and genotype of the emerging HIV-1 strains were determined after sequential passage of WT and mutant HIV-1 at a high MOI in the presence of fixed drug concentrations (2, 10, 40, 200, and 1000 nM). After 32 days in culture, no viral replication was detected in cells infected with HIV-1 subtype B (IIIB) at concentrations of RPV $\geq$ 40 nM (Figure 4). The same results were observed for recombinant clinical HIV-1 isolates from group M subtypes A1, AE, AG, BG, C, D, F1, G, and H and from

two HIV-1 HXB2 Site Directed Mutants (SDMs) containing either the NNRTI resistance associated mutation (RAM) K103N or Y181C.

Figure 4 Selection of viruses resistant to RPV, ETR, EFV, or NVP starting from wild-type HIV-1 IIIB



Data Source: TMC278-IV1-AVMR, Figure 4

In Vitro Selection From Wild-type and Mutant HIV-1 at Low MOI

For the low-MOI and escalating drug concentration experiments, mutant strains resistant to RPV were isolated from cell cultures containing initial RPV concentrations ranging from 5 nM to 16 µM starting from wild-type and NNRTI resistant strains from various HIV-1 group M subtypes.

4.2.2.3. Description of HIV-1 Mutant Strains Selected in the Presence of RPV

The results from the high MOI selection experiments showed that 10 nM RPV was a suboptimal permissive concentration at which new HIV-1 strains emerged from subtypes A1, B, BG, and D and from the two HIV-1 SDMs resistant to RPV. These emerging HIV-1 strains were sequenced and harbored combinations of the NNRTI RAMs L100I, K101E, V106I, Y181C, Y181I, and/or M230I. Diversity in the number of emergent NNRTI RAMs was observed under the selective pressure of RPV.

Genotypic analyses of the viral RT of the strains emerging under selective pressure of RPV at low MOI, which were performed with a range of viruses of different origins and genotypic profiles, suggest that the in vitro resistance profile of RPV may include the mutations V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C, and M230I/L.

4.2.2.4. Antiviral Activity of RPV against HIV-1/HXB2 SDMs Containing Reverse Transcriptase Mutations

The analysis of a panel of HIV-1/HXB2 SDMs presented in TMC278-IV1-AVMR and in TMC278-IV2-AVMR showed that RPV retains antiviral activity against 63.0% (136 of 216) of the HIV-1/HXB2 SDMs carrying single, double, triple and quadruple RT mutations; as compared to 57.7% for ETR, 45.8% for EFV and 36.2% for NVP.

In Table 24 and Table 25, all 216 HIV-1/HXB2 SDMs were presented together with the determined median FC for RPV, EFV, ETR, and NVP. The analysis of this panel of HIV-1/HXB2 SDMs showed that:

- RPV retained activity against 64 of 67 single HIV-1/HXB2 SDMs analyzed and only the 3 HIV-1/HXB2 SDMs with K101P, Y181I, or with Y181V were resistant to RPV. More than one, and usually more than two NNRTI RAMs, were necessary to confer resistance to RPV in vitro. Resistance to RPV was mostly driven by the combination of specific NNRTI RAMs rather than the total number of NNRTI RAMs. K103N in isolation was not associated with resistance to RPV or ETR.
- From all the double HIV-1/HXB2 SDMs with a combination containing V90I, only those with E138Q or Y181I were resistant to RPV in vitro. From the various combinations with K101E, only those with L100I, E138K, or M184V were sensitive to RPV in vitro.
- The combination of E138K+M184I was resistant to RPV and ETR, but not to EFV and NVP. In contrast, the combinations of E138A+M184I, E138G+M184I, E138K+M184V and K101E+E138K+M184V were sensitive to RPV.
- The addition of M184V to any of the combinations of RT mutations did not modify their sensitivity to RPV, EFV, ETR or NVP. M184I and M184V were not selected in vitro in the presence of RPV.
- RPV and ETR retained activity against most of the single and a small number of the double and triple HIV-1/HXB2 SDMs resistant to NVP and EFV. However, considerable cross-resistance between RPV and ETR was observed among double, triple and quadruple SDMs.

Rilpivirine, as well as EFV, ETR, and NVP, retained activity against HIV-1/SDMs harbouring exclusively single or multiple NRTI RAMs.

Table 24 Antiviral Activity of RPV, EFV, ETR, and NVP against HIV-1/HXB2 SDMs Containing Reverse Transcriptase Mutations

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
V090I	1.7	1.6	1.5	4.4
L100I	0.9	20.3	1.3	7.3
K101A	2.2	4.1	1.8	12.8
K101D	1.4	5.7	1.0	17.0
K101E	2.4	3.8	2.7	ND
K101N	1.3	0.9	1.3	ND
K101P	51.7	72.3	5.3	>166.1
K101Q	1.6	2.4	1.4	2.5

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
K103H	0.5	14.4	0.6	7.6
K103N	0.9	32.5	0.9	>42.1
K103R	1.1	1.0	1.0	1.8
K103S	1.6	4.8	0.8	59.4
K103T	0.4	1.5	0.6	33.7
V106A	0.6	2.0	0.5	49.0
V106I	1.2	1.3	1.1	1.4
V106L	0.2	0.8	0.3	0.5
V106M	0.9	2.6	0.9	6.3
V108I	0.7	1.5	0.7	3.1
V108L	0.9	0.4	0.5	0.3
Y115F	1.0	1.7	1.1	4.3
E138A	2.5	1.6	2.9	2.3
E138G	1.6	0.9	2.4	2.8
E138K	2.8	2.0	2.6	1.1
E138Q	2.7	3.4	3.0	5.1
E138R	3.3	2.2	3.6	4.4
E138S	2.7	1.4	2.8	3.8
T139K	2.2	1.9	2.8	4.8
T139R	1.4	2.2	1.2	7.3
I178L	1.7	2.0	2.1	4.4
V179D	1.7	2.7	1.9	4.6
V179E	1.2	5.7	1.3	2.1
V179F	<0.1	<0.4	<0.2	0.6
V179G	0.2	0.3	0.4	0.1
V179I	0.9	1.0	0.9	1.3
V179L	0.8	0.7	1.0	1.7
V179M	0.5	0.3	0.7	1.2
V179N	0.9	1.1	0.8	1.6
V179T	1.5	1.0	0.7	0.8
V179Y	0.1	0.2	0.2	0.2
Y181C	2.7	2.1	4.0	>43.0
Y181F	0.3	0.4	0.4	1.5
Y181I	15.3	1.6	12.5	>65.7
Y181V	12.2	3.0	15.1	2155.9

Data Source: TMC278-IV1-AVMR Table 3 and TMC278IV2-AVMR Table 6
Note: Median FC values above the respective BCO of the tested drug were shaded in grey.

Table 25 Antiviral Activity of RPV, EFV, ETR, and NVP Against HIV 1/HXB2 SDMs Containing Reverse Transcriptase Mutations (Continued)

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
M184V	0.8	0.9	0.8	1.2
Y188C	0.1	1.5	0.2	25.5
Y188F	0.5	0.4	0.4	1.7
Y188L	2.8	42.6	1.1	>42.1
V189I	1.0	1.0	0.8	1.4
G190A	1.1	8.1	1.1	>86.6
G190S	0.2	94.8	0.2	96.9

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
G190T	0.6	11.3	0.7	ND
K219D	1.6	1.3	1.1	3.7
K219H	1.3	1.1	1.7	2.1
H221L	1.3	1.6	1.1	4.3
H221Y	1.8	1.6	1.6	4.3
P225H	0.4	1.5	0.6	2.1
F227C	3.1	4.5	2.5	ND
F227L	0.4	0.6	0.5	5.1
F227Y	0.8	1.0	1.1	1.1
M230I	2.7	5.0	3.5	13.6
M230L	3.4	5.9	3.6	20.4
M230V	2.1	1.1	0.8	1.4
M236L	1.1	1.0	1.2	3.4
K238N	0.9	1.3	1.4	3.3
K238T	1.4	2.1	1.3	9.2
Y318F	1.3	0.8	1.1	2.8
Y318W	0.5	2.0	0.5	17.4
V090I E138K	2.9	2.0	2.8	2.6
V090I E138Q	5.5	4.1	6.1	ND
V090I H221Y	1.8	1.8	1.6	3.9
V090I Y181C	2.3	2.6	5.1	269.3
V090I Y181I	30.2	3.7	36.8	>501.3
A098G K101E	6.1	12.8	3.1	53.8
L100I T139K	1.2	37.1	1.8	9.5
L100I Y181C	2.0	20.3	12.2	222.7
L100I Y188L	293.7	12785.0	42.8	ND
L100I, K101E	2.1	49.1	0.9	18.1
L100I, K103N	7.0	>575.8	4.0	>42.5
K101E E138K	1.9	1.8	2.6	3.6
K101E F227C	10.6	28.5	5.0	106.4
K101E H221Y	8.1	9.3	5.7	ND
K101E M184I	5.8	6.1	5.8	25.8
K101E M184V	2.2	4.7	2.8	10.6
K101E M230L	7.0	22.7	7.5	69.0
K101E V189I	5.0	6.1	3.3	24.2
K101H Y181C	11.3	8.2	13.1	>542.4
K101P G190A	20.2	3414.0	3.2	ND
K101P I167V	31.7	27.8	2.7	237.0
K101P K103S	429.3	1788.5	20.0	>747.9
K101P V108I	41.5	61.4	2.2	>718.1
K101E, K103N	2.0	56.4	1.8	>41.6
K102L Y188L	10.0	230.5	2.6	>22.7
K103N E138R	1.3	11.0	1.6	116.0
K103N H221L	1.7	ND	0.9	>79.6
K103N K238T	0.9	42.9	0.8	133.0
K103N M184V	1.1	40.2	0.9	121.9
K103N V179I	1.1	14.7	0.9	34.8
K103N Y181F	0.3	5.8	0.2	23.7
K103N Y188F	0.9	ND	0.7	>61.8

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
K103N Y318F	1.0	57.5	1.0	124.2
K103R V179D	2.2	8.7	2.7	15.2
K103R Y181C	3.4	1.3	3.9	>130.7
K103N, F227L	0.5	8.9	0.5	141.1
K103N, V108I	0.5	96.0	0.7	>205.2
K103N, Y181C	3.5	36.5	4.1	>41.8
K103N, Y181I	94.9	6.4	16.1	>71.5
V106A F227L	2.4	11.0	1.2	>478.2
V106A Y181C	1.8	2.8	2.2	>456.4
V106I E138K	2.8	1.9	3.9	2.2
V106I V179I	1.5	1.4	1.3	1.7
V108I E138K	2.6	2.3	2.6	4.4
V108I E138R	3.0	3.1	3.4	7.6
V108I M184V	0.7	1.4	0.9	2.6
Y115F M184V	0.9	1.0	0.9	1.8
V118I V179L	0.7	0.8	0.9	1.9
E138A M184I	2.8	1.4	3.3	1.3
E138A Y181I	92.1	2.7	56.4	>449.2
E138G M184I	1.7	1.1	2.3	ND
E138G V179G	0.5	0.4	0.7	0.2
E138K M184I	6.7	2.4	5.1	3.8
E138K M184V	3.1	1.9	3.2	1.8
E138K T139K	3.8	3.0	4.6	ND
E138K V189I	4.9	3.6	4.8	ND
E138R M184V	3.0	2.2	3.5	3.5
E138R V189I	3.2	3.8	5.2	7.7
E138K, M230L	22.6	18.7	19.3	>63.7
I167V Y181C	2.8	1.6	4.1	90.0
V179I G190A	1.1	4.7	1.0	203.4
V179T Y181C	6.0	2.6	13.0	170.8
V179Y G190A	<0.1	1.0	<0.1	16.5
V179D, Y181C	6.0	9.3	10.8	>71.5
V179E, Y181C	6.8	13.1	30.6	>71.5
V179F, Y181C	8.7	4.6	158.9	>358.3
V179F, Y181I	11.4	1.0	122.8	>71.5
V179I, Y181C	3.7	1.3	4.6	139.9
Y181C Y188C	0.4	1.4	0.7	>373.4
Y181C G190A	2.1	13.3	2.7	511.8
Y181C L234I	1.6	3.6	4.9	>43.4
Y181C M184I	2.5	2.0	3.0	156.4
Y181C, F227C	23.6	12.1	25.3	>77.3
Y181C, G190S	3.4	486.0	20.4	>71.5
Y181C, Y188L	30.2	237.5	6	>157.7
M184V F227C	1.4	2.8	2.5	ND
M184V T215Y	0.3	0.4	0.3	0.7
F223C L234I	2.3	30.0	4.2	>59.6
F227C M230L	20.2	43.0	16.5	234.3
C038R V108I Y181C	1.7	3.6	3.1	>22.7
I050T L100I K103N	4.4	1511.4	3.8	>85.9

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
L074V L100I K103N	6.2	2354.3	2.8	>105.0
V090I E138A M184I	2.8	1.2	2.0	1.3
V090I E138A Y181I	150.9	2.1	87.6	>501.3
V090I E138K H221Y	5.6	3.6	7.2	3.9
V090I E138K M184I	4.6	3.7	3.9	2.3
V090I E138K M184V	2.9	2.0	3.7	1.6
V090I E138Q V189I	6.1	6.3	9.8	20.5
V090I H221Y M230L	6.9	12.6	7.3	ND
V090I Y181C M184I	1.8	2.1	3.0	166.4
L100I E138K K219E	12.9	8.0	3.9	3.7
L100I E138K M184V	1.8	4.5	1.0	1.5
L100I E138K T139K	2.9	6.7	3.3	ND
L100I K101E F227C	132.3	520.3	5.1	>433.7
L100I K103N E138Q	52.9	3334.9	12.9	299.3
L100I K103N M184V	4.1	1531.1	1.7	>68.6
L100I K103N V179I	20.3	2396.6	4.0	>118.4
L100I, K103N, E138G	33.2	1695.3	20.8	>58.1
L100I, K103N, T386A	22.8	10866.5	12.2	>51.6
L100I, K103N, V179L	46.1	5660.6	13.4	>71.5
L100I, K103N, Y181C	80.8	1812.0	58.1	468.1
L100I, V179I, Y181C	15.2	16.9	34.1	>205.2
K101E E138K H221Y	4.2	3.7	3.7	9.6
K101E E138K M184I	2.0	1.3	2.6	2.5
K101E E138K M184V	1.8	1.6	1.6	ND
K101E Y181C H221Y	12.8	13.3	14.2	>628.7
K101E Y181C M184V	4.5	4.7	2.7	247.3
K101H K103R Y181C	7.6	11.1	11.2	>503.2
K101Q K103N V108I	0.9	96.2	0.7	33.4
K101P, K103N, V108I	>162.1	12931.1	18.4	>51.6
K103N E138Q Y181C	10.5	25.3	8.2	>85.9
K103N K219D Y181C	13.1	72.9	20.2	>79.6
K103N T139R Y181C	7.4	61.2	7.0	>22.7
K103N V108I Y181C	4.1	110.2	2.1	>456.4
K103N V179I G190A	0.4	208.0	0.6	>415.9
K103N V179T Y181C	5.2	21.8	8.4	>591.5
K103N Y181C E194G	4.3	ND	3.9	ND
K103N Y181C G190A	1.0	555.5	1.9	>456.4
K103N Y181C K219H	11.3	49.0	14.5	>79.6
K103N Y181C Y318F	7.8	89.2	6.9	>376.7
K103N Y188S Y318F	0.5	32.4	0.6	241.5
K103R V179D Y181C	14.1	60.4	46.3	>542.4
K103R V179F Y181C	3.5	3.4	7.3	ND
K103N, V179I, Y181C	10.5	16.7	14.5	>429.9
V106A E138K F227L	39.9	12.0	5.5	>501.3
V106A E138K V179I	4.9	1.0	1.6	111.6
V106I E138K V179I	2.7	1.1	2.1	1.2
V106M V179D Y181C	2.4	2704.1	28.8	>484.9
V108I E138K M184V	2.1	1.9	2.2	3.3
V108I E138K V179I	5.4	2.0	3.4	7.6

RT Mutations	Median RPV FC	Median EFV FC	Median ETR FC	Median NVP FC
V108I Y181C G190A	1.2	55.7	1.9	>456.4
E138A Y181I M184I	33.0	1.2	20.0	>501.3
E138K M184V M230L	1.8	1.9	2.7	6.0
E138K V179I M184V	2.2	1.1	2.8	1.4
E138K V189I H221Y	7.5	5.7	10.9	9.1
T139R Y181C Y188L	114.3	ND	26.6	>22.7
V179I Y181C G190A	1.2	9.8	2.1	661.8
V179F, Y181C, F227C	553.8	25.7	638.6	>71.5
Y181C M184V H221Y	2.1	3.5	3.5	>494.3
M184V K219N M230V	4.1	2.4	3.4	2.1
F227C M230L M184V	19.3	56.2	14.3	352.1
L074V L100I K103N M184V	5.5	1642.4	3.2	>79.0
V090I E138A Y181I M184I	20.5	0.8	17.3	>478.3
V090I E138K M184V H221Y	5.2	4.2	5.1	4.3
L100I E138K M184V K219E	6.9	7.7	2.9	2.6
K101E Y181C M184V H221Y	8.0	5.8	7.3	>470.0
V106A E138K V179I F227L	47.5	13.2	9.2	>501.3
V106I E138K V179I M184V	2.2	1.3	3.0	1.4
E138K V179I M184V K219E	1.7	1.3	ND	1.2

Data Source: TMC278-IV1-AVMR Table 3 and TMC278IV2-AVMR Table 6, and Table 8
Note: Median FC values above the respective BCO of the tested drug were shaded in grey.

4.2.2.5. Antiviral Activity in Combination with Current HIV-1 Inhibitors

The in vitro antiviral activity of RPV in combination with current HIV-1 inhibitors was examined and was scored as additive, synergistic or antagonistic. The following combinations with RPV were studied: the NRTIs zidovudine (AZT), lamivudine (3TC), emtricitabine (FTC), didanosine (ddI), stavudine (d4T), and abacavir (ABC), the NtRTI tenofovir (TFV), the NNRTIs EFV, ETR, and NVP, the Protease Inhibitors (PIs) amprenavir (APV), atazanavir (ATV), darunavir (DRV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), ritonavir (RTV), saquinavir (SQV), and tipranavir (TPV), the integrase inhibitor raltegravir (RAL), the fusion inhibitor enfuvirtide (ENF), and the binding inhibitor maraviroc (MVC). On the basis of the methodologies used, all combinations were scored as additive, except for the combinations with 3TC, AZT, and RAL, which showed low levels of synergy (TMC278-IV1-AVMR).

4.2.3. Conclusions of the in Vitro Virology Data

RPV is a NNRTI that showed sub-nanomolar EC_{50} values against wild type HIV-1 group M isolates A, B, C, D, E, F, and G (0.07–1.01 nM or 0.03–0.37 ng/mL), HIV-1/IIIB

(0.73 nM or 0.27 ng/mL) and nanomolar EC_{50} values against HIV-1 group O isolates (2.88–8.45 nM or 1.06– 3.10 ng/mL). The RPV EC_{50} values observed in human monocyte-derived-macrophages infected with HIV-1/Ba-L or HIV-1/ADA were comparable to those observed for HIV-1 group M isolates showing the broad and robust spectrum of the antiviral activity exhibited by this NNRTI. RPV had antiviral activity in the micromolar range against HIV-2 and SIV, but no activity was observed against several non-HIV related viruses like the human hepatitis B virus, herpes simplex virus 2, human corona virus, influenza A virus, and vaccinia virus. A selectivity index of ±8,000 indicated that RPV was a potent and specific inhibitor of HIV-1. The in vitro cytotoxicity experiments performed in cell lines of various origins confirmed that the RPV selectivity index was robust.

The crystal structure of RPV bound to the HIV-1 RT complex revealed that RPV adapted to changes in the NNRTI-binding pocket which could explain the increased genetic barrier to the development of resistance in vitro to this compound.

RPV retained antiviral activity against 63.0% (136 of 216) of the HIV-1/HXB2 SDMs carrying single, double, triple and quadruple RT mutations; as compared to 57.7% for ETR, 45.8% for EFV and 36.2% for NVP. This panel of HIV-1/HXB2 SDMs was created on the basis of resistance to ETR and the information on emerging RT mutations in patients failing RPV enrolled in the Phase IIb and Phase III trials. The analysis of this panel showed that:

- RPV retained activity against 64 of 67 single HIV-1/HXB2 SDMs analyzed in vitro and only the 3 HIV-1/HXB2 SDMs with K101P, Y181I, or with Y181V were resistant to RPV. More than one, and usually more than two NNRTI RAMs, were necessary to confer resistance to RPV in vitro. Resistance to RPV was mostly driven by the combination of specific NNRTI RAMs rather than the total number of NNRTI RAMs. K103N in isolation was not associated with resistance to RPV or ETR. Furthermore, some of the NNRTI RAMs present in the SDMs that showed resistance to RPV were uncommon in NNRTI treatment-experienced patients.
- Analysis of the double HIV-1/HXB2 SDMs with a combination containing V90I showed that only those with E138Q or Y181I were resistant to RPV in vitro. From the various combinations with K101E, only those with L100I, E138K, or M184V were sensitive to RPV in vitro.
- The combination of E138K+M184I was resistant to RPV and ETR, but not to EFV and NVP. In contrast, the combinations of E138A+M184I, E138G+M184I, E138K+M184V and K101E+E138K+M184V were sensitive to RPV.
- The addition of M184V to any of the combinations of RT mutations did not modify their sensitivity to RPV, EFV, ETR and NVP. M184I and M184V were not selected in vitro in the presence of RPV.
- RPV and ETR retained activity against most of the single and a small number of the double and triple site-directed mutants resistant to NVP and EFV. However, considerable cross-resistance between RPV and ETR was observed among double, triple and quadruple SDMs.

RPV, as well as EFV, ETR, and NVP retained activity against HIV-1/SDMs harbouring exclusively single or multiple NRTI RAMs.

Analysis of sensitivity to RPV of a panel of 4,786 HIV-1 recombinant clinical isolates resistant to at least one of the first-generation NNRTIs (EFV or NVP) showed that the in vitro cross-resistance that existed between EFV and NVP. This cross-resistance was not shared to the same extent by RPV and ETR, with the majority of the isolates (62%) retaining sensitivity to these novel NNRTIs. Considerable in vitro cross-resistance was observed between RPV and ETR.

Results from in vitro selection experiments performed at high multiplicity of infection showed that RPV was capable of inhibiting viral replication at concentrations where first-generation NNRTIs fail to do so. The rate of in vitro selection of RPV-resistant strains at low multiplicity of infection was comparable among HIV-1 group M subtypes. NNRTI RAMs emerging in HIV-1 under selective pressure of RPV included combinations of V90I, L100I, K101E, V106A/I, V108I, E138G/K/Q/R, V179F/I, Y181C/I, V189I, G190E, H221Y, F227C, and M230I/L where E138R represented a newly identified NNRTI RAM.

The antiviral activity of RPV in the presence of human serum proteins was comparable to that of EFV. RPV did not show antagonism when studied in combination with other antiretroviral agents. Low-level synergy was observed in the presence of 3TC, AZT, and RAL.

The current in vitro data demonstrated that RPV, an inhibitor of the HIV RT, is highly potent against a wide range of wild type HIV-1 group M and NNRTI-resistant HIV-1 variants that typically emerged after failing EFV- or NVP-containing regimens.

4.3. Clinical Virology -Dolutegravir

Table 26 Summary of Studies that were Previously Submitted as Part of the TIVICAY or EDURANT Registration and are "Supportive" Studies to the DTG/RPV FDC Submission

Study Number (component)	Study Title	Key Conclusion
ING113086 (DTG)	A Phase III, randomized, double blind study of the safety and efficacy of dolutegravir 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naive adult subjects.	Overall, there was a low rate of discontinuation due to virologic failure in both treatment arms, with only three additional subjects with protocol defined virologic failure (PDVF) identified after Week 48. The durability of the virologic response on DTG and RAL was maintained through Week 96. Both INI (RAL) and NRTI primary resistance mutations were observed in subjects on RAL with PDVF up to Week 96. No treatment emergent primary INI or NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study
ING114467 (DTG)	A Phase III, randomized, double-blind study of the safety and efficacy of DTG plus abacavir-lamivudine fixed-dose combination therapy administered once daily compared to EFV/ tenofovir (TDF)/FTC over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects.	DTG + ABC/3TC demonstrated long term durability with a low rate of discontinuation due to virologic failure through 96 weeks. No treatment emergent primary INI or NRTI resistance mutations were observed through 96 weeks for those subjects on DTG plus ABC/3TC FDC with PDVF. Both EFV and NRTI primary resistance mutations were observed in subjects on Atripla with PDVF.
ING114915 (DTG)	A Phase IIIb, randomized, open-label study of the safety and efficacy of DTG 50 mg once daily compared to darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily each administered with fixed-dose dual nucleoside reverse transcriptase inhibitor therapy over 48 weeks in HIV-1 infected antiretroviral naïve adult subjects.	DTG + ABC/3TC demonstrated long term durability with a low rate of discontinuation due to virologic failure through 96 weeks. No treatment emergent primary INI or NRTI resistance mutations were observed through 96 weeks for those subjects on DTG plus ABC/3TC FDC with PDVF. Both EFV and NRTI primary resistance mutations were observed in subjects on Atripla with PDVF.
ING111762 (DTG)	A Phase III Randomized, Double-blind Study of the Safety and Efficacy of GSK1349572 50 mg Once Daily Versus Raltegravir 400 mg Twice Daily, Both Administered with an Investigator-selected Background Regimen over 48 Weeks in HIV-1 Infected, Integrase Inhibitor-Naïve, Antiretroviral Therapy-Experienced Adults – Week 48 Results.	DTG exhibits a higher barrier to treatment failure than RAL. In a prespecified and multiplicity controlled analysis, there was a statistically significant difference in favor of DTG for the proportion of subjects who failed therapy with treatment-emergent evidence of INI resistance through Week 48.
C209 (RPV)	C209 was a 96-week, randomized, double-blind, double dummy, active-controlled, international, Phase III trial in HIV-1 infected ARV treatment-naïve adult subjects.	
C215 (RPV	C215 was a 96-week, randomized, double-blind, double-dummy, active-controlled,	

Study Number (component)	Study Title	Key Conclusion
	international, Phase III trial in HIV-1 infected, ARV treatment-naïve adult subjects.	

Note: Supportive Studies are available upon request

4.3.1. Treatment-Naive Subjects

4.3.1.1. ING113086 (SPRING-2)

Study Design: ING113086 is a Phase III randomized, double-blind, double dummy, active-controlled, multicenter, parallel group, fully-powered non-inferiority study. Subjects were randomized to DTG 50 mg once daily or 400 mg RAL twice daily, both in combination with either abacavir/lamivudine (ABC/3TC), or tenofovir/emtricitabine (TDF/FTC). Protocol defined virologic failure (PDVF) required two consecutive HIV-1 ribonucleic acid (RNA) values ≥50 c/mL HIV-1 RNA on or after Week 24. At the Week 96 visit, subjects randomized to RAL are discontinued from the study, while subjects randomized to DTG are given the opportunity to remain on the study while receiving DTG 50 mg once daily during the Open-label Phase of the study.

4.3.1.1.1. Viral genotyping and phenotyping study population

High response rates in ING113086 were observed despite the application of a strict PDVF criterion – namely, two consecutive HIV-1 RNA values ≥50 c/mL HIV-1 RNA on or after Week 24, which mandated withdrawal from the trial (if confirmed before Week 48) and testing for resistance. The majority of subjects who met PDVF in study ING113086 through Week 96 [GlaxoSmithKline Document Number 2013N158737_01] had low-level viremia; 76 to 77% of subjects in both arms with PDVF failed with <200 c/mL HIV-1 RNA (Table 27). All 22 subjects with PDVF on DTG had <1000 c/mL HIV-1 RNA at confirmed failure, while 3 (10%) of subjects with PDVF on RAL had >10,000 c/mL HIV-1 RNA at the time of confirmed failure (Table 27).

Table 27 Distribution of HIV-1 RNA at Time of PDVF

	DTG 50 mg once daily (N=411) n (%)	RAL 400 mg BID (N=411) n (%)
Subjects with PDVF	**22 (5)**	**29 (7)**
Suspected PDVF HIV-1 RNA (c/mL)		
50 to <200	14 (64)	24 (83)
200 to <400	2 (9)	1 (3)
400 to <1000	3 (14)	0
1000 to <10,000	2 (9)	1 (3)
10,000 to <50,000	1 (5)	0
50,000 to 100,000	0	3 (10)
>100,000	0	0
Confirmed PDVF HIV-1 RNA (c/mL)		
50 to <200	17 (77)	22 (76)
200 to <400	4 (18)	2 (7)
400 to <1000	1 (5)	2 (7)
1000 to <10,000	0	0
10,000 to <50,000	0	2 (7)
50,000 to 100,000	0	0
>100,000	0	1 (3)

Data Source: ING113086 Week 96 clinical study report (CSR) Table 7.23

As seen in Table 27, 22 subjects (5%) in the DTG treatment group met the definition of PDVF while 29 (7%) subjects in the RAL treatment group met the definition of PDVF. Subjects with PDVF predominantly had HIV-1 subtype B, with A1 being the next most common. In other subjects, a variety of subtypes were seen in small numbers, including AG, BF, C, F1, and G. Integrase, reverse transcriptase (RT) and protease (PR) genotypes and phenotypes were attempted at Baseline and time of PVDF for all subjects with PDVF.

Three subjects had PDVF after Week 48 (DTG 2; RAL 1). No treatment emergent IN or NRTI resistance mutations were detected in any of these subjects. Confirmation HIV-1 RNA levels were below 200 c/mL, hence all three were allowed to remain in the study as per subject management criteria of the amended protocol.

Ten subjects of the 22 with PDVF in the DTG treatment arm had IN genotype at both Baseline and at the time of PDVF, while 20 subjects of the 29 with PDVF in the RAL treatment arm had IN genotype at both Baseline and time of PDVF (Table 29). Fourteen of the 22 with PDVF in the DTG treatment arm had PR/RT genotype at both baseline (BL) and time of PDVF while 20 of the 29 with PDVF in the RAL treatment arm had PR/RT genotype at both Baseline and time of PDVF (Table 29).

4.3.1.1.2. Integrase genotyping and phenotyping results

Since the primary analysis of the study demonstrated non-inferiority, a secondary analysis testing for superiority using the same CMH weights was conducted at a two-sided 5% level of significance. The upper end of the 95% confidence interval associated with the adjusted estimate of the difference (DTG - RAL) in proportions was not below

0% and hence superiority of DTG with respect to INSTI resistance was not concluded (Table 28).

Table 28 Analysis of Proportion of Subjects with Genotypic or Phenotypic Evidence of INI Resistance at Time of PDVF by Week 96

	DTG 50 mg once daily N=411 n/N (%)	RAL 400 mg BID N=411 n/N (%)
Proportion meeting criteria of INI resistance	**1/411 (<1)**	**2/411 (<1)**
Difference in Proportion (95% CI) (DTG-RAL)	-0.2 (-1.1, 0.6)	
Adjusted Difference[a] in Proportion (95% CI) (DTG-RAL)	-0.2 (-1.1, 0.6)	

a. Adjusted Difference Based on Cochran-Mantel Haenszel stratified analysis adjusting for the Baseline stratification factors: Baseline HIV-1 RNA and background dual NRTI.

Data Source: ING113086 Week 96 CSR Table 7.10

Ten subjects of the 22 with PDVF in the DTG treatment arm had IN genotype at both Baseline and at the time of PDVF, while 20 subjects of the 29 with PDVF in the RAL treatment arm had IN genotype at both Baseline and time of PDVF. None of the ten subjects in the DTG treatment arm had treatment emergent INI resistance mutations while 1/20 (5%) of the subjects on the RAL treatment arm had treatment emergent INSTI resistance mutations (Table 29).

Three subjects ([redacted], [redacted], and [redacted]) had genotypic or phenotypic indication of treatment emergent integrase resistance and are discussed below.

Subject [redacted] was randomized to the RAL treatment group and received TDF/FTC as the nucleoside backbone. This subject had 3,346,333 c/mL HIV-1 RNA at Baseline, reached a nadir of 11,959 c/mL HIV-1 RNA at Week 2, and increased to 88,126 c/mL HIV-1 RNA at Week 24.

Of note in Subject [redacted]:

- Treatment emergent INI resistance mutations at Week 24 were T97T/A, E138E/D, V151V/I, and N155H.
- Week 24 virus had a 34 fold change (FC) to RAL and 2.02 FC to DTG, as compared to 1.15 FC to RAL and 1.48 FC to DTG at Baseline.
- Week 24 virus also had treatment emergent NRTI mutations A62A/V, K65K/R, K70K/E, and M184V with accompanying 1.44 FC to TDF and MAX FC to FTC.

Two additional subjects ([redacted] and [redacted]) had treatment emergent elevated FC to RAL (Table 29). Subject [redacted], who was randomized to the DTG group and received TDF/FTC, had 2.01 FC to RAL (0.96 FC to DTG) at PDVF (Week 32). As there were no treatment emergent INI resistance mutations at Week 32, all IN substitutions at Baseline and Week 32 were compared.

Of note in Subject [redacted]:

- Baseline virus had IN substitutions K14R, V32I, E48E/K, V72I, Y99F, L101I, V113I, S119P, T122I, T124A, T125A, G134N, K136T, K188R, V201I, T206S, Y227F, S255N, D256E, and S283G.
- IN substitutions at Week 32 were identical to those observed at Baseline with the exception that E48K was a full substitution at Week 32.

Subject [redacted], who received RAL and TDF/FTC as the nucleoside backbone, had 1.62 FC to RAL (1.40 FC to DTG) at PDVF (Week 24). As there were no treatment emergent INSTI resistance mutations at Week 24, all IN substitutions at Baseline and Week 24 were compared.

Of note in Subject [redacted]:

- Baseline virus had IN substitutions E11E/D, V31I, V72I, L101I, V113I, V201I, T206S, K215T, Q216Q/K, T218I, I220L, V234L, and D256E.
- IN substitutions at Week 24 were identical to those observed at Baseline with the exceptions that E11D was a full substitution at Week 24 and Q216 was fully Q at Week 24.

Table 29 Treatment Emergent Phenotypic or Genotypic Evidence of Integrase Inhibitor Resistance

Subjects with PDVF	DTG N=22	RAL N=29
IN Genotypic Results at Baseline and PDVF	N=10	N=20
INI resistance mutations	0	1/208 (5%)[a]
Phenotypic evidence of INSTI resistance		
Subject [redacted]		RAL FC = 34[a]
Subject [redacted]	RAL FC = 2.01	
Subject [redacted]		RAL FC = 1.62

a. T97T/A, E138E/D, V151V/I, N155H
Data Source: ING113086 Week 96 CSR Table 7.22, Listing 44

4.3.1.1.3. Reverse transcriptase genotyping and phenotyping results

Fourteen (14) of the 22 subjects with PDVF in the DTG treatment group had PR/RT genotype at both Baseline and time of PDVF, while 20 of the 29 with PDVF in the RAL treatment group had PR/RT genotype at both Baseline and time of PDVF (Table 30). None of the 14 subjects with Baseline and PDVF RT and PR genotypic data in the DTG treatment arm had treatment emergent NRTI resistance mutations while 4/20 (20%) of the subjects on the RAL treatment arm had treatment emergent NRTI resistance mutations (Table 30). In addition to Subject [redacted] (NRTI treatment emergent mutations A62A/V, K65K/R, K70K/E, and M184V) described above, subjects [redacted], [redacted], and [redacted] had treatment emergent NRTI resistance mutations at PDVF.

- Subject [redacted], who was in the RAL treatment group and received TDF/FTC as the NRTI backbone, had treatment emergent mutation M184M/I at PDVF (Week 24) with no accompanying phenotypic change to TDF or FTC.
- Subject [redacted], who was randomized to RAL and received TDF/FTC as the NRTI backbone, had treatment emergent mutation A62A/V at PDVF (Week 24) with no phenotypic change to TDF or FTC.
- Subject [redacted], who was randomized to RAL and received ABC/3TC as the NRTI backbone, had treatment emergent mutation M184M/V with 2.56 FC to ABC and MAX FC to 3TC.

Table 30 Treatment Emergent Genotypic Evidence of NRTI Resistance

Subjects with PDVF	DTG N=22	RAL N=29
RT/PR Genotype Results at BL and PDVF	14	20
Subjects with NRTI resistance mutations	0	4/20 (20%)
Genotypic Evidence of NRTI resistance		
[redacted]		A62A/V, K65K/R, K70K/E, M184V
[redacted]		M184M/I
[redacted]		A62A/V
[redacted]		M184M/V

Data Source: ING113086 Week 96 CSR Table 7.22, Listing 43

If subjects with PDVF with <400 c/mL HIV-1 RNA are censored from this analysis, there were only 6 subjects with PDVF in the DTG treatment group, none of whom had any treatment emergent resistance mutations, and only 4 subjects with PDVF in the RAL treatment group, including the one subject with RAL resistance mutations T97T/A, E138E/D, V151V/I, and N155H and NRTI resistance mutations A62A/V, K65K/R, K70K/E, and M184V.

4.3.1.1.4. Discussion

In this study, IN, RT, and PR genotypes and phenotypes were attempted at Baseline and the time of PDVF for all subjects with PDVF, even though the HIV-1 RNA levels were <400 c/mL for a vast majority of PDVF samples. As a result, IN genotypes were obtained at both time points for only 10/22 subjects on the DTG treatment group and 20/29 subjects on the RAL treatment group. Similarly, RT/PR genotypes were obtained at both time points for just 14 and 20 subjects on the DTG and RAL treatment groups, respectively.

Even though subjects with PDVF after week 48 were allowed to remain on the study up to a HIV-1 RNA of 200 c/mL, no subject in the DTG treatment group had treatment emergent INSTI resistance mutations through Week 96, and no additional subjects on RAL developed INSTI resistance between Weeks 48 and 96. One subject in the RAL treatment group had treatment emergent INSTI resistance mutations with an accompanying high RAL FC and only a slight increase in DTG FC at Week 24. This subject received TDF/FTC as the NRTI backbone and by the time of PDVF, the virus also had genotypic and phenotypic resistance to TDF and FTC.

No subject in the DTG treatment group had treatment emergent NRTI resistance mutations. Three subjects, all in the RAL treatment arm, had treatment emergent NRTI resistance mutations prior to Week 48; only one of these subjects also had phenotypic resistance to the nucleoside backbone. Two of these three subjects, and three of the four subjects with treatment emergent resistance mutations, had TDF/FTC as the NRTI backbone. Although numbers are small, this finding may suggest decreased NRTI mutations when NRTIs are co-administered with DTG in treatment-naive subjects.

No subjects in the DTG treatment group had any treatment emergent mutations in either IN or RT, including two subjects with PDVF after week 48. The four subjects with treatment emergent resistance mutations were all in the RAL treatment group and experienced PDVF prior to Week 48, including the subject with four INI resistance mutations and four NRTI resistance mutations.

DTG, when given to ART naive subjects along with two NRTIs, has demonstrated long term durability without the selection of treatment emergent resistance mutations.

4.3.1.1.5. Conclusions

- Overall, there was a low rate of discontinuation due to virologic failure in both treatment arms, with only three additional subjects with PDVF identified after Week 48. The durability of the virologic response on DTG and RAL was maintained through Week 96.
- Both INI (RAL) and NRTI primary resistance mutations were observed in subjects on RAL with PDVF up to Week 96. No treatment emergent primary INSTI or NRTI resistance mutations were observed for those subjects on DTG with PDVF throughout the study.

4.3.1.2. ING114467 (SINGLE)

Study Design: ING114467 was a Phase 3 randomized, stratified, double-blind, double-dummy, active-controlled, multicentre, parallel group, fully-powered non-inferiority study. Subjects were randomized 1:1 to receive DTG 50 mg plus ABC/3TC FDC therapy once daily or EFV/TDV/FTC once daily. Subjects were stratified by screening HIV-1 RNA and CD4 cell count. PDVF required two consecutive HIV-1 RNA values ≥50 c/mL HIV-1 RNA on or after Week 24. The primary analysis took place after the last subject completed 48 weeks on therapy; additional analyses were conducted after the last subject completed Week 96 and at Week 144.

4.3.1.2.1. Viral Genotyping and Phenotyping Study Population

High response rates were observed despite the application of a strict PDVF criterion – namely, two consecutive HIV-1 RNA values ≥50 c/mL HIV-1 RNA on or after Week 24), which mandated testing for resistance [GlaxoSmithKline Document Number 2013N167896_00].

As seen in Table 31, 39/414 subjects (9%) in the DTG + ABC/3TC treatment group met the definition of PDVF and 33/419 (8%) subjects in the Atripla treatment group met the definition of PDVF at 144 weeks.

Table 31 Distribution of HIV-1 RNA Results at Suspected and Confirmation of PDVF

	DTG 50 mg + ABC/3TC QD, 48 Weeks N=414 n (%)	EFV/TDF/FTC QD, 48 Weeks N=419 n (%)	DTG 50 mg + ABC/3TC QD, 144 Weeks N=414 n (%)	EFV/TDF/FTC QD, 144 Weeks N=419 n (%)
Subjects with PDVF	18 (4)	17 (4)	39 (9)	33 (8)
Suspected PDVF HIV-1 RNA (c/mL)				
50 to <200	12 (67)	11 (65)	22 (56)	22 (67)
200 to <400	3 (17)	0	4 (10)	2 (6)
400 to <1000	1 (6)	1 (6)	2 (5)	1 (3)
1000 to <10,000	2 (11)	2 (12)	5 (13)	5 (15)
10,000 to <50,000	0	2 (12)	2 (5)	2 (6)
50,000 to 100,000	0	1 (6)	0	1 (3)
>100,000	0	0	4 (10)	0
Confirmed PDVF HIV-1RNA (c/mL)				
50 to <200	16 (89)	11 (65)	29 (74)	23 (70)
200 to <400	0	3 (18)	3 (8)	5 (15)
400 to <1000	0	1 (6)	2 (5)	3 (9)
1000 to <10,000	1 (6)	1 (6)	1 3)	1 (3)
10,000 to <50,000	1 (6)	0	2 (5)	0
50,000 to 100,000	0	0	0	0
>100,000	0	1 (6)	2 (5)	1 (3)

Data Source: ING114467 Week 48 CSR Table 7.29; ING114467 Week 144 CSR Table 7.29

The majority of subjects who met PDVF by Week 144 in study ING114467 had low-level viremia (44/72, or 61% of subjects in the combined treatment groups with PDVF failed with <200 c/mL HIV-1 RNA). At confirmed failure by Week 144 29/39 (74%) subjects with PDVF on DTG + ABC/3TC had <200 c/mL HIV-1 RNA, while 23/33 (70%) of subjects with PDVF on Atripla had <200 c/mL HIV-1 RNA.

4.3.1.2.2. Integrase Genotyping and Phenotyping Results

through Week 144, 19 subjects in the DTG + ABC/3TC treatment arm had IN genotype and phenotype at both Baseline and at the time of PDVF, while 11 subjects in the Atripla treatment arm had IN genotype at and phenotype at both Baseline and time of PDVF.

None of the 30 subjects in either the DTG + ABC/3TC treatment group or the Atripla treatment group had treatment emergent INI resistance mutations. One subject ([redacted]) in the DTG + ABC/3TC treatment group had a treatment emergent substitution E157Q/P at Week 24, without accompanying DTG phenotypic resistance (Table 32). These substitutions were subsequently generated using site directed mutagenesis. The replication capacity of the E157P mutant was too low to evaluate. The E157Q substitution did not alter susceptibility to integrase inhibitors, giving a FC of 0.85, 0.92 and 1.1 for DTG, RAL and EVG, respectively Section 4.1.11.1.

Of note in Subject [redacted]:

- Treatment emergent IN substitution at Week 24 was E157Q/P. Replicative capacity could not be determined.
- Week 24 virus had a 1.13 fold change (FC) to DTG and 1.26 FC to RAL, as compared to 1.02 FC to DTG and 1.22 FC to RAL at Baseline.
- HIV-1 RNA at Baseline was 330,641 c/mL, reached a nadir of 79 c/mL at Week 12, and increased to 275 c/mL at Week 24.

Table 32 Treatment Emergent Genotypic or Phenotypic Evidence of Integrase Inhibitor Resistance

Subjects with PDVF	DTG + ABC/3TC, Week 48 N=18	EFV/TDF/FTC, Week 48 N=17	DTG + ABC/3TC, Week 144 N=39	EFV/TDF/FTC, Week 144 N=33
IN Genotypic Results at baseline and PDVF	N=7	N=7	19	11
IN substitution E157Q/P	1[a]	None	1[a]	None
IN Phenotypic Results at PDVF	N=7	N=7	19	11
Increase in DTG FC	None [a]	None	None	None

Data Source: ING114467 Week 48 CSR Table 12.2 and Table 12.5, ING114467 Week 144 CSR Table 12.1 and Table 12.8

a. Subject [redacted]; IN E157Q/P at Week 24. DTG FC = 1.13; RAL FC = 1.26

4.3.1.2.3. Non-Nucleoside Genotyping and Phenotyping Results

Seventeen subjects in the DTG + ABC/3TC treatment group had NNRTI genotypic and phenotypic data at both Baseline and time of PDVF. There were no treatment emergent NNRTI resistance mutations or treatment emergent NNRTI phenotypic changes in any of the subjects with PDVF in the DTG + ABC/3TC treatment group.

Twelve subjects in the Atripla treatment group had NNRTI genotypic and phenotypic data at both Baseline and time of PDVF. Six subjects (Subjects [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) in the Atripla treatment group had treatment emergent NNRTI resistance mutations. Phenotypic changes to EFV were observed in five of these subjects (Table 33)

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 48 was K101E.
- Week 48 virus had a 1.9 FC to EFV, as compared to 0.75 FC at Baseline.
- HIV-1 RNA at Baseline was 2212 c/mL, reached <50 c/mL at Week 16. Suspected Virologic Failure at Week 24 was not confirmed. HIV-1 RNA was 992 c/mL at Week 48.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 32 was K103K/N.
- Week 48 virus had a 14 FC to EFV, as compared to 1.66 FC at Baseline.
- HIV-1 RNA at Baseline was 53,961 c/mL, reached a nadir of <50 c/mL at Week 16, and increased to 6882 c/mL at Week 32.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutations at Week 24 were K103N and G190G/A.
- Week 24 virus had a 22 FC to EFV, as compared to 1.03 FC to at Baseline.
- HIV-1 RNA at Baseline was 112,284 c/mL, reached a nadir of <50 c/mL at Week 16, and increased to 40,751 c/mL at Week 24.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 24 was G190G/A. Additional treatment emergent NNRTI mutations were K103R and V179V/D.
- Week 24 virus had a 20 FC to EFV, as compared to 1.05 FC to at Baseline.
- HIV-1 RNA at Baseline was 5218 c/mL, reached a nadir of 89 c/mL at Week 16, and increased to 29.777 c/mL at Week 24.

Of note in Subject [redacted]

- Treatment emergent NNRTI resistance mutation at Week 60 was K103K/N.
- Week 60 virus had a 12 fold change (FC) to EFV, as compared to 0.76 FC to at Baseline.
- HIV-1 RNA at Baseline was 39,271 c/mL. This subject had unconfirmed virologic failure at Weeks 24 and 40. This subject had 2183 c/mL HIV-1 RNA at Week 60 and confirmed with 449 c/mL HIV-1 RNA.

Of note in Subject [redacted]:

- Treatment emergent NNRTI resistance mutation at Week 72 was K103N.
- Week 72 virus had an 11 fold change (FC) to EFV, as compared to 0.77 FC to at Baseline.

- HIV-1 RNA at Baseline was 12,078 c/mL. This subject had unconfirmed virologic failure at Week 40. This subject had 9043 c/mL HIV-1 RNA at Week 72 and confirmed with 77 c/mL HIV-1 RNA.

Table 33 Treatment Emergent Genotypic or Phenotypic Evidence of NNRTI Resistance

Subject Number	Treatment Group	Mutation	NNRTI Phenotype
[redacted]	Atripla	K101E	1.9 FC to EFV
[redacted]	Atripla	K103K/N	14 FC to EFV
[redacted]	Atripla	K103N, G190G/A	22 FC to EFV
[redacted]	Atripla	G190G/A	20 FC to EFV
[redacted]	Atripla	K103K/N	12 FC to EFV
[redacted]	Atripla	K103N	11 FC to EFV

Data Source: ING114467 Week 96 CSR Table 12.4, Listing 47 and Listing 48

4.3.1.2.4. Nucleoside Reverse Transcriptase Genotyping and Phenotyping Results

Seventeen subjects with PDVF in the DTG + ABC/3TC treatment group had NRTI and PI genotypic and phenotypic data at both Baseline and time of PDVF, while 12 subjects with PDVF in the Atripla treatment group had NRTI and PI genotypic and phenotypic data at both Baseline and time of PDVF.

There were no treatment emergent PI resistance mutations in either treatment group.

There were no treatment emergent NRTI resistance mutations in any of the subjects with PDVF in the DTG + ABC/3TC treatment group, though one subject did experience a minor increase in FC to the NRTI DDI (Table 34).

One subject in the Atripla treatment group (Subject [redacted]) had the treatment emergent NRTI resistance mutation K65K/R. This subject did not have treatment emergent phenotypic changes, although the [redacted] predicted resistance to all NRTIs with the exception of AZT and d4T (Table 34).

Of note in Subject [redacted]:

- Treatment emergent NRTI resistance mutation at Week 24 was K65K/R.
- Week 24 virus had a 0.69 FC to TDF and 1.27 FC to FTC, although the [redacted] predicted resistance to FC to ABC, DDI, FTC, 3TC, and TDF.
- HIV-1 RNA at Baseline was 376,229 c/mL. HIV-1 RNA was 131 c/mL at Week 24.

Of note in Subject [redacted]:

- Week 32 virus had a 1.39 FC to DDI (clinical cut off = 1.3), without treatment emergent NRTI resistance mutations.

- HIV-1 RNA at Baseline was 564,854 c/mL, was <50 c/mL at Week 12 and Week 24, and increased to 66 c/mL at Week 32.

Table 34 Treatment Emergent Genotypic Evidence of NRTI Resistance

Subject number	Treatment Group	Mutation	NRTI Phenotype
[redacted]	Atripla	K65K/R	No change
[redacted]	DTG + ABC/3TC	0	1.39 FC to DDI

Data Source: ING114467 Week 96 CSR Table 12.4, Listing 47 and Listing 48

If subjects with PDVF with <400 c/mL HIV-1 RNA are censored from this analysis, there were only 8 subjects with PDVF in the DTG + ABC/3TC treatment group, none of whom had any treatment emergent resistance mutations, and only 9 subjects with PDVF in the EFV/TDV/FTC treatment group, including the 6 subjects with NNRTI resistance mutations.

4.3.1.2.5. Discussion

Dolutegravir, when given to ART naive subjects along with ABC/3TC, has demonstrated long term durability without the selection of treatment emergent resistance mutations. The results of this study support those obtained in ING112276 and ING113086, indicating that DTG protects the nucleoside backbone better than EFV and RAL and support the belief that DTG has a higher barrier to resistance than EFV. No subjects in the DTG + ABC/3TC treatment group had any treatment emergent resistance mutations in either IN or RT, while six subjects in the Atripla treatment arm had treatment emergent NNRTI resistance mutations and one subject had a treatment emergent NRTI resistant mutation.

Even though subjects with PDVF after week 48 were allowed to remain on the study up to a HIV-1 RNA of 200 c/mL, no subject in the DTG treatment group had treatment emergent INI resistance mutations through Week 144

In an effort to obtain as much virology data as possible, Baseline and time of PDVF samples were evaluated for resistance for all subjects with PDVF (two consecutive HIV-1 RNA values ≥50 c/mL). This is in contrast to most clinical studies, including STARTMRK [Lennox, 2010; Sax 2012] where resistance testing is performed only on samples with >400 c/mL HIV-1 RNA.

No subject in the DTG + ABC/3TC treatment group had treatment emergent INSTI resistance mutations. The integrase substitution E157Q/P observed in one subject ([redacted]) in the DTG + ABC/3TC treatment group was not accompanied by increased FC to either DTG or RAL. Replication capacity could not be determined for this virus clinical isolate. The activities of DTG, RAL and EVG were tested for site directed mutant HIV-1 with E157P or E157Q (4.1.11.1). The replication capacity of the E157P mutant was too low to evaluate. The E157Q substitution did not alter susceptibility to integrase inhibitors, giving a FC of 0.85, 0.92 and 1.1 for DTG, RAL and EVG, respectively.

The E157P substitution has not been described, but the E157Q substitution has been observed in 5/112 (4.5%) patients with acute HIV-1 infection [Low, 2009]. This substitution has been selected along with H51Y, E92Q, and E147G during in vitro

passage with EVG [Shimura, 2008]. Shimura, et al., demonstrated that the enzyme carrying the E157Q substitution had reduced strand transfer activity relative to wild type levels, but they were able to determine that it remained susceptible to elvitegravir. The virus containing this substitution had only minimally decreased susceptibility to EVG.

In an analysis of clinical isolates obtained during RAL treatment, including a patient with IN substitution E157Q, it was shown that the E157Q enzyme was almost completely inactive in both 3' processing and strand transfer. In addition, the in vitro activity of this virus was too low for antiviral activity to be tested [Malet, 2008].

Six subjects in the Atripla treatment group had treatment emergent NNRTI resistance mutations; five of the six had treatment emergent phenotypic resistance to EFV. Four of the six subjects had K103N or K103K/N; two of the subjects had G190G/A (one with and one without a mutation at K103). These five subjects had 11 to 22 FC to EFV at PDVF. The sixth subject selected for K101E and had a 1.90 FC to EFV at PDVF.

No subject in the DTG + ABC/3TC treatment group had treatment emergent NRTI resistance mutations, although one subject had 1.39 FC to DDI with no accompanying resistance mutations.

One subject in the Atripla treatment group had treatment emergent K65K/R. While this virus did not have high level resistance to TDF, the [redacted] predicted resistance to ABC, DDI, FTC, 3TC, and TDF.

4.3.1.2.6. Conclusions

- DTG + ABC/3TC demonstrated long term durability with a low rate of discontinuation due to virologic failure through 144 weeks.
- No treatment emergent primary INI or NRTI resistance mutations were observed through 96 weeks for those subjects on DTG plus ABC/3TC FDC with PDVF. Both EFV and NRTI primary resistance mutations were observed in subjects on Atripla with PDVF.

4.3.1.3. ING114915 (FLAMINGO)

Study Design: ING114915 was a Phase IIIb randomized, open-label, active-controlled, multicenter, parallel group, non-inferiority study being conducted in 484 HIV-1 infected, ART-naïve adult subjects. This trial was designed to demonstrate the non-inferior antiviral activity of dolutegravir (DTG) 50 mg once daily versus darunavir/ritonavir (DRV/r) 800 mg/100 mg once daily over 48 weeks (with a non-inferiority margin of 12%). Both DTG and DRV/r were given in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) therapy (abacavir/lamivudine [ABC/3TC] or tenofovir/emtricitabine [TDF/FTC]). In an effort to obtain as much virology data as possible, baseline and time of PDVF samples were evaluated for resistance for all subjects with PDVF (confirmed plasma HIV-1 RNA >200 c/mL on or after Week 24, as compared to ≥ 50 c/mL HIV-1 RNA for ING113086 and ING114467).

4.3.1.3.1. Viral Genotyping and Phenotyping Study Population

Two subjects (<1%) in the DTG treatment group and 4 subjects (2%) in the DRV+RTV treatment group met PDVF [GlaxoSmithKline Document Number 2014N204382_01] through Week 96. The two subjects in the DTG treatment group had TDF/FTC as their nucleoside backbone and had PDVF at Week 24 (Subject [redacted] had 668 c/mL HIV-1 RNA, and Subject [redacted] had 2270 c/mL HIV-1 RNA). In the DRV+RTV treatment group 1 subject had low-level viremia (between 50 and 400 c/mL), 2 subjects had intermediate-level viremia (between 400 and 10,000 c/mL) and 1 subject had high-level viremia (between 50,000 and 100,000 c/mL) Three of the subjects in the DRV+RTV treatment arm had ABC/eTC as their nucleoside backbone, and the other had TDF/FTC as nucleoside backbone. No new cases of PDVF occurred in the DTG treatment group after the Week 48 analysis

4.3.1.3.2. Genotyping and Phenotyping Results

Genotype and phenotype for reverse transcriptase (RT), protease (PRO), and integrase (IN) were obtained at Day 1 and the time of PDVF for each subject who met PDVF. None of the subjects had treatment emergent resistance mutations in RT, PRO, or IN. One subject ([redacted], DTG treatment arm, TDF/FTC as the NRTI backbone) had phenotypic resistance to nelfinavir (4.12 FC), in spite of having no treatment emergent PRO resistance mutations. This subject had secondary PI resistance mutations L10V, I13V, K20R, E35D, M36I, I62I/V, L63T, and L89M at baseline and at PDVF (Week 24); no phenotypic resistance to PIs was observed at baseline (Data Source: ING114915 Week 48 CSR Table 12.4, Table 12.6, non-ICH Listing 51 and non-ICH Listing 53).

One subject (Subject [redacted], DRV+RTV treatment group, TDF/FTC as the NRTI backbone) had phenotypic resistance to delavirdine (6.71 FC at Day 1 and 7.91 FC at Week 84 [PDVF]). This subject had NNRTI resistance mutation V179D (not a primary resistance mutation) at both Day 1 and Week 84. This subject also had slightly elevated half maximal inhibitory concentration (2.02 FC to tipranavir at Week 84) in spite of having no treatment-emergent PRO resistance mutations (K20R, E35D, M36I, I62V, L63T, T74S, L89M were present at both Day 1 and Week 84; Data Source: ING114915 Week 96 CSR Table 12.4,

Table 12.6, non-ICH Listing 51, and non-ICH Listing 53). One subject (Subject [redacted], DRV+RTV treatment group, ABC/3TC as the NRTI backbone) had phenotypic resistance to delavirdine (10 FC at Day 1 and 8.23 FC at Week 72 [PDVF]), efavirenz (EFV, 3.38 FC at Day 1 and 3.34 FC at Week 72), nevirapine (9.36 FC at Day 1 and 7.53 FC at Week 72), rilpivirine (2.87 FC at Day 1 and 3.04 FC at Week 72), and zidovudine (2.31 FC at Week 72). The subject did not have NRTI or NNRTI resistance mutations at either Day 1 or Week 72 (Data Source: ING114915 weEK 96 CSR Table 12.4, Table 12.6, non-ICH Listing 51, and non-ICH Listing 53).

4.3.1.3.3. Discussion

No treatment-emergent resistance in either treatment group was noted through Week 96.

Only 2 subjects in the DTG treatment group and 4 subjects in the DRV+RTV treatment group met PDVF; no new cases of PDVF occurred in the DTG treatment group after the Week 48 analysis. No subjects had treatment-emergent INI substitutions of potential interest or treatment-emergent primary NRTI mutations. One subject in the DTG treatment group, who received TDF/FTC as the NRTI backbone, had phenotypic resistance to nelfinavir at PDVF, despite having no treatment-emergent PI resistance mutations. Several reasons for this finding were considered. Variability of the PRO phenotypic assay seems unlikely to fully explain this difference from Baseline. Mixtures in the PRO substitutions might account for the differences in phenotype between Baseline and Week 24 (without PI drug pressure), but only one of the PI secondary mutations for this subject was a mixture (I62I/V). Substitutions at this location are unlikely to result in phenotypic changes for nelfinavir susceptibility. Finally, re-infection with HIV containing nelfinavir resistance seems unlikely as well with no evidence of primary PI mutations at Week 24. The emergence of PI mutation in a subject receiving DTG is likely related to the presence of secondary PI mutations at Baseline and Week 24 for this subject. Also, 2 subjects in the DRV+RTV treatment group had phenotypic resistance in the absence of resistance mutations: one of them, who received TDF/FTC as the NRTI backbone, to delavirdine; and the other, who received ABC/3TC as the NRTI backbone, to delavirdine, efavirenz, nevirapine, and rilpivirine at both Day 1 and at PDVF, and zidovudine at PDVF.This study was consistent with ING113086 and ING114467 where a similar lack of detectable resistance in the DTG arms was noted.

4.3.1.3.4. Conclusions

- Overall, there was a low rate of discontinuation due to virologic failure in both treatment groups (DTG <1%, DRV+RTV 2%).

No treatment-emergent primary INI or NRTI resistance mutations were observed for subjects in the DTG or DRV+RTV treatment groups. One subject (in the DTG group) had phenotypic resistance to nelfinavir at PDVF, despite having no treatment emergent PI resistance mutations; 1 subject (in the DRV+RTV group) had resistance to delavirdine; and 1 subject (in the DRV+RTV group) had resistance to delavirdine, efavirenz, nevirapine, rilpivirine, and zidovudine.

4.3.2. Treatment Experienced, Integrase Inhibitor Naïve Subjects

4.3.2.1. ING111762 (SAILING)

Study Design: ING111762 is a Phase III randomized, double-blind, active-controlled, multicenter, parallel group, fully-powered non-inferiority study. Subjects were randomized to DTG 50 mg once daily or RAL 400 mg twice daily (BID), both in combination with investigator selected background therapy (ISBT) based on Screening and historic resistance results. The background therapy was limited to no more than two antiretroviral agents. At the Week 48 visit, subjects randomized to RAL will be discontinued from the study (if RAL is approved and commercially available in the country), while subjects randomized to DTG will be given the opportunity to remain on the study while receiving DTG 50 mg once daily during the Open-label Phase of the study.

Key results of the Week 48 Virology analyses [GlaxoSmithKline Document Number 2012N154814_01] include the following:

Protocol-defined virologic failure occurred earlier and more frequently in the RAL arm, with Week 48 in 21/354 (6%) and 45/361 (12%) cumulative virologic failures for DTG and RAL respectively. A primary reason for the difference in virologic failures at Week 48 was a higher number of virologic non-responders in the RAL arm n=19/45 (42%) than in the DTG arm n=2/21 (10%).

In a pre-specified key secondary endpoint analysis, there was a statistically significant difference in favor of DTG for the proportion of mITT-E subjects harboring virus with evidence of treatment emergent INI resistance by Week 48 (DTG: 4/354 [1%]; RAL: 17/361 [5%]; p=0.003).

A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects with treatment emergent INI substitutions on DTG that conferred no or low fold change in susceptibility to DTG and to RAL. Clinically relevant and previously described RAL associated genotypic resistance was observed in 16/38 (42%) subjects with confirmed virologic failure in the RAL arm, with high fold change to RAL and limited cross-resistance to DTG demonstrated at Week 48.

Protocol-defined virologic failure (PDVF) was defined as the following:

Virologic Non-response

- A decrease in plasma HIV-1 RNA of less than 1 $\log_{10}$ c/mL by Week 16, with subsequent confirmation, unless plasma HIV-1 RNA is <400 c/mL.
- Confirmed plasma HIV-1 RNA levels ≥400 c/mL on or after Week 24.

Virologic Rebound

- Confirmed rebound in plasma HIV-1 RNA levels to ≥400 c/mL after prior confirmed suppression to <400 c/mL.
- Confirmed plasma HIV-1 RNA levels >1 $\log_{10}$ c/mL above the nadir value where nadir is the lowest HIV-1 RNA value ≥400 c/mL.

4.3.2.1.1. Protocol Defined Virologic Failure

Virologic failure through Week 48 occurred earlier and more frequently in the RAL arm (Table 35). At Weeks 16 and 24, there were respectively 10 (3%) and 15 (4%) confirmed virologic failures for the DTG arm and 21 (6%) and 35 (10%) for the RAL arm. The difference through Week 24 was driven by a greater proportion of protocol defined virologic non-response in the RAL arm 5% versus <1% in the DTG arm, with a similar proportion of virologic rebound in both arms (4%). For DTG, 6 additional PDVFs occurred between Week 24 and Week 48 (none occurring after Week 32) and for RAL, 6 additional PDVFs occurred between Week 32 and Week 48, resulting at Week 48 in 21 (6%) and 45 (12%) cumulative virologic failures for DTG and RAL respectively.

Table 35 Cumulative Summary of Protocol-Defined Virologic Failures by Visit (mITT-E Population) Through Week 48

Week	DTG 50 mg Once Daily N=354 n/N (%)	RAL 400 mg BID N=361 n/N (%)
Week 8	1 (<1)	1 (<1)
Rebound	1 (<1)	1 (<1)
Week 12	4 (1)	6 (2)
Rebound	4 (1)	6 (2)
Week 16	10 (3)	21 (6)
Virologic non-response	0	13 (4)
Rebound	10 (3)	8 (2)
Week 24	15 (4)	35 (10)
Virologic non-response	1 (<1)	19 (5)
Rebound	14 (4)	16 (4)
Week 32	21 (6)	39 (11)
Virologic non-response	2 (<1)	19 (5)
Rebound	19 (5)	20 (6)
Week 40	21 (6)	44 (12)
Virologic non-response	2 (<1)	19 (5)
Rebound	19 (5)	25 (7)
Week 48	21 (6)	45 (12)
Virologic non-response	2 (<1)	19 (5)
Rebound	19 (5)	26 (7)

Data Source: ING111762 Week 48 CSR Table 7.10

Genotypic and Phenotypic Accountability

Integrase PhenoSense, Integrase Geneseq, PhenoSense GT, PhenoSense Entry and Trofile assays were performed at [redacted] ([redacted]). PhenoSense GT, PhenoSense Entry and Trofile were used to assess resistance to other ARTs for eligibility purposes and to aid in the selection of the background regimen; PhenoSense Entry and Trofile tests were performed for Baseline samples only when requested by investigator. Integrase PhenoSense, Integrase Geneseq, and PhenoSense GT assays were always performed at PDVF for both the Day 1 and PDVF timepoints, and PhenoSense Entry and Trofile were performed at these same timepoints when the agents were used in the background regimen. All Baseline and on-treatment genotypic (Table 36) and phenotypic testing (Table 37) were conducted at [redacted].

Due to integrase assay failure, paired data (Baseline and time of PDVF) for IN resistance was not available for 4/21 DTG PDVF samples and 7/45 RAL PDVF samples. This is typically due to viral load < 500 c/mL, reduced viral fitness, or compromised sample collection/handling. The suspect virologic failure Week 16 sample for one subject (Subject [redacted]) in the DTG arm was inadvertently tested instead of the confirmed

Week 24 sample. Additionally, the Day 1 IN resistance data needed for measure of emergent resistance was not available for Subject [redacted] as assay testing failed. The Week 16 sample IN resistance testing revealed no genotypic or phenotypic resistance. IN resistance testing at PDVF for one subject in the RAL arm (Subject [redacted]) was not available prior to database release and therefore was not included in the Week 48 CSR.

Table 36 Genotypes Available in PDVF Genotypic Population through Week 48

Genotype Assessment	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg BID N=44 n (%)
Integrase		
Screen Sample	0	3 (7)
Baseline Sample	19 (100)	43 (98)
On-Treatment PDVF Sample	17 (89)	38 (86)
On-Treatment Non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	17 (89)	38 (86)
Baseline and On-Treatment Non-PDVF	1 (5)	2 (5)
Reverse Transcriptase		
Screen Sample	19 (100)	44 (100)
Baseline Sample	19 (100)	44 (100)
On-Treatment PDVF Sample	19 (100)	44 (100)
On-Treatment Non-PDVF Sample	1(5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	44 (100)
Baseline and On-Treatment Non-PDVF	1(5)	2 (5)
Protease		
Screen Sample	19 (100)	44 (100)
Baseline Sample	19 (100)	44 (100)
On-Treatment PDVF Sample	19 (100)	44 (100)
On-Treatment Non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	44 (100)
Baseline and On-Treatment Non-PDVF	1 (5)	2 (5)

Data Source: ING111762 Week 48 CSR Table 12.5

Table 37 Phenotypes Available in PDVF Phenotypic Population through Week 48

Phenotype Assessment	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg BID N=43 n (%)
Integrase		
Screen Sample	0	3 (7)
Baseline Sample	19 (100)	42 (98)
On-Treatment PDVF Sample	17 (89)	38 (88)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	17 (89)	38 (88)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
Reverse Transcriptase		
Screen Sample	19 (100)	43 (100)
Baseline Sample	19 (100)	43 (100)
On-Treatment PDVF Sample	19 (100)	43 (100)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	43 (100)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
Non Reverse Transcriptase		
Screen Sample	19 (100)	43(100)
Baseline Sample	19 (100)	43 (100)
On-Treatment PDVF Sample	19 (100)	43 (100)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	43 (100)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
Protease		
Screen Sample	19 (100)	43 (100)
Baseline Sample	19 (100)	43 (100)
On-Treatment PDVF Sample	19 (100)	43 (100)
On-Treatment non-PDVF Sample	1 (5)	2 (5)
Baseline and On-Treatment PDVF	19 (100)	46 (98)
Baseline and On-Treatment non-PDVF	1 (5)	2 (5)
CCR5		
Screen Sample	16 (84)	40 (93)
Baseline Sample	16 (84)	40 (93)
On-Treatment PDVF Sample	1 (5)	6 (14)
On-Treatment non-PDVF Sample	0	0
Baseline and On-Treatment PDVF	1 (5)	6 (14)
Baseline and On-Treatment non-PDVF	0	0

Phenotype Assessment	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg BID N=43 n (%)
Fusion		
Screen Sample	12 (63)	32 (74)
Baseline Sample	12 (63)	32(74)
On-Treatment PDVF Sample	1 (5)	1 (2)
On-Treatment non-PDVF Sample	0	0
Baseline and On-Treatment PDVF	0	1 (2)
Baseline and On-Treatment non-PDVF	0	0

Data Source: ING111762 Week 48 CSR Table 12.41

4.3.2.1.2. On treatment Viral Genotyping / Phenotyping

Week 48 Genotypic and Phenotypic Analyses of Virus at Protocol-Defined Virologic Failure

Genotypic evidence of emergent INI resistance was identified according to the presence of IN substitutions specified in the reporting and analysis plan (RAP) that were not present at Baseline, which included substitutions associated with development of resistance to relevant integrase inhibitors (RAL or DTG) based on *in vitro* passage data and *in vivo* data.

Phenotypic evidence of emergent INI resistance was identified as FC in IC50 relative to wild-type, as provided by the PhenoSense HIV assays from [redacted], above the 1.5 biological cutoff for RAL or 2.5 cutoff for DTG (standard cut-off used by [redacted] until clinical or biological cut-off has been determined), if not above the cutoff at Baseline.

Proportion of Subjects with INI Genotypic or Phenotypic Resistance

Key secondary endpoint: For the modified intent to treat exposed (mITT-E) population, 1% of subjects receiving DTG and 5% of subjects receiving RAL had evidence of treatment emergent genotypic or phenotypic INI resistance at the time of protocol defined virologic failure by Week 48 (Table 38). The treatment difference was statistically significant in favor of DTG (p=0.003, less than the pre-specified two-sided 5% type I error cutoff) according to a pre-specified closed testing procedure.

Table 38 Summary of Analysis for Proportion of Subjects with Detectable Virus that has Treatment Emergent Genotypic or Phenotypic Evidence of INI Resistance by Week 48 (mITT-E Population)

Treatment	Number Meeting Criteria / Number Assessed	Difference in Proportion[a] % (95% CI)	Adjusted Difference in Proportion[b] % (95% CI)	P-Value[c]
DTG 50 mg Once Daily	4 / 354 (1%)			
RAL 400 mg BID	17 / 361 (5%)	-3.6 (-6.0, -1.1)	-3.7 (-6.1, -1.2)	0.003

Data Source: ING111762 Week 48 CSR Table 7.14

a. Difference: Proportion on DTG - Proportion on RAL.
b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline phenotypic susceptibility score (PSS) (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3.
c. Two-sided p-value for test of superiority. Type I error rate controlled according to a pre-specified fixed sequence testing procedure.

A statistically significant difference in favor of DTG was observed with the planned sensitivity analysis in Table 39 where the phenotypic resistance component of the endpoint was determined using a common FC cutoff of 2.5 for DTG and RAL.

Table 39 Summary of Sensitivity Analysis for Proportion of Subjects with Detectable Virus that has Treatment Emergent Genotypic or Phenotypic Evidence of INI Resistance by Week 48 (mITT-E Population)

Treatment	Number Meeting Criteria / Number Assessed (%)	Difference in Proportion[a] % (95% CI)	Adjusted Difference in Proportion[b] % (95% CI)
DTG 50 mg Once Daily	4 / 354 (<1%)		
RAL 400 mg BID	16 / 361 (4%)	-3.3 (-5.7, -0.9)	-3.4 (-5.7, -1.0)

Data Source: ING111762 Week 48 CSR Table 7.16

a. Difference: Proportion on DTG - Proportion on RAL.
b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3.

A statistically significant difference in favor of DTG was observed in the second planned sensitivity analysis of Table 40, which looked at additional resistance data. Specifically, this analysis includes evidence of treatment emergent resistance from subjects whose last on-treatment HIV-1 RNA was >400 c/mL at withdrawal for a reason other than virologic failure (DTG: Subject [redacted], discontinued at Week 4; RAL: Subject [redacted], discontinued at Week 48) or from subjects with confirmation of Week 48 PDVF occurring in the open

label phase of the study (RAL: Subjects [redacted] and [redacted]), if resistance testing results were available.

Table 40 Summary of Sensitivity Analysis for Proportion of Subjects with Additional Evidence of INI Resistance by Week 48

Treatment	Number Meeting Criteria / Number Assessed (%)	Difference in Proportion[a] % (95% CI)	Adjusted Difference in Proportion[b] % (95% CI)
DTG 50 mg Once Daily	5 / 354 (1%)		
RAL 400 mg BID	20 / 361 (6%)	-4.1 (-6.8, -1.5)	-4.2 (-6.8, -1.5)

Data Source: ING111762 Week 48 CSR Table 7.15

a. Difference: Proportion on DTG - Proportion on RAL.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (<=50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3.

Proportions of INSTI Resistance Substitutions

At Week 48, there were 17 subjects experiencing PDVF in the DTG arm with matched Baseline and PDVF IN genotypic resistance testing results available. Integrase substitutions emerged at the RAL associated T97, E138, and polymorphic V151 positions, and at R263. At Week 48 there were 38 subjects experiencing PDVF in the RAL arm with matched Baseline and PDVF IN genotypic resistance testing results available. Integrase substitutions emerged at positions commonly observed during virologic failure on RAL-containing therapy including primary resistance mutations at Y143, Q148, and N155 as well as associated secondary mutations (Table 41).

Table 41 Treatment Emergent Integrase Substitutions from Baseline (Week 48 PDVF Genotypic Population - IN results at Baseline and Time of PDVF)

Codon[a]	Treatment Emergent IN Genotype	DTG 50 mg Once Daily N=17 n (%)	RAL 400 mg BID N=38 n (%)
Any		**4 (24)**	**16 (42)**
68	L68L/V	0	1 (3)
74	L74L/M	0	1 (3)
92	E92E/Q	0	1 (3)
97	T97A, T97T/A	1 (6)	4 (11)
138	E138T/A	1 (6)	0
140	G140A, G140S	0	3 (8)
143	Y143Y/C, Y143R, Y143Y/R/H/C	0	5 (13)
148	Q148H, Q148Q/R	0	5 (13)
151	V151I, V151V/I	1 (6)	2 (5)
155	N155H, N155N/H	0	9 (24)
157	E157E/Q	0	1 (3)
163	G163K	0	2 (5)
263	R263K, R263R/K	2 (12)	0

Data Source: ING111762 Week 48 CSR Table 12.12

a. Per RAP definition RAL or DTG associated resistance mutations**:** H51Y, **T66A, T66I, T66K,** L68V, L68I, L74I, L74M, L74R4, **E92Q, E92V,** Q95K, T97A, G118R, E138A, E138K, E138T, G140A, G140C, G140S, **Y143C, Y143H, Y143R,** P145S, S147G, **Q148H, Q148K, Q148R**, V151I, V151L, S153F, S153Y, N155H, E157Q, G163R, G163K, G193E, R263K. IN substitutions listed above in bold were defined from the HIVdb [HIVdb, 2011] database (http://hivdb6.stanford.edu) with a score of >45. Other mutations are secondary IN resistance mutations from the Stanford database detected during INI clinical investigation, or were observed during other clinical investigation or in vitro studies with DTG.

INI Phenotypic Susceptibility by Fold Change Ranges

At PDVF within the DTG arm, 16/17 subjects with matched Baseline and PDVF IN phenotypic resistance testing results available had a DTG fold change of <2.5 ([redacted] DTG [standard] cutoff) and 16/17 RAL fold change of <1.5 ([redacted] RAL biological cutoff). The one subject (Subject [redacted]) receiving DTG with elevated DTG and RAL fold changes at PDVF enrolled with pre-existing RAL resistance mutations and with Baseline fold changes above cutoff for both DTG and RAL. Therefore, no DTG subjects had treatment-emergent INI phenotypic resistance at PDVF.

At PDVF within the RAL arm, four of the subject samples had a DTG fold change of ≥2.5 and 14 had RAL fold changes of ≥1.5 (Table 42). One of these subjects (Subject [redacted]) was also above the RAL cutoff at Baseline and enrolled with pre-existing RAL resistance mutations. Therefore, thirteen subjects receiving RAL had evidence of treatment-emergent INI phenotypic resistance to RAL at PDVF.

Table 42 Summary of Fold Change to DTG and RAL at Time of PDVF (Week 48 PDVF Phenotypic Population)

Investigational Product	Fold-Change Compared to Wildtype Virus	DTG 50 mg Once Daily N=19 n (%)	RAL 400 mg Twice Daily N=43 n (%)
DTG	n	17	38
	0 to 2.5	16 (84)	34 (79)
	>2.5 to 4	0	1 (2)
	>4 to 8	0	2 (5)
	>8 to 10	0	0
	>10 to 15	0	0
	>15 to 20	0	1 (2)
	>20 to 25	0	0
	>25	1(5)	0
	Median (Range)	0.92 (0.57 – 148.23)	1.08 (0.67 – 18.00)
RAL	n	17	38
	0 to 1.5	16 (84)	24 (56)
	>1.5 to 4	0	3 (7)
	>4 to 8	0	0
	>8 to 10	0	0
	>10 to 20	0	2 (5)
	>20 to maximum of assay limit	0	4 (9)
	>maximum of assay limit	1 (5)	5 (12)
	Median (Range)	0.93 (0.39 – 109.58)	1.13 (0.59 – 140.36)

Data Source: ING111762 Week 48 CSR Table 12.48

Emergent Integrase Resistance and Virologic Characteristics

Subjects on DTG or RAL with emergent integrase genotypic or phenotypic resistance through Week 48 are summarized in Table 43.

There were four PDVF subjects in the DTG arm (Subjects [redacted], [redacted], [redacted], and [redacted]) with emergent integrase-defined substitutions. Three of four subjects experienced virologic rebound and one experienced non-response. Three had no defined integrase resistance substitutions at Baseline; two of these three acquired a substitution at R263 and one acquired a polymorphic V151V/I substitution in the integrase open reading frame. In all three cases the DTG fold change was <2, as was the RAL fold change. None of the three subjects with emergent substitutions at R263 or V151V/I had RAL-associated secondary mutations at Baseline. At Baseline, one subject (Subject [redacted]) in the DTG arm harbored virus with RAL associated resistance mutations at Q148H, E138A, G140S, and elevated DTG FC of 12 at Baseline and RAL FC >Max measureable. At PDVF integrase substitutions E138T/A and T97A emerged and DTG and RAL FCs both increased to >Max measureable.

Subject [redacted] randomized to DTG and receiving DRV/r and TDF as the background regimen experienced virologic rebound PDVF at Week 16 and had treatment emergent R263R/K in integrase without significant change in DTG susceptibility (fold change at Baseline 0.96 and at PDVF 1.12). This subjects HIV-1 RNA response varied:

(c/mL)	Day 1		Week 4								Week16		Confirm
HIV-1 RNA	41,179	→	<50	→	57	→	1305	→	308	→	6446	→	903

The Baseline PSSf score was 2 and genotypic susceptibility score (GSS) score was 2 on a regimen of tenofovir and darunavir/r. The Week 4 C0 value was 0.5706 μg/mL. The fluctuating RNA between Day 1 and PDVF confirmation suggests adherence may have been incomplete.

Subject [redacted] randomized to DTG and receiving EFV and TDF as the background regimen experienced virologic rebound PDVF at Week 24 and had treatment emergent R263K in integrase with change in DTG susceptibility (fold change at Baseline 0.92 and at PDVF 1.93). A novel additional and conserved IN substitution V260I proximal to R263 was also present. This subject had an initial HIV-1 RNA response from Day 1: 876610 c/mL to Week 4: 1461 c/mL, followed by HIV-1 RNA 684 c/mL with sequential HIV-1 RNA values of 1852, 900, and at Week 24 PDVF timepoint. HIV-1 RNA 9367 c/mL followed by confirmation timepoint HIV-1 RNA of 59400 c/mL. The BL PSSf score was 1 and GSS score was 0.75 on a regimen of tenofovir (inactive) and efavirenz. The Week 4 C0 value was below the limit of quantitation (<0.02 ug/mL) and Week 24 C0 was 0.2525. The Week 4 C0 value of <0.02 ug/mL suggests adherence may have been incomplete.

Subject [redacted] randomized to DTG and receiving ABC and EFV as the background regimen experienced virologic non-response at Week 24 and had emergent polymorphic integrase substitution V151V/I with no change in DTG susceptibility (DTG Baseline FC = 0.94 to PDVF FC = 0.92). This subject had HIV-1 RNA at Day 1 of 171,984 c/mL to Week 4: 167,931 c/mL, followed by sequential HIV-1 RNA values of 180,560 c/mL, 95,477 c/mL, 126,925 c/mL and Week 24 PDVF timepoint HIV-1 RNA of 6,832 c/mL, followed by confirmation timepoint HIV-1 RNA of 29,432 c/mL. Of note resistance testing sample was not available for testing at the Week 24 PDVF timepoint; testing was carried out on the Week 24 confirmation timepoint sample and is provided in Table 43. In addition, Week 16 timepoint sample was tested, and, the same results were obtained with emergent polymorphic integrase substitution V151V/I with no change in DTG or RAL susceptibility (0.92 and 0.94 respectively). The Week 4 C0 value was below the limit of quantitation (<0.02 ug/mL).

Subject [redacted] randomized to DTG and receiving ATV/r and TDF as the background regimen experienced virologic rebound at Week 16 and had treatment emergent E138T/A and T97A added onto Baseline Q148H, E138A, G140S and with change in DTG susceptibility fold change from Baseline 12 to PDVF >Max. Subject [redacted] had 6.9 years ART experience but no reported RAL experience. This subject had an initial HIV-1 RNA response from Day 1: 153,533 c/mL to Week 16 PDVF timepoint HIV-1 RNA of 266,065 c/mL, followed by confirmation timepoint HIV-1 RNA of 608,458 c/mL. The BL PSSf score was 1 and GSS score was 0.25 on a regimen of atazanavir (active) and

tenofovir (inactive). The Week 4 C0 value was 0.94 ug/mL and Week 24 C0 value was below the limit of quantitation (<0.02 ug/mL).

There were 16 PDVF subjects in the RAL arm with emergent clinically relevant RAL associated genotypic integrase resistance at Week 48, seven of which were virologic non-responders, and nine were rebounders Table 43. Four of the 16 subjects in the RAL arm with emergent RAL associated genotypic integrase resistance had Baseline L74I present, one of the 16 had baseline E157Q, and one of the 16 had Baseline G193E. Five of the 16 subjects in the RAL arm had emergent DTG fold change >2 (Subjects [redacted], [redacted], [redacted], [redacted], and [redacted]). Three of these five experienced PDVF as virologic non-response, two at Week 16 and one at Week 24, and two experienced PDVF as virologic rebound. All five subjects with DTG FC >2 acquired (new) RAL associated primary resistance mutations at Y143 and/or Q148, or N155 at PDVF, plus additional secondary resistance mutations.

Table 43 Summary of Subjects with Paired Baseline and PDVF IN Genotype and/or Phenotype Exhibiting Genotypic or Phenotypic Changes Through Week 48

Arm / Subj	PDVF Visit	Baseline PSSf / GSS	Virologic Failure	HIV-1 RNA (c/mL)		DTG FC		RAL FC		IN Genotype	
				Baseline	PDVF	Baseline	PDVF	Baseline	PDVF	Baseline	PDVF
DTG / [redacted]	Week 16	2 / 2	Rebound	41179	6446	0.96	1.12	1.02	0.94	None	R263R/K
DTG / [redacted]	Week 16	1 / 0.5	Rebound	153533	266065	12	>Max[a]	>Max	>Max	E138A, G140S, Q148H	T97A,E138T/A,G140S,Q148H
DTG / [redacted]	Week 24	1 / 0.75	Rebound	876610	9367	0.92	1.93	1.11	1.12	None	R263K
DTG / [redacted]	Week 24	2 / 2	Virologic non-response	171984	6832	0.94	0.92	0.83	0.97	None	V151V/I
RAL / [redacted]	Week 16	2 / 1.25	Virologic non-response	98571	10725	0.71	18	>Max[a]	>Max	L74I/M, Y143R[b]	L68L/V, L74L/M/I, G140A, Y143Y/C, Q148Q/R, E157E/Q
RAL / [redacted]	Week 16	1 / 1	Virologic non-response	641416	84973	1.3	3.73	1.18	117	None	E92E/Q, T97T/A, V151V/I, N155H
RAL / [redacted]	Week 16	0 / 0	Virologic non-response	63449	58433	1.04	1.27	1.46	114	None	T97A, Y143R
RAL / [redacted]	Week 16	1 / 0.5	Virologic non-response	18441	2300	0.83	0.92	1.04	98	L74I	L74I, Y143Y/R/H/C, Q148Q/R
RAL / [redacted]	Week 16	2 / 1.75	Virologic non-response	47713	88989	0.98	0.9	1.25	1.6	V151I	V151I
RAL / [redacted]	Week 24	1 / 1	Virologic non-response	131377	7203	1.28	1.89	1.01	>Max	None	L74L/M, T97T/A, V151I, N155H, G163K
RAL / [redacted]	Week 24	2 / 1	Virologic non-response	856849	28931	1.13	4.12	1.23	>Max	E157Q	G140S, Q148H, E157Q
RAL / [redacted]	Week 24	1 / 1	Rebound	936821	10472	1	2.12	0.96	22	L74I	L74I, N155H
RAL / [redacted]	Week 24	1 / 0.5	Rebound	30711	47371	0.88	1.45	1.09	>Max	L74I	L74I,T97T/A,Y143Y/N/R/S/K/C
RAL /	Week	2 / 2	Virologic non-	28814	2734	1.14	0.89	1.14	1.44	None	N155N/H

Arm / Subj	PDVF Visit	Baseline PSSf / GSS	Virologic Failure	HIV-1 RNA (c/mL)		DTG FC		RAL FC		IN Genotype	
				Baseline	PDVF	Baseline	PDVF	Baseline	PDVF	Baseline	PDVF
[redacted]	24		response								
RAL / [redacted]	Week 24	1 / 1	Rebound	535742	3007185	0.92	1.38	1.09	3.78	L74I	L74I, N155N/H
RAL / [redacted]	Week 32	2 / 2	Rebound	49920	126272	0.59	0.69	0.41	0.66	None	N155N/H
RAL / [redacted]	Week 32	2 / 2	Rebound	93	1875	0.88	1.25	0.81	13	None	Y143Y/C, N155N/H,G163G/R
RAL / [redacted]	Week 32	2 / 1	Rebound	153526	2206	0.86	1.34	1	13	None	N155H
RAL / [redacted]	Week 40	2 / 2	Rebound	21403	860	0.88	4.36	0.8	>Max	G193E	G140S, Q148H, G193E
RAL / [redacted]	Week 40	2 / 2	Rebound	72029	1920	1.09	1.12	1	1.15	None	N155N/H
RAL / [redacted]	Week 40	2 / 2	Rebound	739998	879	1.08	1.13	1.02	2.34	None	Q148Q/R

Data Source: ING111762 Week 48 CSR Table 12.59; Table 12.60

a. Greater than maximum measureable in assay fold change resistance = >Max for DTG=>148; >Max for RAL =>110.

b. Per RAP definition RAL or DTG associated resistance mutations: L74M, L74I, T97A, E92Q, E138A, E138K, G140S, Y143C, Y143H, Y143R, Q148H, Q148K, Q148R, V151I, N155H, S153Y, S153F, G163K, G163R, G193E, R263K.

Treatment Emergent Resistance to Background Regimen

There was a statistically significant difference in favor of DTG with more emergent resistance to the background regimen in the RAL arm (12/361 versus 4/354 in the DTG arm) (Table 44), based on having evidence of a decrease in background regimen genotypic or phenotypic susceptibility scores from baseline to time of PDVF.

Table 44 Summary of Emergence of Genotypic and/or Phenotypic Resistance to the Background Regimen at Time of PDVF (mITT-E Population)

Treatment	Number meeting Criteria / Total Assessed	Difference in Proportion (95% CI) (DTG - RAL)	Adjusted Difference in Proportion[a] (95% CI) (DTG - RAL)
DTG 50 mg Once Daily	4 / 354 (1%)		
RAL 400 mg BID	12 / 361 (3%)	-2.2 (-4.3, 0.0)	-2.2 (-4.3, -0.1)

Data Source. ING111762 Week 48 CSR Table 7.30

a. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following Baseline stratification factors: Baseline HIV-1 RNA (≤50,000 vs. >50,000 c/mL), DRV/r use without primary PI mutations (yes vs. no), and Baseline PSS (2 vs. <2) to background regimen. PSS based on full susceptibility, category '2' includes two subjects with PSS=3. . Statistical significance was assessed relative to a nominal 5% type I error rate, without adjustment for multiple comparisions.

There were four subjects on DTG with emergent resistance to background regimen at PDVF; one had pre-existing RAL primary and secondary resistance mutations and additional emergent IN mutations at PDVF, and two other subjects also had emergent substitutions within the integrase open reading frame.

- **Subject [redacted]:** received TDF, ATV/r and had a PSSf score of 2 and GSS of 2.0 at Baseline. At Week 12 PDVF the PSSf score remained 2 while GSS score changed to 1.5 and the NNRTI mutation K101P/Q emerged, and no integrase substitutions emerged.
- **Subject [redacted]**: received TDF, EFV and had a PSSf of 1 and GSS of 0.75, with tenofovir inactive at Baseline. At Week 24 PDVF the PSSf score changed to zero and GSS score to 0.5 as NNRTI mutation G190S emerged, and integrase substitution R263K emerged.
- **Subject [redacted]:** received ABC, EFV and had a PSSf and GSS of 2. At Week 24 PDVF the PSSf and GSS scores changed to 1, as NNRTI mutations K101K/E/Q and G190A emerged. In addition, the polymorphic integrase substitution V151V/I emerged.
- **Subject [redacted]:** received TDF, ATV/r and had a PSSf score of 1 and GSS of 0.25. At Week 16 PDVF the PSSf and GSS scores changed to 0, and the PI mutation V32V/I emerged. Of note Subject [redacted] also had Baseline RAL integrase mutations Q148H, E138A, G140S and treatment emergent E138T/A and T97A at PDVF.

Twelve subjects in the RAL arm had treatment emergent resistance to the background regimen. Six subjects (Subjects [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) had treatment emergent background resistance and also emergent INI resistance (as shown in Table 43).

- **Subject [redacted]:** received ABC, TDF and had a PSSf score of 2 and GSS of 1. At Week 16 PDVF, the PSSf score was unchanged and GSS score changed to 0.75, with emergent RT mutations K70K/R and T215F. Of note, Subject [redacted] also had Baseline RAL integrase mutations Y143R, L74I/M and treatment emergent Q148Q/R, G140A, and E157E/Q at PDVF.
- **Subject [redacted]:** received received TDF, TPV/r and had a PSSf score of 2 and GSS of 2. At Week 24 PDVF, the PSSf and GSS scores changed to 1, with emergent PRO mutation I47I/V**.**
- **Subject [redacted]:** received MVC, ZDV and had a PSSf score of 2 and GSS of 2. At Week 32 PDVF, the PSSf and GSS scores changed to 1 as tropism changed from R5 to CXCR4 tropic.
- **Subject [redacted]:** received FTC, TDF and had a PSSf score of 2 and GSS of 2. At Week 40 PDVF, the PSSf score changed to 1 and the GSS score changed to 1, with emergent RT mutations K103N, P255H and M184V.
- **Subject [redacted]:** received 3TC, ABC and had a PSSf score of 1 and GSS of 0.5. At Week 24 PDVF, the PSSf score was unchanged and the GSS score changed to 0.25, without emergent IAS mutations but had increased resistance to ABC Stanford algorithm at PDVF.
- **Subject [redacted]:** received 3TC, ABC and had a PSSf score of 1 and GSS of 0.5. At Week 24 PDVF, the PSSf score changed to 0 and the GSS score changed to 0, with emergent RT mutation L74L/V.

Six other PDVF subjects in the RAL arm (Subjects [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted]) with treatment emergent background resistance did not have emergent integrase resistance at PDVF.

- **Subject [redacted]:** received DRV/r, TDF and had a PSSf score of 1 and GSS of 1.5. At Week 40 PDVF, the PSSf score was unchanged and the GSS score changed to 1.25 without emergent IAS mutations but increased resistance to TDF by Stanford algorithm at PDVF.
- **Subject [redacted]:** received DRV/r, ETR and had a PSSf score of 2 and GSS of 2. At Week 24 PDVF, the PSSf score changed to 1 and the GSS score changed to 1.25, with emergent RT mutations K101K/E, Y181Y/C, M230M/L and M41M/L, M184M/V, T215T/F/I/S, K219K/E.
- **Subject [redacted]:** received DRV/r, ETR and had a PSSf score of 2 and GSS of 2. At Week 16 PDVF, the PSSf score changed to 1 and the GSS score changed to 1, with emergent RT mutation Y181Y/C.
- **Subject [redacted]**: received ETR, LPV/r and had a PSSf score of 2 and GSS of 2. At Week 24 PDVF, the PSSf score was unchanged and the GSS score changed to 1.25, with emergent RT mutation Y181Y/C.

- **Subject** [redacted]: received ATV/r, TDF and had a PSSf score of 0 and GSS of 1. At Week 16 PDVF, PSSf score was unknown due to phenotypic assay failure, and the GSS score changed to 0.5, with emergent PRO mutation I84V.
- **Subject** [redacted]: received fosamprenavir (FPV)/r, TDF and had a PSSf score of 2 and GSS of 0.5. At Week 24 PDVF, the PSSf score changed to 0 and the GSS score was unchanged, without emergent IAS mutations.

Looking at all subjects there was negligible change from Baseline in number of classes for which at least one drug was available for both DTG and RAL.

Genotypic and Phenotypic Analysis of Virus for Other Samples

Subject [redacted] randomized to the DTG arm and was a virologic non-responder PDVF at Week 24. In addition to the testing at the confirmation timepoint for Week 24 PDVF due to lack of sample of actual PDVF, IN resistance testing was performed at the preceding Week 16 timepoint; as at Week 24 confirmation and provided in Table 43, the emergent polymorphic integrase substitution V151V/I was also observed with no change in DTG or RAL susceptibility.

4.3.2.1.3. Post Randomized Phase Results and Analyses Based on Data to Date

Protocol-Defined Virologic Failure Post Randomized Phase

Two subjects (Subjects [redacted] and [redacted]) in the DTG arm experienced suspected PDVF at the Week 48 visit which was confirmed during the open label phase of the study following the Week 48 visit. An additional 6 subjects experienced virologic rebound on DTG during the Open Label Phase: three at Week 60 (Subjects [redacted], [redacted], and [redacted]), two at Week 72 (Subjects [redacted] and [redacted]), and one at Week 84 (Subject [redacted]) (Table 45). Of note, Subject [redacted] was identified as a Protocol deviation due to non-compliance with investigational product (IP) treatment.

Three subjects (Subjects [redacted], [redacted], and [redacted]) in the RAL arm experienced suspected PDVF at the Week 48 visit which was confirmed during the open-label phase of the study following the Week 48 visit. An additional two subjects experienced virologic rebound on RAL during the open label phase at Week 60 (Subjects [redacted] and [redacted]). Resistance testing data was not complete for Subject [redacted] before database freeze.

Table 45 IN Genotypic and Phenotypic Data for Protocol Defined Virologic Failures Confirmed During the Open-Label Phase

Arm / Subj	PDVF Visit	HIV-1 RNA (c/mL)		DTG FC		RAL FC		IN Genotype	
		Baseline	PDVF	Baseline	PDVF	Baseline	PDVF	Baseline	PDVF
DTG / [redacted]	Week 48	346	80599	0.87	0.68	0.98	0.83	None	None
DTG / [redacted]	Week 48	20153	6691	0.83	0.94	0.85	0.92	None	None
DTG / [redacted]	Week 60	14749	282669	1.11	1.11	1.11	1.02	None	None
DTG / [redacted]	Week 60	1780	6164	0.83	0.87	0.83	0.87	None	None
DTG / [redacted][a]	Week 72	84313	27050	0.66	2.4	0.52	113	None	T97A, N155H
DTG / [redacted]	Week 72	461	82460	0.99	1.05	1.11	1.24	None	None
DTG / [redacted]	Week 84	6977	2035	0.96	NA	0.96	NA	None	NA[b]
RAL / [redacted]	Week 48	807	880	1.41	2.27	1.57	31	None	E92E/Q, N155H
RAL / [redacted]	Week 48	26387	1848	1.18	1.13	0.93	0.85	None	None
RAL / [redacted]	Week 48	85943	1871	0.82	2	0.82	30	L74L/I	L74I, T97T/A, N155H
RAL / [redacted]	Week 60	2417	46664	1.17	1.32	1.06	7.99	None	N155H
RAL / [redacted]	Week 60	5967	3862	1.01	NA	0.86	NA	None	NA

Data Source: ING111762 Week 48 CSR Table 12.59, Other Listing 71

a. Protocol deviation due to non-compliance with IP treatment

b. Resistance assay failure or data not available before database freeze.

4.3.2.1.4. Additional Virology Results

IN Viral Genotypic and Phenotypic Data for the Last On-Study Visit

To further monitor the development of resistance to INSTIs, the genotypic and phenotypic susceptibilities were determined at the last time point on study meeting the following criteria: unconfirmed suspected protocol-defined virologic failure HIV-1 RNA ≥400 c/mL. At Week 48, six subjects in the DTG arm and eight subjects in the RAL arm had resistance results that met these testing criteria (Table 46). Data for Subject [redacted] at Week 16 is included here and at Week 24 is included in Table 54; sample for resistance testing was not available for a timepoint between these two. One subject (Subject [redacted]) in the RAL arm was tested at the post Week 40 timepoint and the data is provided below, though the HIV-1 RNA is <400 c/mL for the tested timepoint. The polymorphic L74I/M substitution was observed as emerging on study only once for uncomfirmed suspect virologic failure on DTG (Subject [redacted]); the lack of substantive viral load decrease from Day 1 to Week 4 in the absence of any primary IN resistance mutation, and the stable DTG and RAL fold changes (<1) from Day 1 to Week 4, is

consistent with a stochastic presence of L74L/M/I mixture rather than DTG clinical selection pressure.

Table 46 Summary of Subjects with Elevated HIV-1 RNA who Discontinued Without Confirmation

Arm / Subject	Visit (Week)	HIV-1 RNA Baseline (c/mL)	HIV-1 RNA Resistance Testing (c/mL)	IN Genotype		DTG Fold Change		RAL Fold Change	
				Day 1	Final	Day 1	Final	Day 1	Final
DTG / [redacted]	16	66035	19896	none	none	0.90	0.81	0.87	1.03
DTG / [redacted]	4	4155	1929	none	L74L/M/I	0.88	0.88	0.73	0.75
DTG / [redacted]	8	371109	668	L74I	L74I	1.03	0.96	1.05	1.07
DTG / [redacted]	16	171984	126925	none	V151V/I	0.94	0.92	0.83	0.91
DTG / [redacted]	16	15447	2202	none	none	1.25	1.27	0.9	0.98
DTG / [redacted]	12	433019	1486	L74I	L74I	0.91	0.94	1.02	1.06
DTG / [redacted]	2	4695	2007	T97A	none	0.70	0.87	1.85	1.01
RAL / [redacted]	48	64707	458	None	None	0.97	0.81	0.8	0.77
RAL / [redacted]	8	663584	1375311	None	None	1.41	1.07	1.09	1.2
RAL / [redacted]	4	381204	105809	L74I	L74I	1.00	0.95	1.22	1.06
RAL / [redacted]	16	233573	44202	L74I	L74I	0.93	0.86	0.97	0.87
RAL / [redacted]	8	624823	247888	None	None	0.73	0.72	0.94	0.89
RAL / [redacted]	40	625	281	None	None	1.31	0.95	1.39	1.12
RAL / [redacted]	48	64707	458	None	None	0.97	0.81	0.8	0.77
RAL / [redacted]	16	120085	17972	None	None	0.68	0.83	0.56	0.9
RAL / [redacted]	16	33112	30725	L74I	L74I	0.91	0.75	1.33	1.33
RAL / [redacted]	48	16624	1153	L74I	L74I, N155H	0.75	1.38	1.07	26

Data Source: ING111762 Week 48 CSR Table 12.61; ICH Listing 9

4.3.2.1.5. Discussion

Results from this Week 48 analysis show DTG has a higher barrier to resistance in this patient population and a distinct resistance profile from RAL. A statistically significant difference in favor of DTG was demonstrated by planned virologic analyses for emergent integrase resistance. The proportion of subjects harboring virus with evidence of INI resistance by Week 48 was statistically lower for DTG vs RAL, with 1% (4/354) of subjects receiving DTG and 5% (17/361) of subjects receiving RAL harboring treatment emergent genotypic or phenotypic INI resistance at the time of protocol-defined virologic failure. A prespecified sensitivity analysis of the same endpoint but using a common FC cutoff to determine phenotypic resistance to RAL and DTG also confirmed a statistically significant difference in favor of DTG.

DTG exhibits a higher barrier to treatment failure than RAL. PDVF occurred earlier and more frequently in the RAL arm compared with the DTG arm, which reflects the greater suppressive effect in this ART-experienced patient population for DTG versus RAL.

Four of the 16 subjects in the RAL arm with treatment emergent INI resistance had baseline L74I polymorphism present, one of 16 had baseline E157Q, and one had baseline G193E. None of these positions have been associated with decreased response or greater frequency of virologic failure during INSTI therapy; they were included in the pre-defined list of potential INI resistance mutations along with clinically identified INSTI resistance mutations (e.g., at IN positions Q148, Y143, and N155) based on in vitro passage studies with relevant INIs to be comprehensive in studying this investigational INI (DTG).

At the previous Week 24 interim analysis, 2 of the 9 (22%) subjects with confirmed virologic failure in the DTG treatment arm had treatment emergent INSTI resistance substitutions which were both at position R263 in the IN open reading frame, and 9 (33%) of 27 in the RAL arm had treatment emergent INI resistance mutations commonly observed during RAL therapy including the primary resistance mutations at Y134, Q148, and N155 as well as associated secondary mutations. At Week 48, four PDVF subjects on DTG and 19 subjects on RAL with matched Baseline and PDVF resistance testing developed treatment emergent integrase genotypic and/or phenotypic changes. For all subjects in the RAL arm the observed mutations were, as expected, clinically relevant INSTI resistance mutations commonly observed during RAL therapy, and included the primary resistance mutations at Y134, Q148, and N155 and associated secondary mutations. For subjects in the DTG arm without Baseline RAL resistance, no primary or secondary resistance mutations commonly selected during RAL therapy emerged. In one case of emergent integrase resistance for the DTG arm, the IN substitution observed was at position V151 with no increase to DTG FC compared to wildtype. For the other DTG subjects with emergent integrase resistance, the IN mutations observed were at position R263 (max PDVF FC =1.93).

The R263K mutation has been selected during passage with EVG [Jones, 2007], has been infrequently observed during RAL therapy [Armenia, 2012; Blanco, 2011; Brenner, 2011], and most recently was selected during in vitro passage with DTG [Quashie, 2012; Oliveira, 2012]. Fold changes from R263K in vitro studies to date demonstrate some

variability with DTG fold changes ranging from 2.5 to 11.2, and the R263K substitution conferred decreased replication, strand transfer activity, and integration into host DNA in cell based assays [Oliveira, 2012; Mesplede, 2012; Quashie, 2012]. Fold change measures with site directed mutants HIV-1 gave DTG FC of 1.5 [GlaxoSmithKline Document Number 2013N167276_00, Section 4.1.11.1, similar to the FC <2 generated in this study. IN-DNA complexes with IN substitutions V260I, R263K, and V260I_R263K with BH-10 based integrase proteins were tested; all showed DTG half-life of dissociation (t½) greater than 50 h [GlaxoSmithKline Document Number 2013N181427_00].

Position 263 is in the C-terminal domain of the IN protein, resides within a posited integrase nuclear localization motif [De Houwer, 2012], and is distal from the typical location of strand transfer integrase inhibitor mutations which usually are positioned at or near component residues of the catalytic pocket or its sublayers. Based on a set of 2997 aligned integrase sequences selected from integrase inhibitor naive subjects, R263 was highly conserved at a 99.77% level, with 263K present at 0.11% frequency [Vavro, 2013].

Overall, RAL and EVG have strongly overlapping resistance profiles while DTG has been demonstrated to have a distinct resistance profile based on in vitro [Kobayashi, 2011] and now ex vivo evaluations of patient samples from this study.

While low levels of HIV-1 RNA were observed at PDVF for the ART-naive DTG studies ING113086 and ING114467, subjects experiencing virologic failure through Week 48 in this study typically had higher HIV-1 RNA levels that were more broadly distributed across HIV-1 RNA ranges. Most HIV-1 RNA levels were above 1000 c/mL and >40% were above 10,000 c/mL. Thus, the virologic failures in this study had sufficient viral replication for a robust assessment of integrase resistance. Despite these higher viral loads at failure, clinically relevant resistance to DTG was not observed, while clinically relevant RAL resistance was observed.

4.3.2.1.6. Conclusions

- DTG exhibits a higher barrier to treatment failure than RAL.
- In a prespecified and multiplicity controlled analysis, there was a statistically significant difference in favor of DTG for the proportion of subjects who failed therapy with treatment-emergent evidence of INI resistance through Week 48.

A unique IN substitution was observed (R263K or R263R/K mixture) in 2 subjects with treatment emergent resistance on DTG that conferred little change in susceptibility to DTG and to RAL.

4.4. Clinical Virology - Rilpivirine

4.4.1. Phase III Registrational Trials – C209, C215, and the Pooled Phase III Trials

4.4.1.1. Trial Design

C209 (TMC278-C209-W96-CSR) was a 96-week, randomized, double-blind, double dummy, active-controlled, international, Phase III trial in HIV-1 infected ARV treatment-naïve adult subjects. The trial was designed to evaluate the long term efficacy, safety, and tolerability of RPV 25 mg q.d. compared with EFV 600 mg q.d. (control), each in combination with a background regimen consisting of TDF and FTC. Adult subjects with an HIV-1 viral load of ≥5,000 c/mL, who were ARV treatment-naïve, susceptible to their background regimen at screening, and had no NNRTI RAMs in their screening genotype were eligible for the trial.

C215 (TMC278-C215-W96-CSR) was a 96-week, randomized, double-blind, double-dummy, active-controlled, international, Phase III trial in HIV-1 infected, ARV treatment-naïve adult subjects. The trial was designed to evaluate the long-term efficacy, safety and tolerability of RPV 25 mg q.d. compared with EFV 600 mg q.d. (control). Each of these NNRTIs was given in combination with a background regimen containing two nucleoside/nucleotide reverse transcriptase inhibitor [N(t)RTIs]. The investigator-selected N(t)RTIs were either ABC/3TC, AZT/3TC, or TDF/FTC. Adult subjects with a viral load of ≥5,000 c/mL, who were treatment-naïve, susceptible to their background regimen at screening, and had no NNRTI RAMs in their screening genotype were eligible for the trial.

In both trials, HIV-1 infected subjects were to be randomized in a 1:1 ratio to RPV 25 mg q.d. (n = 346 and n = 340 in C209 and C215, respectively) or to EFV 600 mg q.d. (n = 344 and n = 338 in C209 and C215, respectively). The primary objective of these trials was to demonstrate non-inferiority of RPV versus EFV in regard to the proportion of subjects achieving a confirmed viral load of <50 c/mL at 48 weeks of treatment [using time to loss of virological response (TLOVR) imputation].

4.4.1.2. Baseline Characteristics

The baseline disease characteristics of the subjects participating in C209 and C215 and of the Pooled Phase III trials are shown in Table 47.

Table 47 Baseline Disease Characteristics of the C209, C215 and the Pooled Phase III Trials

Baseline Disease Parameters Specification	C209		C215		Pooled	
	RPV N=346	Control N=344	RPV N=340	Control N=338	RPV N=686	Control N=682
Viral load (c/mL), N'	346	344	340	338	686	682
Median (Min–Max)	94,950.0 (156–3,300,000)	105,000.0 (1010–3,360,000)	83,950.0 (836–20,800,000)	105,000.0 (1140–4,550,000)	90,450.0 (156–20,800,000)	105,000.0 (1010–4,550,000)
Categorized baseline viral load, n (%)	346	344	340	338	686	682
≤100,000 c/mL	181 (52.3)	163 (47.4)	187 (55.0)	166 (49.1)	368 (53.64)	329 (48.2)
>100,000 to ≤500,000 c/mL	131 (37.9)	134 (39.0)	118 (34.7)	136 (40.2)	249 (36.1)	270 (39.6)
>500,000 c/mL	34 (9.8)	47 (13.7)	35 (10.3)	36 (10.7)	69 (10.0)	83 (12.2)
Log_{10} viral load (c/mL), N'	346	344	340	338	686	682
Median (Min–Max)	5.0 (2–7)	5.0 (3–7)	4.9 (3–7)	5.0 (3–7)	5.0 (2–7)	5.0 (3–7)
Absolute CD4+ cell count (cells/µL), N'	346	344	339	338	685	682
Median (Min–Max)	240.0 (1–888)	257.0 (1–757)	263.0 (2–744)	263.0 (1–1137)	249.0 (1–888)	260.0 (1–1137)
Relative CD4+ cell count (%), N'	346	344	339	338	685	682
Median (Min–Max)	18.7 (0–42)	17.8 (0–43)	17.6 (0–45)	17.0 (0–44)	18.3 (0–45)	17.5 (0–44)
Clinical Stage of HIV Infection at Screening (n [%]), N'	346	344	340	338	686	682
CDC Category A	248 (71.7)	242 (70.3)	237 (69.7)	232 (68.6)	485 (70.7)	474 (69.5)
CDC Category B	84 (24.3)	79 (23.0)	82 (24.1)	90 (26.6)	166 (24.2)	169 (24.8)
CDC Category C	14 (4.0)	23 (6.7)	21 (6.2)	16 (4.7)	35 (5.1)	39 (5.7)
Subtype (n [%]), N'	346	344	340	338	686	682
B	247 (71.4)	243 (70.6)	238 (70.0)	219 (64.8)	485 (70.7)	462 (67.7)
C	40 (11.6)	41 (11.9)	36 (10.6)	48 (14.2)	76 (11.1)	89 (13.0)
CRF01_AE	34 (9.8)	27 (7.8)	42 (12.4)	43 (12.7)	76 (11.1)	70 (10.3)
CRF02_AG	4 (1.2)	11 (3.2)	6 (1.8)	5 (1.5)	10 (1.5)	16 (2.3)
F1	6 (1.7)	8 (2.3)	4 (1.2)	6 (1.8)	10 (1.5)	14 (2.1)
A1	4 (1.2)	6 (1.7)	7 (2.1)	2 (0.6)	11 (1.6)	8 (1.2)
CRF12_BF	4 (1.2)	4 (1.2)	0	2 (0.6)	4 (0.6)	6 (0.9)
D	3 (0.9)	0	1 (0.3)	3 (0.9)	4 (0.6)	3 (0.4)
CRF07_BC	0	0	3 (0.9)	3 (0.9)	3 (0.4)	3 (0.4)
CRF14_BG	2 (0.6)	2 (0.6)	0	1 (0.3)	2 (0.3)	3 (0.4)
CRF03_AB	1 (0.3)	0	1 (0.3)	1 (0.3)	2 (0.3)	1 (0.1)
A1/CRF01_AE	0	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.1)	2 (0.3)
CRF08_BC	0	0	1 (0.3)	1 (0.3)	1 (0.1)	1 (0.1)
F2	1 (0.3)	0	0	0	1 (0.1)	0
CRF06_CPX	0	1 (0.3)	0	0	0	1 (0.1)
CRF16_A2D	0	0	0	1 (0.3)	0	1 (0.1)
CRF18_CPX	0	0	0	1 (0.3)	0	1 (0.1)

Data Source: TMC278-C209-C215-C904-W96-AVMR.
N=number of subjects per treatment group; N'=number of subjects with data; n=number of observations *At screening visit.
Note: percentages are based on the number of subjects with data available for each characteristic.

4.4.1.3. Antiviral Activity Data

The Week 96 analysis is based on the primary parameter of confirmed viral load <50 c/mL after 96 weeks of treatment according to the TLOVR algorithm. An overview of the key efficacy findings in the intent-to-treat (ITT) population at 96 weeks of treatment in trials C209 and C215 individually and pooled is presented in Table 48 (C904 AVMR, TMC278-C209 96 Week CSR, and TMC278C215 Week 96 CSRs).

Table 48 Efficacy Parameters at Week 96 (Phase III Trials C209, C215 and the Pooled Phase III Trials)

Efficacy parameters: Viral load <50 c/mL, n (%)	C209		C215		Pooled	
	RPV N=346	Control N=344	RPV N=340	Control N=338	RPV N=686	Control N=682
TLOVR	263 (76.0)	271 (78.8)	269 (79.1)	258 (76.3)	532 (77.6)	529 (77.6)
% Difference [95% CI][a] RPV-Control	-2.8 [-9.0; 3.5]		2.8 [-3.5; 9.1]		0.0 [-4.4; 4.4]	
Snapshot[b]	265 (76.6)	268 (77.9)	259 (76.2)	254 (75.1)	524 (76.4)	522 (76.5)
% Difference [95% CI][a] RPV-Control	-1.3 [-7.6; 4.9]		1.0 [-5.4; 7.5]		-0.2 [-4.7, 4.3]	

Data Source: TMC278 C209 Week 96 CSR, TMC278 C215 Week 96 CSR

a. 95% CI estimated using normal approximation of the binomial distribution method.

b. Snapshot analysis: missing equals failure imputation was applied and the last available viral load value in the Week 96 time point window (Weeks 90–103) was used.

N = number of subjects per treatment group; n = number of observations

Response rates were high and the efficacy results of the individual trials at 96 weeks were consistent in the demonstration of non-inferior efficacy for RPV versus (vs.) control. In the pooled Phase III trials, the proportion of subjects with viral load <50 c/mL (TLOVR) at Week 96 was 77.6% in both the RPV group and the control group.

In the Snapshot analysis of the pooled data (Table 49), 15.6% of subjects in the RPV group and 9.5% of subjects in the control group were virologic failures according to the Snapshot criterion (VF_{ss}) at Week 96. The majority of VF_{ss} occurred in the first 48 weeks of the trial, with few additional VF_{ss} up to the Week 96 time point in either the RPV or control group (18 and 3 additional VF_{ss}, respectively), indicating that the virologic responses seen were durable. There were fewer subjects in the RPV group than control with no viral load data in the Week 96 window (8.0% vs. 13.9%, respectively) and in this subset of subjects, there were fewer subjects who discontinued due to AE/death (3.7% vs. 8.5%, respectively).

Table 49 Outcome (<50 HIV-1 RNA c/mL, Snapshot) at Weeks 48 and 96 (Phase III Trials C209, C215 and the Pooled Phase III Trials)

Outcome Specification, n (%)	C209		C215		Pooled	
	RPV N=346	Control N=344	RPV N=340	Control N=338	RPV N=686	Control N=682
Week 48						
Virologic Response (<50 c/mL)	285 (82.4)	282 (82.0)	280 (82.4)	266 (78.7)	565 (82.4)	548 (80.4)
Non-responder						

Outcome Specification, n (%)	C209		C215		Pooled	
	RPV N=346	Control N=344	RPV N=340	Control N=338	RPV N=686	Control N=682
Virologic failure: Snapshot criteria (VFss)	47 (13.6)	25 (7.3)	42 (12.4)	37 (10.9)	89 (13.0)	62 (9.1)
Viral load ≥50 c/mL	17 (4.9)	13 (3.8)	17 (5.0)	15 (4.4)	34 (5.0)	28 (4.1)
Discontinued due to reaching a virologic endpoint, according to investigator's opinion	21 (6.1)	5 (1.5)	11 (3.2)	8 (2.4)	32 (4.7)	13 (1.9)
Discontinued due to other reason[a] and last available viral load ≥50 c/mL	9 (2.6)	7 (2.0)	9 (2.6)	9 (2.7)	18 (2.6)	16 (2.3)
Switch in background N(t)RTIs not permitted by protocol	0	0	5 (1.5)	5 (1.5)	5 (0.7)	5 (0.7)
No viral load data in Week 48 window	14 (4.0)	37 (10.8)	18 (5.3)	35 (10.4)	32 (4.7)	72 (10.6)
Discontinued due to AE	6 (1.7)	25 (7.3)	8 (2.4)	21 (6.2)	14 (2.0)	46 (6.7)
Discontinued due to death	0	0	1 (0.3)	3 (0.9)	1 (0.1)	3 (0.4)
Discontinued due to other reason[a] and last available viral load <50 c/mL (or missing)	5 (1.4)	11 (3.2)	8 (2.4)	11 (3.3)	13 (1.9)	22 (3.2)
Missing data during window but in the trial	3 (0.9)	1 (0.3)	1 (0.3)	0	4 (0.6)	1 (0.1)
Week 96						
Virologic Response (<50 c/mL)	265 (76.6)	268 (77.9)	259 (76.2)	254 (75.1)	524 (76.4)	522 (76.5)
Non-responder						
Virologic failure: Snapshot criteria (VFss)	54 (15.6)	27 (7.8)	53 (15.6)	38 (11.2)	107 (15.6)	65 (9.5)
Viral load ≥50 c/mL	13 (3.8)	11 (3.2)	20 (5.9)	10 (3.0)	33 (4.8)	21 (3.1)
Discontinued due to reaching a virologic endpoint, according to investigator's opinion	29 (8.4)	7 (2.0)	15 (4.4)	11 (3.3)	44 (6.4)	18 (2.6)
Discontinued due to other reason[a] and last available viral load ≥50 c/mL	12 (3.5)	9 (2.6)	9 (2.6)	11 (3.3)	21 (3.1)	20 (2.9)
Switch in background N(t)RTIs not permitted by protocol	0	0	9 (2.6)	6 (1.8)	9 (1.3)	6 (0.9)
No viral load data in Week 96 window	27 (7.8)	49 (14.2)	28 (8.2)	46 (13.6)	55 (8.0)	95 (13.9)
Discontinued due to AE	10 (2.9)	29 (8.4)	15 (4.4)	23 (6.8)	25 (3.6)	52 (7.6)
Discontinued due to death	0	3 (0.9)	1 (0.3)	3 (0.9)	1 (0.1)	6 (0.9)
Discontinued due to other reason[a] and last available viral load <50 c/mL (or missing)	16 (4.6)	16 (4.7)	11 (3.2)	19 (5.6)	27 (3.9)	35 (5.1)
Missing data during window but in the trial	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)

Source: TMC278-C209-W48-CSR, TMC278-C215-W48-CSR, TMC278-C209-W96-CSR, TMC278-C215-W96-CSR

a. Reason other than AE, death or discontinuation for reaching a virologic endpoint according to investigator's opinion

Note: The Snapshot analysis was based on the last observed viral load data within the Week 48 window (Weeks 44 – 54) or Week 96 window (Weeks 90 – 103).

N = number of subjects per treatment group; n = number of observations

4.4.1.4. Resistance Data

The resistance analysis of RPV at Week 96 for C209, C215, and the pooled Phase III trials was conducted on all the subjects, who experienced VF_{res} (rebounder, stopped treatment while not suppressed [STWNS] or never suppressed). The definition of VF_{res} is different from the definition used for virologic failure according to the primary efficacy criteria [time to loss of virologic response, Food and Drug Administration (FDA)-TLOVR, VF_{eff}] in order to capture as much data associated with resistance as possible.

Overall resistance data are presented in Section 4.2.2, whereas resistance data by baseline viral load are presented in the following Section.

The proportion of VF_{res} was higher in the RPV group (14.0% [96/686]) than in the control group (7.6% [52/682]) ($p < 0.0001$). The median time to VF_{res} in the RPV group (221.0 days) was shorter than in the control group (280.0 days) ($p = 0.0005$). The majority of the VF_{res} occurred within the first 48 weeks of the trial (10.6% for the RPV and 5.3% for the control group)[1]. Beyond Week 48 there were fewer VF_{res} and their proportion among the 2 treatment groups was comparable with 3.2% (22/686) for the RPV and 2.3% (16/682) for the control group. In both treatment groups, the vast majority of 'never suppressed' had occurred at or before Week 48(Table 50 and Table 51) whereas beyond Week 48 most VF_{res} in both treatment groups were 'rebounders'.

Table 50 Summary of VF_{res} (Phase III Trials C209 and C215, and the Pooled Phase III Trials)

	RPV			Control		
n (%)	C209 N = 346	C215 N = 340	Pooled N = 686	C209 N = 344	C215 N = 338	Pooled N = 682
VF_{res} Overall	56 (16.2)	40 (11.8)	96 (14.0)	23 (6.7)	29 (8.6)	52 (7.6)
Up to and Including Week 48	46 (13.3)	27 (7.9)	73 (10.6)	16 (4.7)	20 (5.9)	36 (5.3)
Beyond Week 48 and Up to and Including Week 96	10 (2.9)	12 (3.5)	22 (3.2)	7 (2.0)	9 (2.7)	16 (2.3)

Source: TMC278-C209-C215-C904-W96-AVMR
Note: There was one RPV VFres who occurred beyond Week 96

Table 51 Summary of VF_{res} by Virologic Failure Definition (Phase III Trials C209 and C215, and the Pooled Phase III Trials)

	RPV			Control		
VF_{res}, n (%)	**C209**	**C215**	**Pooled**	**C209**	**C215**	**Pooled**
All	N' = 56	N' = 40	N' = 96	N' = 23	N' = 29	N' = 52
Rebounder	27 (48.2)	23 (57.5)	50 (52.1)	15 (65.2)	17 (58.6)	32 (61.5)
STWNS	2 (3.6)	0	2 (2.1)	1 (4.3)	1 (3.4)	2 (3.8)
Never Suppressed	27 (48.2)	17 (42.5)	44 (45.8)	7 (30.4)	11 (37.9)	18 (34.6)
Up to and Including Week 48	N' = 46	N' = 27	N' = 73	N' = 16	N' = 20	N' = 36
Rebounder	19 (41.3)	10 (37.0)	29 (39.7)	8 (50.0)	10 (50.0)	18 (50.0)
STWNS	1 (2.2)	0	1 (1.4)	1 (6.3)	0	1 (2.8)
Never Suppressed	26 (56.5)	17 (63.0)	43 (58.9)	7 (43.8)	10 (50.0)	17 (47.2)
Beyond Week 48 and Up to Week 96	N' = 10	N' = 12	N' = 22	N' = 7	N' = 9	N' = 16
Rebounder	8 (80.0)	12 (100)	20 (90.9)	7(100)	7 (77.8)	14 (87.5)
STWNS	1 (10.0)	0	1 (4.5)	0	1 (11.1)	1 (6.3)
Never Suppressed	1 (10.0)	0	1 (4.5)	0	1 (11.1)	1 (6.3)

Data Source: TMC278-C209-C215-C904-W96-AVMR
N' = number of VF_{res} at failure

The proportion of VF_{res} was similar among subjects with HIV-1 subtype B and non-subtype B in both the RPV (14.8% [72/485] vs. 11.9% [24/201]) (p = 0.3364) and the control group (7.4% [34/462] vs. 8.2% [18/220]) (p = 0.7579).

Resistance data at failure are presented below. Failure is the most clinically relevant time point because the subject should withdraw from treatment when experiencing VF_{res}. Data at the last visit are presented in the antiviral microbiology report (TMC278-C209-C215-C904-W96-AVMR). Minor differences were found between 'failure' and 'last visit' and those are also described in TMC278-C209-C215-C904-W96-AVMR.

Genotypic data were available at failure for 86 RPV VF_{res} and 42 control VF_{res} (TMC278-C209-C215-C904-W96-AVMR, Table 6) For 10 VF_{res} in each treatment group, genotypic data were not available, usually due to too low viral load values.

The proportions of RPV VF_{res} versus control VF_{res} with at least one treatment-emergent RT mutation (80.2% [69/86] vs. 85.7% [36/42]) and with at least one NNRTI RAM (53.5% [46/86] vs. 47.6% [20/42]) were comparable (p = 0.5754) (Table 52). The proportion of RPV VF_{res} with at least one treatment-emergent N(t)RTI RAM was higher than that observed in control VF_{res} (55.8% [48/86] vs. 26.2% [11/42]) (p = 0.0023) as was the proportion with at least one treatment-emergent RPV RAM (48.8% [42/86] vs. 7.1% [3/42]) (Table 52 Consequent to the greater proportion of RPV VF_{res} with treatment-emergent N(t)RTI RAMs there were also more RPV VF_{res} with both NNRTI and N(t)RTI RAMs (50.0% [43/86]) than control VF_{res} (19.0% [8/42]) (p < 0.0001) (Table 52).

The NNRTI RAMs observed in the RPV VF_{res} were V90I, L100I, K101E/P, K103N, V106A/I, V108I, E138K/Q, V179I, Y181C/I, V189I, G190E, H221Y, F227C/L, and M230L; of which some were observed in only 1 RPV VF_{res} (K101P, K103N, V106A/I, V108I, Y181I, G190E, F227L, and M230L). The NNRTI RAMs observed in the control VF_{res} were V90I, L100I, K101E/Q, K103N, V106M, V108I, E138K, V179D, Y188C/H, P225H, and K238T; of which some were observed in only 1 control VF_{res} (V90I, L100I, K101Q, E138K, V179D, Y188H, G190E, P225H, and K238T). The most frequently observed NNRTI RAMs were E138K in 36.0% of the RPV VF_{res} and K103N in 33.3% of the control VF_{res} (Table 53).

Most RPV RAMs were found in the RPV VF_{res} (K101E/P, E138K/Q, Y181C/I, H221Y, F227C, and M230L). In control VF_{res}, few RPV RAMs were observed (Table 53).

The N(t)RTI RAMs observed in the RPV VF_{res} were A62V, K65R, D67N, V75I, Y115F, M184I/V, and K219E and were M184I, M184V and K65R in the control VF_{res}. The most frequently observed N(t)RTI RAM was M184I in 37.2% of RPV VF_{res} and M184V in 14.3% of the control VF_{res} (Table 53).

In the RPV VF_{res}, 2 treatment-emergent NNRTI RAMs (V106I and Y188H) and 1 treatment-emergent N(t)RTI RAMs (K70E [at last visit only]) which were not observed in the Week 48 analysis were newly reported in the Week 96 analysis (ad hoc analysis).

Table 52 Distribution of VF_{res} at Failure by Number of Treatment-emergent RT Mutations (Phase III Trials C209 and C215, and the Pooled Phase III Trials)

Treatment-emergent RT Mutations	RPV			Control		
	C209	C215	Pooled	C209	C215	Pooled
VF_{res}, n (%)	N' = 52	N' = 34	N' = 86	N' = 18	N' = 24	N' = 42
RT Mutations – Any	43 (82.7)	26 (76.5)	69 (80.2)	15 (83.3)	21 (87.5)	36 (85.7)
0	9 (17.3)	8 (23.5)	17 (19.8)	3 (16.7)	3 (12.5)	6 (14.3)
1	4 (7.7)	5 (14.7)	9 (10.5)	6 (33.3)	7 (29.2)	13 (31.0)
2	7 (13.5)	4 (11.8)	11 (12.8)	3 (16.7)	5 (20.8)	8 (19.0)
3	10 (19.2)	2 (5.9)	12 (14.0)	3 (16.7)	3 (12.5)	6 (14.3)
4	8 (15.4)	5 (14.7)	13 (15.1)	2 (11.1)	4 (16.7)	6 (14.3)
5	6 (11.5)	4 (11.8)	10 (11.6)	0	2 (8.3)	2 (4.8)
6	2 (3.8)	3 (8.8)	5 (5.8)	0	0	0
7	2 (3.8)	1 (2.9)	3 (3.5)	0	0	0
8	1 (1.9)	0	1 (1.2)	1 (5.6)	0	1 (2.4)
9	1 (1.9)	1 (2.9)	2 (2.3)	0	0	0
10	1 (1.9)	1 (2.9)	2 (2.3)	0	0	0
18	1 (1.9)	0	1 (1.2)	0	0	0
RT RAMs – Any	33 (63.5)	18 (52.9)	51 (59.3)	10 (55.6)	13 (54.2)	23 (54.8)
N(t)RTI RAMs – Any	31 (59.6)	17 (50.0)	48 (55.8)	5 (27.8)	6 (25.0)	11 (26.2)
0	21 (40.4)	17 (50.0)	38 (44.2)	13 (72.2)	18 (75.0)	31 (73.8)
1	25 (48.1)	14 (41.2)	39 (45.3)	5 (27.8)	6 (25.0)	11 (26.2)
2	5 (9.6)	3 (8.8)	8 (9.3)	0	0	0
3	1 (1.9)	0	1 (1.2)	0	0	0
NNRTI RAMs – Any	29 (55.8)	17 (50.0)	46 (53.5)	9 (50.0)	11 (45.8)	20 (47.6)
0	23 (44.2)	17 (50.0)	40 (46.5)	9 (50.0)	13 (54.2)	22 (52.4)
1	14 (26.9)	8 (23.5)	22 (25.6)	7 (38.9)	6 (25.0)	13 (31.0)
2	10 (19.2)	5 (14.7)	15 (17.4)	1 (5.6)	3 (12.5)	4 (9.5)
3	5 (9.6)	3 (8.8)	8 (9.3)	0	2 (8.3)	2 (4.8)
4	0	1 (2.9)	1 (1.2)	0	0	0
5	0	0	0	1 (5.6)	0	1 (2.4)
RPV RAMs – Any	26 (50.0)	16 (47.1)	42 (48.8)	0	3 (12.5)	3 (7.1)
0	26 (50.0)	18 (52.9)	44 (51.2)	18 (100)	21 (87.5)	39 (92.9)
1	19 (36.5)	10 (29.4)	29 (33.7)	0	3 (12.5)	3 (7.1)
2	5 (9.6)	5 (14.7)	10 (11.6)	0	0	0
3	2 (3.8)	1 (2.9)	3 (3.5)	0	0	0
NNRTI RAMs and N(t)RTI RAMs – Any	27 (51.9)	16 (47.1)	43 (50.0)	4 (22.2)	4 (16.7)	8 (19.0)
0	25 (48.1)	18 (52.9)	43 (50.0)	14 (77.8)	20 (83.3)	34 (81.0)
2	12 (23.1)	4 (11.8)	16 (18.6)	2 (11.1)	2 (8.3)	4 (9.5)
3	7 (13.5)	8 (23.5)	15 (17.4)	1 (5.6)	2 (8.3)	3 (7.1)
4	5 (9.6)	3 (8.8)	8 (9.3)	0	0	0
5	2 (3.8)	1 (2.9)	3 (3.5)	0	0	0
6	1 (1.9)	0	1 (1.2)	1 (5.6)	0	1 (2.4)

Data Source: TMC278-C209-C215-C904-W96-AVMR

Table 53 Individual Treatment-emergent RT Mutations in the RPV or Control Group at Failure (Phase III Trials C209 and C215, and the Pooled Phase III Trials)

	RPV			Control		
	C209	C215	Pooled	C209	C215	Pooled
VF_{res}, n (%)	N' = 52	N' = 34	N' = 86	N' = 18	N' = 24	N' = 42
NNRTI RAMs – Any	29 (55.8)	17 (50.0)	46 (53.5)	9 (50.0)	11 (45.8)	20 (47.6)
E138K	18 (34.6)	13 (38.2)	31 (36.0)	0	1 (4.2)	1 (2.4)
K101E	5 (9.6)	3 (8.8)	8 (9.3)	0	2 (8.3)	2 (4.8)
H221Y	4 (7.7)	3 (8.8)	7 (8.1)	0	0	0
V90I	4 (7.7)	2 (5.9)	6 (7.0)	0	1 (4.2)	1 (2.4)
Y181C	5 (9.6)	1 (2.9)	6 (7.0)	0	0	0
V189I	4 (7.7)	2 (5.9)	6 (7.0)	0	0	0
E138Q	3 (5.8)	0	3 (3.5)	0	0	0
L100I	1 (1.9)	1 (2.9)	2 (2.3)	1 (5.6)	0	1 (2.4)
V179I	1 (1.9)	1 (2.9)	2 (2.3)	0	0	0
F227C	1 (1.9)	1 (2.9)	2 (2.3)	0	0	0
K103N	1 (1.9)	0	1 (1.2)	8 (44.4)	6 (25.0)	14 (33.3)
V108I	1 (1.9)	0	1 (1.2)	1 (5.6)	1 (4.2)	2 (4.8)
G190E	1 (1.9)	0	1 (1.2)	0	1 (4.2)	1 (2.4)
K101P	0	1 (2.9)	1 (1.2)	0	0	0
V106A	0	1 (2.9)	1 (1.2)	0	0	0
V106I	1 (1.9)	0	1 (1.2)	0	0	0
Y181I	1 (1.9)	0	1 (1.2)	0	0	0
F227L	0	1 (2.9)	1 (1.2)	0	0	0
M230L	0	1 (2.9)	1 (1.2)	0	0	0
V106M	0	0	0	1 (5.6)	2 (8.3)	3 (7.1)
Y188C	0	0	0	0	2 (8.3)	2 (4.8)
K101Q	0	0	0	1 (5.6)	0	1 (2.4)
V179D	0	0	0	0	1 (4.2)	1 (2.4)
Y188H	0	0	0	0	1 (4.2)	1 (2.4)
P225H	0	0	0	1 (5.6)	0	1 (2.4)
K238T	0	0	0	1 (5.6)	0	1 (2.4)
N(t)RTI RAMs – Any	31 (59.6)	17 (50.0)	48 (55.8)	5 (27.8)	6 (25.0)	11 (26.2)
M184I	24 (46.2)	8 (23.5)	32 (37.2)	3 (16.7)	1 (4.2)	4 (9.5)
M184V	7 (13.5)	10 (29.4)	17 (19.8)	3 (16.7)	3 (12.5)	6 (14.3)
K219E	3 (5.8)	2 (5.9)	5 (5.8)	0	0	0
K65R	3 (5.8)	0	3 (3.5)	0	2 (8.3)	2 (4.8)
A62V	1 (1.9)	1 (2.9)	2 (2.3)	0	0	0
Y115F	2 (3.8)	0	2 (2.3)	0	0	0
D67N	0	1 (2.9)	1 (1.2)	0	0	0
V75I	0	1 (2.9)	1 (1.2)	0	0	0

Data Source: TMC278-C209-C215-C904-W96-AVMR
RPV RAMs are underlined
N' =number of VF_{res} with genotypic data at failure

RPV VF_{res} with E138K and RPV VF_{res} with M184I were more frequent within the first 48 weeks of treatment (40.3% [27/67] and 40.3% [27/67], respectively]) and less after Week 48 (16.7% [3/18] and 22.2% [4/18], respectively). The same trend was observed with K103N and M184V in control VF_{res} (Table 54).

Table 54 Distribution of VF_{res} with the Most Common Treatment-emergent RT RAMs over Time at Failure (Pooled Phase III Trials)

Treatment-emergent RT RAMs VF_{res}, n (%)	RPV			Control		
	Up to Week 48[a] N' = 67	Week 48 to Week 96 N' = 18	Overall N' = 86	Up to Week 48 [a] N' = 28	Week 48 to Week 96 N' =14	Overall N' = 42
None	19 (28.4)	8 (44.4)	27 (31.4)	10 (35.7)	8 (57.1)	18 (42.9)
NNRTI RAMs – Any	39 (58.2)	6 (33.3)	46 (53.5)	16 (57.1)	4 (28.6)	20 (47.6)
E138K	27 (40.3)	3 (16.7)	31 (36.0)	1 (3.6)	0	1 (2.4)
K103N	0	1 (5.6)	1 (1.2)	11 (39.3)	3 (21.4)	14 (33.3)
N(t)RTI RAMs – Any	41 (61.2)	6 (33.3)	48 (55.8)	9 (32.1)	2 (14.3)	11 (26.2)
M184I	27 (40.3)	4 (22.2)	32 (37.2)	2 (7.1)	2 (14.3)	4 (9.5)
M184V	15 (22.4)	2 (11.1)	17 (19.8)	6 (21.4)	0	6 (14.3)

Data Source: TMC278-C209-C215-C904-W96-AVMR
a. Up to and including Week 48
N' = number of VFres with genotypic data at failure.

Of the 81 RPV VF_{res} with phenotypic data at failure, 43.2% (35/81) had phenotypic resistance to RPV. Similarly, 41.5% (17/41) of control VF_{res} were resistant to EFV. Resistance to FTC and 3TC was observed for 58.0% and 57.0% RPV VF_{res}, respectively; and for 19.5% and 24.4% control VF_{res}, respectively. Most of the VF_{res} in both treatment groups retained sensitivity to ABC, TDF and AZT (Table 55).

RPV VF_{res} resistant to RPV were generally cross-resistant to EFV (85.7%) and ETR (91.4%) and to a lesser degree to NVP (45.7%), while control VF_{res} with phenotypic resistance to EFV retained sensitivity to ETR (94.1%) and RPV (100.0%), and were resistant to NVP (88.2%). RPV VF_{res} who retained sensitivity to RPV generally retained sensitivity to EFV (95.7%), ETR (91.3%) and NVP (100.0%) and to all tested N(t)RTIs. A similar observation was made in control VF_{res} who retained sensitivity to EFV (respectively, 100.0% to RPV, 100% to ETR, and 91.7% to NVP) (TMC278-C209-C215-C904-W96-AVMR) (Table 55).

Table 55 Cross-resistance of VF_{res} to NNRTIs and N(t)RTIs at Failure (Pooled Phase III Trials)

	RPV VF_{res}		Control VF_{res}	
	Resistant to RPV	Sensitive to RPV	Resistant to EFV	Sensitive to EFV
VF_{res}, n (%)	N' = 35	N' = 46	N' = 17	N' = 24
Resistant to RPV	–	–	0	0
EFV	30 (85.7)	2 (4.3)	–	–
ETR	32 (91.4)	4 (8.7)	1 (5.9)	0
NVP	16 (45.7)	0	15 (88.2)	2 (8.3)
3TC	34 (100.0[a])	11 (24.4[b])	6 (35.3)	4 (16.7)
ABC	5 (14.3)	1 (2.2)	0	0
AZT	0	2 (4.3)	0	1 (4.2)
FTC	35 (100.0)	12 (26.1)	6 (35.3)	2 (8.3)
TDF	1 (2.9)	1 (2.2)	0	1 (4.2)

	RPV VF_{res}		Control VF_{res}	
	Resistant to RPV	**Sensitive to RPV**	**Resistant to EFV**	**Sensitive to EFV**
VF_{res}, n (%)	**N' = 35**	**N' = 46**	**N' = 17**	**N' = 24**
Sensitive to RPV	–	–	17 (100.0)	24 (100.0)
EFV	5 (14.3)	44 (95.7)	–	–
ETR	3 (8.6)	42 (91.3)	16 (94.1)	24 (100.0)
NVP	19 (54.3)	46 (100.0)	2 (11.8)	22 (91.7)

Data Source: TMC278-C209-C215-C904-W96-AVMR
a. N' = 34;
b. N' = 45

E138K and M184I were the most commonly observed RAMs present in combination, comprising 44.2% of all RPV VF_{res} having a combination of least 1 treatment-emergent N(t)RTI RAM and at least 1 treatment-emergent NNRTI RAM (N' = 43)(Table 56). When these 2 RAMs were present in the absence of any other NNRTI or N(t)RTI RAM (n = 6), they conferred a median RPV FC of 6.45, with 5/6 of these VF_{res} having a FC above the BCO for RPV. Similar observations were made with the VF_{res} having the second most common combination of mutations K101E + M184I/V. The data presented in Table 56 are similar to those reported in the Week 48 analysis and should be interpreted with caution as the number of VF_{res} in the individual categories is small

Table 56 Distribution at Failure (Pooled Phase III) of the Most Prevalent NNRTI RAMs and N(t)RTI RAMs among the RPV VF_{res} with Combinations of NNRTI RAMs + N(t)RTI RAMs, the Median TM278 FC and the Distribution of RPV VF_{res} with Phenotypic Resistance to RPV (Pooled Phase III Trials)

RPV VF_{res}	n (%) [N' = 43]	Median RPV FC (Q1 – Q3)	RPV FC >BCO n
E138K + M184I (All)	19 (44.2)	8.10 (6.30 – 9.60)	17
Exclusively	6 (14.0)	6.45 (4.90 – 8.70)	5
+ other RT RAMs	13 (30.2)	8.30 (6.90 – 10.50)	12
E138K + M184V (All)	9 (20.9)	8.30 (6.50 – 10.90)	7
Exclusively	3 (7.0)	2.60 (1.80 – 6.50)	1
+ other RT RAMs	6 (14.0)	10.25 (8.30 – 21.20)	6
E138K + K101E + M184I (All)	4 (9.3)	3.45 (1.25 – 5.65)	2
Exclusively	1 (2.3)	5.40 (5.40 – 5.40)	1
+ other RT RAMs	3 (7.0)	1.50 (1.00 – 5.90)	1
E138K + K101E + M184V + other RT RAMs	2 (4.7)	3.45 (1.00 – 5.90)	1
K101E + M184I exclusively	2 (4.7)	4.60 (4.60 – 4.60)	2
K101E + M184V + other RT RAMs	1 (2.3)	24.50 (24.50 – 24.50)	1

Source: TMC278-C209-C215-C904-W96-AVMR
N' = RPV VFres having a combination of at least 1 treatment-emergent N(t)RTI RAM + at least 1 treatment-emergent NNRTI RAM

Genotypic and phenotypic profiles of the 81 RPV VF_{res} with paired genotypic and phenotypic data are presented inTable 57 for those without RT RAMS and Table 58 who

have RT RAMs at failure; they are distributed by BL viral load (VL) category using a cut-off at 100,000 c/mL.

Most of the RPV VF_{res} without NNRTI RAMs were sensitive to all NNRTIs. All the RPV VF_{res} with phenotypic resistance to RPV (FC >3.7) had a combination of at least one NNRTI and at least one treatment-emergent N(t)RTI RAM (Table 57).

The most common combination of RT mutations in the RPV VF_{res} was E138K + M184I. E138K was always observed in RPV VF_{res} in combination with an N(t)RTI RAM (most often with M184I/V) (Table 58) as summarized above in Table 56.

These analyses also indicate that subjects who failed their RPV regimen in C209 and C215 had a unique resistance profile, which appears to be independent of HIV-1 subtype and BL VL (Table 58).

Table 57 Resistance Profiles of the 25 RPV VF_{res} with Paired Geno/Pheno Data and without RT RAMs by Baseline Viral Load at Failure (Pooled Phase III Trials)

Subject ID	Subtype	Phenotype (FC)								
		RPV	EFV	ETR	NVP	3TC	FTC	TDF	ABC	AZT
VF_{res} with BL VL ≤100,000 C/mL										
[redacted]	B	2.6	0.9	1.3	0.7	0.6	1.0	0.9	0.3	0.6
	C	1.8	1.2	1.5	1.5	1.4	1.0	0.7	0.5	0.7
	C	1.7	0.6	1.0	1.8	0.8	1.6	0.5	0.6	1.3
	C	1.5	1.4	1.1	2.7	0.9	1.6	0.7	0.8	1.5
	C	1.1	1.3	0.8	0.8	1.0	0.8	0.5	0.4	0.7
	B	1.0	0.4	1.2	1.4	0.8	0.4	0.3	0.3	0.9
	B	0.9	1.0	1.0	0.6	1.1	1.0	0.6	1.2	2.0
	B	0.8	0.9	0.6	0.8	0.7	0.6	0.2	0.5	1.0
	C	0.8	0.7	0.8	1.5	1.3	1.6	1.4	0.5	0.7
	C	0.6	0.7	0.8	0.5	0.7	0.8	0.5	0.4	1.4
	B	0.6	0.5	0.1	0.6	0.6	0.9	0.7	0.4	1.1
	B	0.6	0.9	0.8	0.4	1.1	0.9	0.7	0.6	0.5
	B	0.6	0.6	1.1	0.4	0.6	0.7	0.8	0.4	1.1
VF_{res} with BL VL >100,000 C/mL										
[redacted]	F1	3.5	4.5	3.9	4.4	1.5	1.0	0.6	1.3	3.8
	B	2.3	2.3	1.5	2.3	0.9	1.1	0.8	1.0	1.1
	B	1.4	1.0	1.1	0.7	0.4	0.5	0.4	0.2	1.5
	B	1.4	1.2	1.2	0.8	0.8	1.2	0.7	0.7	0.5
	C	1.4	1.1	1.2	0.7	1.4	2.0	0.8	0.7	0.7
	B	1.3	0.7	1.0	0.6	0.6	1.0	0.6	0.7	1.8
	B	1.3	1.5	1.5	1.3	0.8	0.8	0.5	1.6	1.1
	B	1.3	1.7	1.1	1.2	0.8	1.4	0.6	1.2	1.4
	B	1.3	1.1	0.9	2.5	0.9	0.9	0.7	0.5	1.3
	B	1.1	1.1	1.0	0.7	0.8	1.0	0.7	1.4	1.0
	B	1.0	1.0	1.2	2.6	0.8	0.9	0.9	1.1	1.5
	B	0.6	0.6	0.8	0.9	0.6	0.4	0.5	0.5	0.9

Data Source: TMC278-C209-C215-C904-W96-AVMR
FC >BCO/CCO

Table 58 Resistance Profiles of the 56 RPV VF_{res} with Paired Geno/Pheno Data and with RT RAMs at Failure by Baseline Viral Load (Pooled Phase III Trials)

Subject ID	Sub type	Genotype	Phenotype (FC)								
			RPV	EFV	ETR	NVP	3TC	FTC	TDF	ABC	AZT
VFres with BL VL ≤100,000 c/mL											
[redacted]	B	(A98G), (V179I), Y181C, M184V, K219E	18.7	8.2	64.5	79.2	93.7	48.5	0.9	2.3	0.7
[redacted]	B	E138K, (V179I), M184I, K219E	10.5	2.6	5.6	0.7	34.9	34.8	0.1	1.9	0.8
[redacted]	B	M184I, (K219E)	8.6	1.2	1.8	1.8	37.2	19.3	0.3	0.9	0.2
	D	V90I/V, E138K, M184I	8.1	7.8	22.5	3.6	32.2	57.1	0.4	1.3	0.5
	B	V90I, E138K, M184I	6.5	6.9	7.3	2.3	70.0	48.5	0.7	2.3	0.7
	B	E138Q, M184I	3.2	2.6	4.6	1.1	68.9	30.6	0.4	1.5	0.7
	C	E138K, M184V	2.6	5.2	7.1	4.3	62.5	32.9	0.3	1.3	0.5
	C	V179I	2.0	1.8	1.5	3.0	0.3	0.5	0.2	0.6	0.7
	AE*	(V90I), (A62V)	2.0	2.4	2.3	2.7	0.6	0.8	0.5	0.6	1.0
	B	M184I/M	1.9	1.2	0.9	0.5	NA	3.6	0.3	0.5	0.8
	B	M184I	1.8	1.9	1.4	2.6	10.9	17.4	0.4	1.8	0.6
	B	E138K, M184I	1.6	1.2	2.5	0.8	34.9	24.9	0.6	1.7	0.6
[redacted]	B	L100I/L, K101E/K, E138E/K, M184I	1.5	3.2	2.9	5.0	21.9	32.4	0.4	1.0	0.4
[redacted]	B	K101E/K, E138E/K, M184I/M/V	1.0	2.5	3.1	1.9	29.2	19.8	0.5	1.9	0.4
VFres with BL VL >100,000 c/mL											
[redacted]	B	V90I, (E138A), Y181I, M184I	621.3	4.4	311.9	75.0	54.9	36.4	1.2	3.8	1.6
[redacted]	AE*	K101P/T, V75I/V, (M184V)	138.1	313.6	9.1	63.4	44.3	33.3	0.2	0.5	0.4
[redacted]	C	L100I, E138K/Q, M184I, K219E/K	64.4	35.7	63.9	32.8	53.3	23.0	1.1	2.3	1.7
[redacted]	B	E138K, (V179I), M184I/M/V	31.6	7.3	17.1	6.5	78.1	40.4	0.4	3.1	0.9
[redacted]	B	V108I, (V179I), Y181C, M184V, K219E	28.3	14.4	32.4	79.0	104.2	28.7	0.7	1.7	0.5
[redacted]	B	K101E, Y181C, H221Y, K65K/R, M184V	24.5	33.2	12.2	66.8	30.6	35.3	0.5	2.5	0.7
[redacted]	B	V106A, E138K, V179I, F227L, D67N	21.2	6.0	1.5	57.1	19.3	5.3	0.4	0.9	0.2
[redacted]	B	E138K, A62A/V, M184V	21.2	10.2	15.0	13.9	59.0	24.8	0.6	1.9	0.7
	B	F227C, M230L, M184V	17.5	41.7	13.7	56.7	63.8	40.8	0.3	1.1	0.2
	B	V90I/V, E138K, M184I	13.1	5.3	7.0	5.7	54.9	36.4	0.8	1.9	0.7
	B	E138K, H221Y, M184V	10.9	8.1	7.7	7.8	93.7	48.5	0.8	2.6	0.8
[redacted]	B	K101E, Y181C, V189I, K65R, K219E	10.0	4.3	14.0	51.3	12.6	24.9	1.5	6.6	0.3
[redacted]	B	E138K, V189I/V, H221H/Y, M184I/M/V	9.6	4.4	12.1	5.4	70.8	60.9	0.9	4.2	2.2
[redacted]	C	E138E/K, Y181C/Y, H221H/Y, A62A/V, K65K/R, M184I	9.0	13.0	14.0	25.4	45.9	25.6	0.5	1.7	0.7
[redacted]	C	E138K, M184I	8.8	3.8	4.9	1.6	62.4	27.9	0.5	1.4	0.3
	B	E138K, M184I	8.7	5.7	14.6	6.7	32.3	27.6	0.5	3.0	0.7
	B	E138K, M184I/M/V	8.3	3.7	9.1	2.1	144.6	55.5	0.6	3.3	0.7
[redacted]	B	V90I, E138K/Q, V189I/V, M184I	7.9	4.5	8.1	10.0	37.8	24.2	0.5	2.5	1.1
[redacted]	AG*	E138K, M184I	7.8	6.7	11.8	2.8	19.5	13.3	0.6	1.2	0.6

[redacted]	B	E138K, V189I/V Y115F/Y, M184V	7.5	3.3	10.8	4.4	72.7	28.7	0.5	3.2	1.1
[redacted]	B	(V90I), E138K, H221H/Y, M184I	6.9	2.2	8.0	1.3	106.2	37.0	0.7	1.6	1.0
[redacted]	B	E138K, M184V	6.5	2.1	6.7	1.4	57.7	22.9	0.6	4.2	1.5
	B	V90I, E138K, M184I	6.3	3.8	6.2	1.2	36.5	1.0	0.7	1.5	0.4
[redacted]	B	K101E/K, (V106I), E138E/K, H221H/Y, M184I/M/V	5.9	7.1	11.1	4.3	NA	16.9	0.2	1.5	0.4
[redacted]	B	K101E/K, E138E/K, M184I	5.4	7.2	9.4	4.1	144.6	47.4	1.0	0.8	0.6
	B	E138K, M184I	5.1	4.0	4.6	1.1	28.4	19.6	0.5	1.4	1.1
[redacted]	B	(V106I), Y181C, H221H/Y, M184I	5.1	4.9	15.4	65.3	29.7	50.9	0.3	2.6	0.7
[redacted]	B	E138K, M184I	4.9	4.9	6.4	1.9	52.7	24.2	0.6	2.5	1.0
	B	K101E, M184I	4.6	3.8	4.1	4.1	22.2	22.1	0.6	1.5	0.7
	B	K101E, M184I	4.6	5.0	3.0	2.1	26.6	23.1	0.2	0.4	0.4
	B	E138K, Y115F	3.6	1.8	4.0	1.2	22.8	16.4	1.8	5.7	0.3
	B	E138K, M184V	1.8	0.8	0.9	0.9	53.3	23.0	0.5	1.2	0.8
	B	M184I	1.7	1.4	2.4	0.9	39.4	23.8	0.7	1.0	0.5
	B	(D67N), (K219Q)	1.5	1.2	1.2	1.0	1.9	2.3	0.5	1.0	2.7
[redacted]	B	(V90I), E138K, (V179I), G190E/G, F227C/F, M184I	1.4	1.6	2.5	0.7	37.5	15.6	0.2	1.0	0.6
[redacted]	B	V106I	1.3	1.3	1.6	2.0	0.8	0.5	0.4	0.4	1.1
	B	V189I/V	1.3	0.8	0.8	1.3	0.3	1.4	0.5	0.5	1.1
	C	M184V	1.3	1.1	1.3	1.2	103.7	50.0	0.9	2.3	0.5
	B	(V179I)	1.0	0.7	1.4	0.9	0.9	1.2	0.8	0.4	1.0
	B	(V179I)	0.8	0.6	0.8	0.3	0.6	0.8	0.5	0.5	0.6
	AE*	(V179I)	0.7	1.3	0.9	1.4	0.7	1.0	0.8	0.8	1.9
	B	(V106I)	0.4	0.5	0.8	0.7	0.6	1.0	0.7	0.4	1.1

Data Source: TMC278-C209-C215-C904-W96-AVMR
RT RAM present at baseline/screening are in parentheses, NNRTI RAM, RPV RAM, N(t)RTI RAM, FC >BCO/CCO,
NA: not applicable
*AE = CRF01_AE and AG = CRF02_AG

4.4.1.5. Resistance Data at Week 96 by Baseline Viral Load

The proportion and number of RPV VF_{res} were lower among RPV treated subjects with BL VL ≤100,000 c/mL (7.6% [28/368]) than among those with BL VL >100,000 c/mL (21.4% [68/318]) ($p < 0.0001$). However, no difference was observed in the control group, with 6.1% (20/329) VF_{res} among subjects with BL VL ≤100,000 c/mL and 9.1% (32/353) VF_{res} with BL VL >100,000 c/mL ($p = 0.1512$).

Additionally, the proportions of VF_{res} with BL VL ≤100,000 c/mL were comparable between treatment groups ($p = 0.4568$) while there was a higher proportion of RPV VF_{res} than control VF_{res} with BL VL >100,000 c/mL ($p < 0.0001$). These observations were true for the VF_{res} occurring up to Week 48 and the VF_{res} occurring between Week 48 and Week 96 (Table 59).

A greater proportion of RPV VF_{res} with BL VL ≤100,000 c/mL were classified as 'rebounders' (60.7% [17/28]) than as 'never suppressed' (35.7% [10/28]). A similar trend was observed among control VF_{res} with 70.0% (14/20) classified as 'rebounders' and 20.0% (4/20) as 'never suppressed' (Table 60).

Table 59 Summary of VF_{res} over Time by Baseline Viral Load (Pooled Phase III Trials)

VF_{res}, n (%)	RPV		Control	
	BLVL ≤100,000 c/mL N = 368	BLVL >100,000 c/mL N = 318	BLVL ≤100,000 c/mL N = 329	BLVL >100,000 c/mL N = 353
Overall	28 (7.6)	68 (21.4)	20 (6.1)	32 (9.1)
Up to and Including Week 48	20 (5.4)	53 (16.7)	14 (4.3)	22 (6.2)
Beyond Week 48 up to and Including Week 96	7 (1.9)	15 (4.7)	6 (1.8)	10 (2.8)

Source: TMC278-C209-C215-C904-W96-AVMR
N= number of subjects in each subgroup

Table 60 Summary of the VF_{res} by Virologic Failure Definition and by Baseline Viral Load (Pooled Phase III Trials)

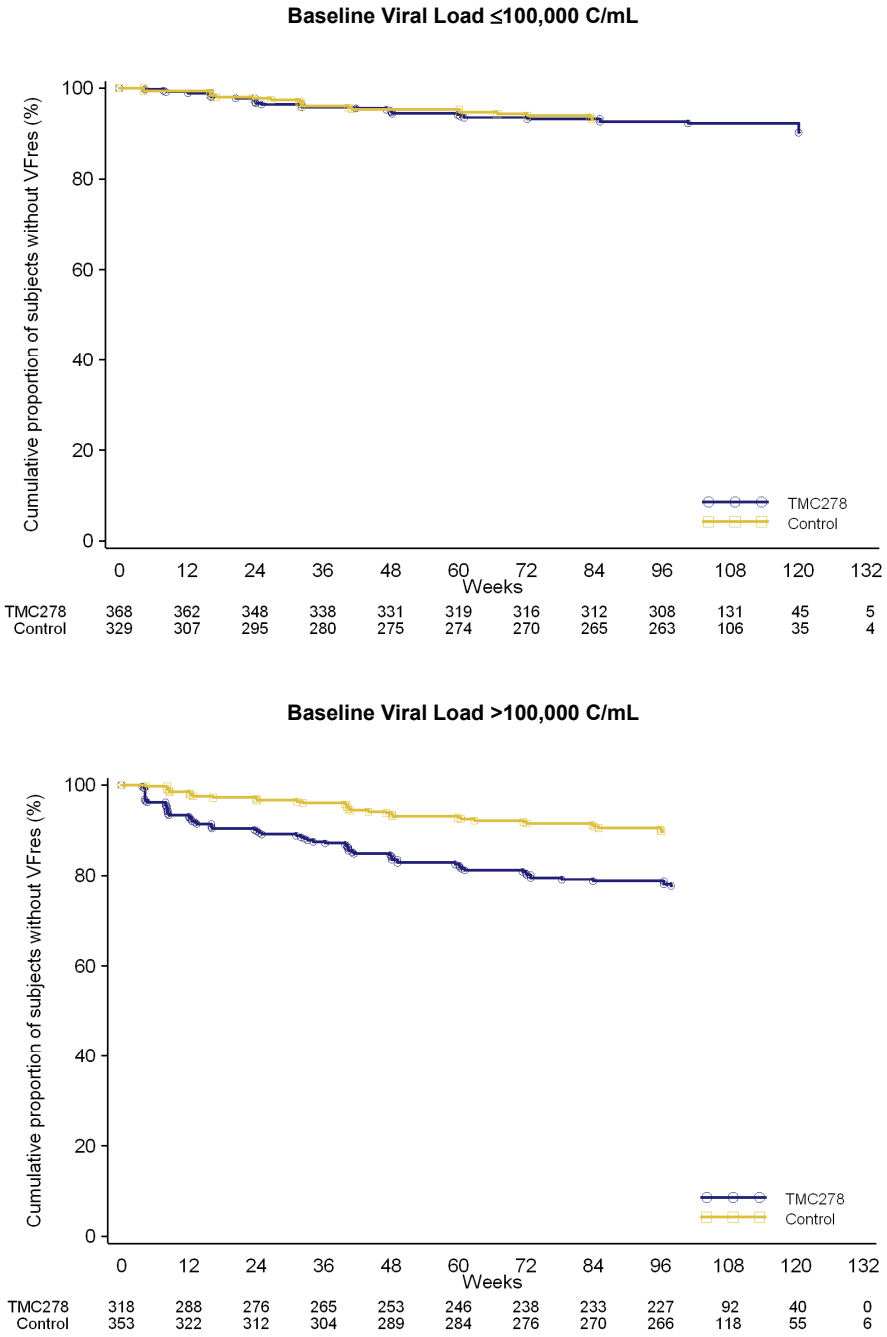
VF_{res}, n (%)	RPV		Control	
	BL VL ≤100,000 c/mL	BL VL >100,000 c/mL	BL VL ≤100,000 c/mL	BL VL >100,000 c/mL
	N' = 28	N' = 68	N' = 20	N' = 32
Rebounder	17 (60.7)	33 (48.5)	14 (70.0)	18 (56.3)
STWNS	1 (3.6)	1 (1.5)	2 (10.0)	0
Never Suppressed	10 (35.7)	34 (50.0)	4 (20.0)	14 (43.8)

Source: TMC278-C209-C215-C904-W96-AVMR
N' = number of VFres

For the VF_{res} with BL VL ≤100,000 c/mL, the median time to VF_{res} was not different in RPV group (226.0 days; interquartile range [Q1 – Q3] = 32 – 841) and in the control group (224.5 days; interquartile range [Q1 – Q3] = 30 – 585) (p = 0.6).

However, a shorter median time to VF_{res} was seen in the RPV group for the VF_{res} with BL VL >100,000 c/mL (196.5 days; interquartile range [Q1 – Q3] = 26 – 685) than in the control group (282.0 days; interquartile range [Q1 – Q3] = 30 – 673) (p <0.0001) (Ad hoc analysis). These data are illustrated by the corresponding Kaplan-Meier plots of the 'time to VF_{res}' by BL VL presented in Figure 5 and TMC278-C209-C215-C904-W96-AVMR.

Figure 5 Graphical Presentation of the 'Time to VF_{res}' by Baseline Viral Load (≤100,000 c/mL [Upper Panel] and >100,000 c/mL [Lower Panel]) (Pooled Phase III Trials). (Ad Hoc Analysis)



The proportion of VF_{res} with treatment-emergent RT mutations, NNRTI RAMs, RPV RAMs, N(t)RTI RAMs, and combination of NNRTI RAMs + N(t)RTI RAMs was lower among VF_{res} with BL VL ≤100,000 c/mL than among VF_{res} with BL VL >100,000 c/mL, in both treatment groups (Table 61 and TMC278-C209-C215-C904-W96-AVMR). There

were also fewer NNRTI RAMs and/or N(t) RTI RAMs per RPV VF_{res} with BL VL <100,000 c/mL. Nevertheless, the resistance profile of RPV (i.e. type of mutations) was independent of BL VL (Table 58).

Table 61 Distribution of the VF_{res} by Number of Treatment-emergent RT Mutations and by Baseline Viral Load at Failure (Pooled Phase III Trials)

	RPV		Control	
VF_{res}, n (%)	BL VL ≤100,000 c/mL N' = 27	BL VL >100,000 c/mL N' = 59	BL VL ≤100,000 c/mL N' = 17	BL VL >100,000 c/mL N' = 25
RT Mutations – Any	20 (74.1)	49 (83.1)	13 (76.5)	23 (92.0)
RT RAMs – Any	13 (48.1)	38 (64.4)	7 (41.2)	16 (64.0)
NNRTI RAMs – Any	10 (37.0)	36 (61.0)	6 (35.3)	14 (56.0)
0	17 (63.0)	23 (39.0)	11 (64.7)	11 (44.0)
1	6 (22.2)	16 (27.1)	5 (29.4)	8 (32.0)
2	3 (11.1)	12 (20.3)	1 (5.9)	3 (12.0)
3	1 (3.7)	7 (11.9)	0	2 (8.0)
4	0	1 (1.7)	0	0
RPV RAMs – Any	9 (33.3)	33 (55.9)	1 (5.9)	2 (8.0)
0	18 (66.7)	26 (44.1)	16 (94.1)	23 (92.0)
1	7 (25.9)	22 (37.3)	1 (5.9)	2 (8.0)
2	2 (7.4)	8 (13.6)	0	0
3	0	3 (5.1)	0	0
N(t)RTI RAMs – Any	12 (44.4)	36 (61.0)	2 (11.8)	9 (36.0)
0	15 (55.6)	23 (39.0)	15 (88.2)	16 (64.0)
1	10 (37.0)	29 (49.2)	2 (11.8)	9 (36.0)
2	2 (7.4)	6 (10.2)	0	0
3	0	1 (1.7)	0	0
NNRTI and N(t)RTI RAMs – Any	9 (33.3)	34 (57.6)	1 (5.9)	7 (28.0)
0	18 (66.7)	25 (42.4)	16 (94.1)	18 (72.0)
2	3 (11.1)	13 (22.0)	0	4 (16.0)
3	5 (18.5)	10 (16.9)	1 (5.9)	2 (8.0)
4	1 (3.7)	7 (11.9)	0	0
5	0	3 (5.1)	0	0
6	0	1 (1.7)	0	1 (4.0)

Source: TMC278-C209-C215-C904-W96-AVMR
N' = number of VF_{res} with genotypic data at failure

Proportionally fewer RPV VF_{res} with BL VL ≤100,000 c/mL had phenotypic resistance to RPV and to other NNRTIs than RPV VF_{res} with BL VL >100,000 c/mL. The proportion of control VF_{res} resistant to EFV was independent of the BL VL. Generally, more VF_{res} with BL VL >100,000 c/mL had resistance to FTC and 3TC in both treatment groups (TMC278-C209-C215-C904-W96-AVMR).

There was less cross-resistance to the other NNRTIs among the RPV VF_{res} resistant to RPV in subjects with BL VL ≤100,000 c/mL than in subjects with BL VL

>100,000 c/mL. Due to the low number of RPV VF_{res} resistant to RPV in the BL VL ≤100,000 c/mL these results should be interpreted with caution.

Table 62 Cross-resistance of VF_{res} to NNRTIs and N(t)RTIs by Baseline Viral Load at Failure (Pooled Phase III Trials)

Resistance to: n (%)	RPV VF_{res}			
	BL VL ≤100,000 c/mL		BL VL >100,000 c/mL	
	Resistant to RPV N' = 5	Sensitive to RPV N' = 22	Resistant to RPV N' = 30	Sensitive to RPV N' = 24
EFV	3 (60.0)	1 (4.5)	27 (90.0)	1 (4.2)
ETR	4 (80.0)	2 (9.1)	28 (93.3)	2 (8.3)
NVP	1 (20.0)	0	15 (50.0)	0
3TC	5 (100)	6[a] (28.6)	29[b] (100)	5 (20.8)
ABC	0	0	5 (16.7)	1 (4.2)
AZT	0	0	0	2 (8.3)
FTC	5 (100)	7 (31.8)	30 (100)	5 (20.8)
TDF	0	0	1 (3.3)	1 (4.2)

Source: TMC278-C209-C215-C904-W96-AVMR
a. N' = 21
b. N' = 29
N' = number of VF_{res} with phenotypic data at failure

4.4.1.6. Conclusions of the Clinical Virology Data

In the pooled Phase III Week 96 analysis, the proportion of VF_{res} was higher among the subjects treated with RPV (14.0% [96/686]) than among those treated with EFV (7.6% [52/682]) ($p < 0.0001$). The majority of the RPV VF_{res} were 'never suppressed', occurred during the first 48 weeks of the trials and were more frequent among subjects with BL VL >100,000 c/mL. Beyond the initial 48 weeks of treatment, there were fewer VF_{res} than within the first 48 weeks in both treatment groups, and their occurrences in the RPV group (3.2% [22/686]) and the control group (2.3% [16/682]), within this second treatment period, were comparable.

These analyses indicate that subjects who failed their RPV regimen in C209 and C215 had a unique resistance profile. A list of the mutations potentially affecting susceptibility to this ARV has been created based on in vitro data and on emergence in VF_{res} in the Phase IIb and Phase III trials. Sixteen NNRTI RAMs (K101E/P, E138A/G/K/Q/R, V179L, Y181C/I/V, Y188L, H221Y, F227C, M230I/L) were identified as potential determinants of decreased susceptibility to RPV and their presence should be considered when starting a RPV-based ART (Section 4.6).

In the RPV VF_{res} the combination of NNRTI RAMs and N(t)RTI RAMs was common (50.0% [43/86]). The most frequently observed NNRTI RAM was E138K (36.0%) and the most frequently observed N(t)RTI RAM was M184I (37.2%). The most common combination of RT mutations was E138K + M184I, and E138K was always observed in the presence of an N(t)RTI RAM (most often with M184I/V). The combination of E138K with M184I was more commonly associated with decreased susceptibility to RPV than its

combination with M184V (similar observation was made for the combination of K101E with M184I/V).

The effect of E138K + M184I on RPV resistance has recently been confirmed using other phenotypic assays (Kulkarini, 2012). Interestingly, this effect was also observed when M184I was found in combination with K101E, another treatment-emergent NNRTI RAM. An alternative explanation could be that M184I, but not M184V, improves the fitness of E138K-containing isolates (Hu, 2011, Xu, 2011) This hypothesis was not confirmed in a recent study that showed that E138K + M184I imposed the highest fitness cost to the virus (Xu, 2011)

Although there were more RPV VF_{res} and the incidence of treatment-emergent RAMs per VF_{res} was higher among VF_{res} with BL VL >100,000 c/mL, the resistance profile of RPV (i.e. type of mutations) was independent of BL VL. The Week 96 resistance analysis revealed no differences in this respect compared to the Week 48 resistance analysis described in the initial Virology Summary

RPV VF_{res} resistant to RPV were generally cross-resistant to EFV and ETR and to a lesser degree to NVP. Control VF_{res} with phenotypic resistance to EFV often retained sensitivity to ETR and RPV, and usually had resistance to NVP. RPV VF_{res} who retained sensitivity to RPV generally retained sensitivity to other NNRTIs and N(t)RTIs. A similar observation was made in control VF_{res} who retained sensitivity to EFV.

In clinical trials, RPV combined with an active background regimen, has demonstrated significant and durable virologic response, particularly in treatment-naïve subjects with a BL VL <100,000 c/mL (Johnson, 2003, Tambuyzer, 2009, Johnson, 2008, Johnson, 2009). The resistance profile of RPV (Pauwels, 1988, Johnson, 2009) was not altered with the substantial increase in patient-years of exposure in the resistance analysis from the combined Phase III studies at 96 weeks.

4.5. Clinical Virology - Dolutegravir and Rilpivirine

4.5.1. 201636 (SWORD-1) and 201637 (SWORD-2)

Study Design: These are two identical 148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study. The study was conducted in 508 (201636) and 516 (201637) randomized adult HIV-1 infected patients who were on stable suppressive cART containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI. Eligible subjects were randomized 1:1 to continue their current antiretroviral regimen (CAR) or be switched to a two-drug regimen DTG + RPV administered once daily. At Week 48, individuals who were originally assigned to continue their current antiretroviral regimen (CAR) and remained virologically suppressed switched to DTG + RPV (at Week 52) and will be followed to Week 148.

4.5.1.1. Viral genotyping and phenotyping results

Key results of the Week 48 Virology analyses include the following:

201636

- Protocol-defined Confirmed Virologic Withdrawal (CVW) through Week 48 was very low, with one subject in each treatment group meeting these criteria at any time during the Early Switch Phase.
- No subject meeting CVW in either treatment group had observed resistance on study.

201637

- Protocol-defined CVW through Week 48 was very low, with one subject in each treatment group meeting these criteria at any time during the Early Switch Phase.
- NNRTI resistance associated substitution K101K/E mixture with no decreased susceptibility to RPV was observed in one subject with identified adherence issues that received DTG/RPV in 201637. Viral load increased to 1,059,771 c/mL at suspected virologic withdrawal (SVW) with subsequent ~1,000-fold decrease to 1,018 c/ml at the confirmatory visit on resumption of their DTG + RPV regimen, and further decreased to <50 c/mL at withdrawal visit. The other subject had no observed resistance on study.

4.5.1.2. Virologic Withdrawal Criteria

The virology populations were defined as follows.

- The Confirmed Virologic Withdrawal (CVW) Population included all subjects in the ITT-E population who met CVW
- The Potential Precautionary Virologic Withdrawal (pPVW) Population included subjects in the ITT-E population having 2 consecutive plasma HIV-1 RNA measurements between 50 and 200 c/mL
- The Precautionary Virologic Withdrawal (PVW) Resistance Population included all subjects in the ITT-E Population who met pPVW and had resistance testing

Virologic Assessment Criteria

Virologic assessment was employed to ensure subjects remained suppressed to <50c/mL. A value of ≥50 c/mL mandated repeat assessment and viral load. The Confirmed Virologic Withdrawal (CVW) Population included all subjects in the ITT-E population who had 2 consecutive Viral loads ≥50 c/mL, with the second one being >200 c/mL (the second being the confirmatory virology sample). The study allowed any subjects with a second virology sample of ≥50 and <200 c/mL to be evaluated for possible mitigating circumstances that could lead to low level elevations. They would be in the possible Precautionary Virologic Withdrawal (pPVW). If they failed to suppress to <50c/mL on a third viral load test, or, if there was no mitigating reason for the repeated elevation to

>50c/mL, then they met virologic withdrawal criteria and are in the Precautionary Virologic Withdrawal (PVW) Resistance Population

4.5.1.3. Occurrence of Time to Plasma HIV-1 RNA >=50 copies/mL

201636

Time to first occurrence of HIV-1 RNA ≥50 c/mL was the same in both treatment groups during the Early Switch Phase (Data Source: 201636 Week 48 CSR Table 2.191).

201637

Time to first occurrence of HIV-1 RNA ≥50 c/mL was the same in both treatment groups during the Early Switch Phase (Data Source: 201637 Week 48 CSR Table 2.192).

4.5.1.4. Subjects Who Met Confirmed Virologic Withdrawal Criteria through Week 48

201636

The numbers of subjects who met the confirmed virologic withdrawal criteria were very low, with 1 subject in each treatment group meeting these criteria at any time during the Early Switch Phase (Table 63).

Table 63 Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit, Studies 201636 (ITT-E Population)

Time Point n (%)	201636	
	DTG + RPV (N=252)	CAR (N=256)
Any time	1 (<1)	1 (<1)
Week 24	1 (<1)	0
Week 36	0	0
Week 48	0	1 (<1)

Data Source:201636 and 201637 Week 48 CSR Table 2.120

201637

The numbers of subjects who met the confirmed virologic withdrawal criteria were very low, with 1 subject in each treatment group meeting these criteria at any time during the Early Switch Phase (Table 64).

Subject [redacted]:

- This subject (randomized to CAR group and receiving DTG + KIVEXA) had a Day 1 viral load of 83 c/mL, and suppressed to < 50 c/mL until Week 24 with a viral load of 86 c/mL and a confirmatory viral load of 217 c/mL at Week 24 retest.
- Resistance testing was not performed on the Week 24 time point sample as the viral load (86 c/mL) was below testing cutoff.

- Subject withdrew from the study with viral load <50 c/mL.

Subject [redacted] and resistance testing results are described in detail in Section 4.5.1.5.

Table 64 Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit, Study 201637 (ITT-E Population)

Time Point n (%)	201637	
	DTG + RPV (N=261)	CAR (N=255)
Any time	1 (<1)	1 (<1)
Week 24	0	1 (<1)
Week 36	1 (<1)	0
Week 48	0	0

Data Source: 201636 and 201637 Week 48 CSR Table 2.120

4.5.1.5. Observed Drug Class Mutations for Subjects Meeting CVW through through Week 48

One subject in 201636 receiving DTG + RPV had an integrase substitution at G193E and no RT- or PRO-associated mutations, and with no change in DTG susceptibility on study. The INSTI substitution G193E was also present at baseline by the DNA archive assay.

201636

Subject [redacted] (201636):

- This subject (randomized to DTG + RPV treatment arm) met Virologic Withdrawal at Week 24 with a viral load of 88 c/mL followed by confirmation time point viral load of 466 c/mL.
- Resistance testing of the Virologic Withdrawal confirmation time point showed integrase substitution G193E with no change in DTG susceptibility; fold change compared with wild-type (FC) = 1.02.
- At baseline, G193E was detected in exploratory HIV DNA archive sequencing assay. No phenotypic data is generated in this assay.
- Subject withdrew from study with a decreased HIV-1 RNA of 162 c/mL.
- Of note resistance testing was carried out on the Week 24 confirmation time point as the viral load at the Week 24 Virologic Withdrawal time point (88 c/mL) was below resistance testing cutoff.

Subject [redacted] (201636):

- This subject (randomized to CAR treatment arm and receiving Truvada+darunavir/r) met Virologic Withdrawal at Week 48 with viral load of 712 c/mL followed by confirmation time point viral load of 323 c/ml.

- No RT-, PRO- or INSTI-associated major IAS resistance mutations were detected at the virologic withdrawal time point.
- Subject withdrew from study with a decreased viral load of 232 c/mL.

Table 65 Summary of Resistance by Drug Class for Subjects with Confirmed Virologic Withdrawal through Week 48, Study 201636 (ITT-E Population)

Treatment	Subject ID	HIV-1 RNA (c/mL) (timepoint)			Mutation by Drug Class[a] mutation (FC)							
					INSTI		NNRTI		NRTI		PI	
		Day 1	SVW	CVW	BL	CVW	BL	CVW	BL	CVW	BL	CVW
DTG + RPV	[redacted]	72	88 (W24)	466 ($W24_{UNS}$)	G193E (nd)	G193E (1.02)	none	none	none	none	none	none
CAR	[redacted]	<50	712 (W48)	323 ($W48_{UNS}$)	none	none	none	none	none	none	none	none

Data Source: 201636 and 201637 Week 48 CSR Table 7.011, 7.013;Linsting 51, Listing 87; Listing 91

a. For IN resistance pre-specified mutations included: H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E; Major resistance mutations to other classes (NRTI, NNRTI, PI) are as defined by the IAS-USA most recent guidelines available at the time of DBF. BL is baseline sample when PBMC/whole blood was collected for HIV-1 DNA sequencing; BL data is HIV-1 RT, PRO, and IN genotype only and provides no phenotype data. "none" indicates no IAS major mutations observed; "nd" indicates no phenotype data available in baseline HIV-1 DNA archive assay.

201637

In one subject in the DTG + RPV group with adherence difficulties, an NNRTI associated resistance mutation K101K/E was observed, with no decreased susceptibility to RPV. Integrase resistance testing failed. The K101K/E mutation mixture was not present at baseline by the DNA archive assay.

Subject [redacted] (201637):

- This subject (randomized to DTG + RPV treatment arm) met Virologic Withdrawal at Week 36 with a viral load of 1,059,771 c/mL. Following resumption of DTG +_ RPV, the subject had a subsequent three $\log_{10}$ decline in viral load at CVW time point with viral load of 1,018 c/mL.
- At the Virologic Withdrawal time point, a K101K/E mutation mixture was detected in RT with with no decreased susceptibility to RPV. Integrase resistance testing failed to work.

- The K101E mutation in RT was not detected alone or as a mixture at Baseline by the DNA archive assay.
- Subject withdrew from study with viral load <50 c/mL.

Table 66 Summary of Resistance by Drug Class for Subjects with Confirmed Virologic Withdrawal through Week 48, Study 201637 (ITT-E Population)

Treatment	Subject ID	HIV-1 RNA (c/mL) (timepoint)			Mutation by Drug Class[a] mutation (FC)							
					INSTI		NNRTI		NRTI		PI	
		Day 1	SVW	CVW	BL	CVW	BL	CVW	BL	CVW	BL	CVW
DTG + RPV	[redacted]	<50	1059771 (W36)	1018 ($W36_{UNS}$)	none	F	none	K101K/E (1.21)	none	none	none	none

Data Source: 201636 and 201637 Week 48 CSR Table 7.022; Table 7.023; Listing 51 Listing 87; Listing 91

a. For IN resistance pre-specified mutations included: H51Y, T66A/I/K, L74M, E92Q/V/G, Q95K, T97A, G118R, F121Y, E138A/K/D, G140A/C/S, Y143C/H/R/K/S/G/A, P145S, Q146P, S147G, Q148H/K/R, V151I/L/A, S153F/Y, N155H/S/T, E157Q, G163R/K, S230R, R263K, L68V/I, L74I, E138T, V151I, G193E; Major resistance mutations to other classes (NRTI, NNRTI, PI) are as defined by the IAS-USA most recent guidelines available at the time of DBF. BL is baseline sample when PBMC/whole blood was collected for HIV-1 DNA sequencing; BL data is HIV-1 RT, PRO, and IN genotype only and provides no phenotype data. "none" indicates no IAS major mutations observed;"F" indicates that resistance testing failed.

4.5.1.6. Subjects Who Met Precautionary Virologic Withdrawal Criteria through Week 48

One subject met precautionary virologic withdrawal criteria in the DTG + RPV arm in 201636.

Subject [redacted]

- This subject (randomized to DTG+RPV treatment arm) had an elevated viral load at Week 36 of 55 c/ml. At subsequent confirmation time point subject met PVW with a viral load of 73 c/mL.
- Resistance testing was not performed on the Week 36 time point sample as the viral load (55 c/mL) was below testing cutoff.
- Subject withdrew from study with viral load < 50 c/mL.

Table 67 Proportion of Subjects Meeting Precautionary Virologic Withdrawal Criteria by Visit, Study 201636 (ITT-E Population)

Time Point n (%)	201636	
	DTG + RPV (N=252)	CAR (N=256)
Any time	1	0
Week 24	0	0
Week 36	1 (<1)	0
Week 48	0	0

Data Source: 201636 and 201637 Week 48 CSR Listing 52
Subject [redacted] (Week 36)

Two subjects met precautionary virologic withdrawal criteria in the CAR arm in 201637.

Subject [redacted]

- This subject (randomized to CAR treatment arm receiving Atripla) had elevated viral load of 853 c/mL at Week 4, followed sequentially by viral loads of 89 c/mL, 86 c/ml, and 60 c/ml thereby meeting PVW criteria.
- Resistance testing of the first sample of the Week 4 time point showed polymorphic integrase substitution V151I with no change in DTG susceptibility (fold change compared with wild-type FC = 0.89). No RT and PRO mutation was observed and the subject was susceptible to all drugs accessed.
- At baseline, V151I was detected with the HIV DNA archive assay. No phenotypic data is generated in this assay.
- Subject withdrew from study with viral load <50 c/mL.

Subject [redacted]

- This subject (randomized to CAR treatment arm and receiving Stribild) had elevated viral load of 74 c/mL at Week 8, followed sequentially by viral loads of 78 c/ml at Week 12, and then 55 c/ml, thus meeting PVW criteria.
- PI identified upper respiratory tract infection was the potential cause of the initial elevated viral load, with subsequent viral load elevations potentially due to multiple vaccines subject received between Week 8 and Week 12. After resolution of intercurrent illness and immunization, and on further discussion between PI and Medical Monitor, subject was allowed to stay on study.
- Resistance testing was not performed on the Week 12 time point sample as the viral load is below testing cutoff.
- At Week 24 subject viral load was suppressed to <50 c/mL and the subject remained on study.

Table 68 Proportion of Subjects Meeting Precautionary Virologic Withdrawal Criteria by Visit, Study 201637 (ITT-E Population)

Time Point n (%)	201637	
	DTG + RPV (N=261)	CAR (N=255)
Any time	0	2
Week 8	0	1 (<1)
Week 12	0	1 (<1)
Week 24	0	0
Week 36	0	0
Week 48	0	0

Data Source: 201636 and 201637 Week 48 CSR Listing 52
Subjects [redacted] (Week 8), [redacted] (Week 12)

4.5.1.7. Subjects Who Met Withdrawal Criteria post-Week 48

One subject in Study 201636 that randomized to the CAR arm and switched to DTG + RPV met CVW at Week 64.

Genotypic Data

Subject [redacted] (201636):

- This subject (randomized to CAR treatment arm and receiving TIVICAY+KIVEXA through Week 48) met Virologic Withdrawal at Week 64 with viral load of 833 c/mL followed by confirmation time point viral load of 1174 c/ml.
- The subject withdrew from study with viral load <50 c/mL. Resistance testing was not reported in time for the Week 48 analysis.

Subjects Who Met Precautionary Virologic Withdrawal Criteria post-Week 48

One subject in Study 201636 that randomized to the CAR arm and switched to DTG + RPV met PVW at Week 64.

Subject [redacted] (201636):

- Subject [redacted] (randomized to CAR treatment arm and receiving ABC+3TC+ATV through Week 48) met PVW at Week 64 with sequential viral loads of 79 c/mL and 162 c/mL.
- Resistance testing was not performed on the Week 64 virologic withdrawal time point sample due to low viral load (79 c/mL).

4.5.1.8. Discussion

A secondary objective for the study was to assess viral resistance in subjects that met virologic withdrawal criteria. Two virologic withdrawal criteria were implemented for subject management. A PVW criterion was included to ensure that subjects on this

2-drug regimen were not subject to prolonged low level ongoing viral replication (i.e., between 50 and<200 c/mL) which might indicate early viral failure, and / or lead to evolving emergent resistance. The CVW criteria used a conservative viral load of ≥50 c/mL as the suspect criterion, with a sequential viral load of ≥200 c/mL acting as confirmation to meet withdrawal criteria.

When the time to first occurrence of viral load ≥50 c/mL (a potential measure of low level replication) was assessed there was no significant difference across arms through Week 48.

On study resistance testing used standard plasma based genotypic and phenotypic resistance testing. However, since subjects entered study suppressed to <50 c/mL, HIV-1 baseline resistance testing could not be run using plasma samples, and was carried out on PBMCs or whole blood samples to evaluate treatment emergence. This used the [redacted] assay which provides HIV-1 PRO, RT, and IN genotype data but not phenotypic data. Of note resistance testing with cell-associated HIV-1 DNA has been shown to be discordant with plasma sample resistance testing [Sharkey, 2005]; as such HIV-1 DNA resistance testing is exploratory and its primary value is in showing whether resistance is present, and it is less definitive at showing resistance is not present.

201636

Protocol-defined CVW through Week 48 was low in 201636, with one subject in each treatment group meeting these criteria at any time during the early switch phase. Neither subject meeting CVW in either treatment group had observed resistance on study. Of note is that overall subjects that met CVW or PVW criteria showed decreased viral loads at the withdrawal visits.

201637

Protocol-defined CVW through Week 48 was low, with one subject in each treatment group meeting these criteria at any time during the early switch phase. In one subject that received DTG/RPV in 201637, NNRTI resistance associated substitution K101K/E mixture with no decreased susceptibility to RPV was observed. Baseline testing with HIV-1 DNA did not reveal K101E in RT. Resistance testing using both integrase genotype and phenotype assays failed to work with the same subject sample. Of note for this subject with identified adherence issues, the viral load had an initial increase from <50 c/mL to 1,059,771 c/mL, followed by consecutive viral load measures of 1,018 c/ml at the confirmatory visit 18 days later. TheHIV-1 load decreased to < 50 c/mL at withdrawal visit while still taking DTG + RPV. This is consistent with resumption of an effective drug regimen.

NNRTI mutation K101E is nonpolymorphic and may be selected in patients receiving multiple NNRTIs and usually occurs in combination with other NNRTI-resistance mutations. Alone it reduces susceptibility to RPV by about 2-fold, and confers resistance at differing levels to other NNRTIs (NVP by 3 to 10-fold, EFV 1 to 5-fold, ETR about 2-fold). Greater increases in resistance are observed when other NNRTI substitutions are

present and if M184 NRTI substitution is present with K101E RPV resistance is increased as well.

It is difficult to fully assess resistance risk based on this case with suboptimal adherence, with a drug regimen that is individual entities, and not yet formulated as a FDC.. However, it remains noteworthy that across both studies, one subject with noted difficulty maintaining adherence had an observed substitution to study drug that allowed resumption of suppression to < 50 c/mL.

4.5.1.9. Conclusions

201636

- Protocol-defined CVW through Week 48 was very low, with one subject in each treatment group meeting these criteria at any time during the early switch phase. Neither subject meeting CVW in either treatment group had observed resistance on study.

201637

- Protocol-defined CVW through Week 48 was very low, with one subject in each treatment group meeting these criteria at any time during the early switch phase. Of the 2 subjects who met CVW criteria, 1 subject in the DTG+ RPV arm was noted as non-adherent and had genotypic substitution K101K/E mixture in RT, with no decrease in RPV susceptibility, and a greater than 3-log decrease in HIV-1 viral load on resumption of their DTG + RPV regimen. The other subject had no observed resistance on study.

4.6. Appendix 1

4.6.1. Rationale for the list of 16 RPV RAMs

In order to provide guidance on the use of RPV based on baseline genotypic information, a list of the mutations potentially affecting susceptibility to this ARV has been proposed for inclusion in the prescribing information.

The selection of these mutations was based on in vitro susceptibility data and mutations emerging both in vitro and in subjects failing a RPV regimen in the Phase IIb and Phase III studies. In total, 49 NNRTI RAMs were considered in this analysis (extended list of 48 RAMs + G190T which was included as one of the 39 NNRTI RAMs used in the protocol list for exclusion in the Phase III studies). Four additional RAMs were not included because they were present at baseline in the Phase III studies and were associated with a virologic response rate comparable to that observed in the overall population of 84.3% (ITT, TLOVR): V90I (14/17, 82.4%), V106I (18/21, 85.7%), V179I (50/57, 87.7%), and V189I (8/8, 100%). Therefore, these 4 NNRTI RAMS are not considered to contribute to decreased susceptibility to RPV when present at baseline as single mutations.

Initially, ten NNRTI RAMs were identified as potential determinants of decreased susceptibility to RPV, when present as single mutations at baseline. Based on recent data, E138A was added to the initial list to give a total of 11 RAMs: K101E, K101P, E138A, E138G, E138K, E138R, E138Q, Y181C, Y181I, Y181V, and H221Y. These 11 NNRTI RAMs were determined to be associated with decreased susceptibility based upon the following criteria:

- They were associated, in vitro, with a RPV FC >3.7 in HIV-1/HXB2 SDMs with a single NNRTI RAM. K101P, Y181I, and Y181V singly had a RPV FC of 51.7, 15.3, and 12.2, respectively, in SDMs in vitro. E138A was found to affect RPV FC in a large panel of clinical isolates from ARV treatment-naïve subjects (data from the [redacted] databases, Haddad, 2011), and/or
- they were found to emerge in at least 3 subjects with VF_{res} in the pooled Phase III studies. K101E, E138K, Y181C, and H221Y emerged in 8, 28, 5, and 6 RPV VF_{res} in the pooled Phase III studies, respectively, and/or
- they impacted virologic response to a RPV-containing regimen when present at baseline. All 3 subjects with E138G at baseline were virologic failures in the Phase IIb study. Two of four subjects (3 in Phase IIb and 1 in Phase III) with E138A at baseline were virologic failures. In addition, the mutations E138R and E138Q were included in this list as well, because they emerged most frequently during in vitro selection experiments and occasionally in subjects failing a TPV-containing regimen.

The K103N mutation was not included in the exclusion list for RPV. K103N is the most frequently observed NNRTI RAM in ARV treatment-naïve subjects due to transmitted resistance, is associated with resistance to the current first-line NNRTIs (EFV and NVP) and is known to be associated with failure to currently available first-line NNRTI therapy. Specifically, K103N was not retained in the list of 11 NNRTI RAMs, because:

- The HIV-1 SDM harboring K103N was sensitive to RPV.
- The same concentration of RPV was sufficient to completely prevent the replication of a wild type and K103N mutant HIV-1 strain.
- In vitro selection experiments initiated with wild type or recombinant HIV-1 strains containing NNRTI RAMs, indicated that K103N was never observed as an emerging mutation (11 experiments have been reported).
- All EFV-treated subjects in the Phase IIb and Phase III studies who had treatment-emergent K103N, retained phenotypic sensitivity to RPV. There were no virologic failures in the RPV group with emerging K103N in the Phase III studies.
- Two ARV treatment-naïve subjects with K103N at baseline were treated with RPV (1 in Phase IIb and 1 in Phase III). Both subjects responded to treatment and viral load remained undetectable up to the time of cut-off for the Week 48 analysis.

In addition to these 11 RPV RAMs, 4 other mutations i.e. V179L, F227C, M230I, and M230L were identified by the Food and Drug Administration (FDA). The Division performed analyses on all submitted in vitro and clinical data for RPV independent from the analyses provided by Janssen. The full details of the criteria used by the FDA to select these 4 additional RPV RAMs were not communicated, but certainly include a different way of defining virologic failure and account for RAMs that occurred in a single subject. These 4 mutations were added to the initial list of 11 RPV RAMs for the following reasons:

- It is important for prescribing physicians and for subjects to have clear and complete resistance information to optimally guide the use of RPV, although it is uncertain whether the 4 additional RPV RAMs selected by the FDA could compromise virologic responses to RPV-containing regimens.
- Several resistance-testing companies base their genotypic interpretation system to determine RPV resistance on the list of RPV RAMs provided in the prescribing information. Therefore, it was considered that consistency between these systems and the prescribing informations would avoid confusion among prescribing physicians.
- The prevalence of most RPV RAMs is relatively low in both Phase III studies and in the general ARV treatment-naïve HIV-1 infected population. Only E138A occurs in just above 2% in the screened population, all others are below 0.5% (Picchio, 2014) In particular, the 4 additional RPV RAMs were either not present (F227C, M230I, and M230L) or present in a single subject only (V179L, screen failure) in the population screened in the Phase III studies. Therefore, it is expected that expanding the list of TMC278 RAMs from 11 to 15 would not significantly impact the target population eligible for treatment with RPV.

The current list of 16 RPV RAMs which may affect the activity of rilpivirine include K101E, K101P, E138A, E138G, E138K, E138R, E138Q, V179L, Y181C, Y181I, Y181V, Y188L, H221Y, F227C, M230I, and M230L. These mutations were identified through this analysis which was based on a relatively limited database of virologic failures. Wider use of the drug could result in a more robust virologic database and therefore, the guidance related to the resistance profile of RPV may be subject to change.

Y188L has been identified as a potential determinant of decreased susceptibility to RPV based on the following data: Haddad et al (Haddad, 2012) presented data from a large database of clinical specimens with both phenotypic and genotypic data as well as from SDM studies at the 19th Conference on Retroviruses and Opportunistic Infections (CROI, 2012) and concluded from these data that the NNRTI RAM Y188L conferred reduced susceptibility to RPV. The median RPV FC of clinical specimens and SDMs with Y188L were 9.2 and 6.1, respectively, both values above the BCO.

Module 2.7.3

Summary of Clinical Efficacy

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ABBREVIATIONS

3TC	Lamivudine, EPIVIR
ABC	Abacavir, ZIAGEN
AE	Adverse event
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
AUC(0-τ)	Area under the concentration-time curve over the dosing interval
C0	Pre-dose concentration of DTG or RPV collected within a 20 to 28 hour window following the most recent dose with no missed doses within 3 days prior to PK sampling
c/mL	copies/milliliter
CAR	Current antiretroviral regimen
cART	Combination antiretroviral therapy
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
Cmax	Maximum concentration
CMH	Cochran-Mantel Haenszel
CPP	Certificate of Pharmaceutical Product
CQA	Critical Quality Attribute
CSR	Clinical Study Report
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
CVW	Confirmed Virologic Withdrawal
DTG	Dolutegravir, TIVICAY
DTG + RPV	Dolutegravir + Rilpivirine
DTG/RPV FDC	Dolutegravir/Rilpivirine Fixed Dose Combination
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
INSTI	INtegrase Strand Transfer Inhibitor
IP	Investigational Product
Ito	cardiac transient outward potassium channel
ITT-E	Intent-to-treat exposed
LOCF	Last observation carried forward
NDA	New Drug Application
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PI	Protease inhibitor
PK	Pharmacokinetic
PP	Per-protocol
QTc	Corrected QT interval

RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid
RPV	Rilpivirine, EDURANT
RTV	Ritonavir
SDM	Symptom Distress Module
STR	Single tablet regimen
SVW	Suspected Virologic Withdrawal
TDF	Tenofovir disoproxil fumarate
TMC278	Tibotec Medicinal Compound 278
TSQ	Treatment Satisfaction Questionnaire
US	United States

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1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

The purpose of this summary of efficacy is to provide evidence to support the efficacy of a new 2-drug regimen combining DTG and RPV in an FDC tablet for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL) without known or suspected resistance to either antiretroviral component.

Dolutegravir (GSK1349572) is an HIV-1 INSTI with low to moderate intersubject PK variability, a predictable exposure-response relationship, and a 14-hour plasma half-life that supports once-daily dosing without the need for a PK booster. In addition, DTG lacks many of the associated drug interactions, specifically with oral contraceptives, statins, antidepressants, anxiolytics, anticoagulants, and other medications commonly taken by HIV-positive patients. To date, the efficacy, PK, safety and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to III clinical trials. Data are summarized in the Investigator Brochure [DTG IB, GlaxoSmithKline Document Number RM2007/00683/10]. On the basis of this development program, DTG was approved for the treatment of HIV-1 infection by the US FDA in August 2013 and by the EMA in January 2014, and is marketed as TIVICAY. Subsequently, DTG/ABC/3TC FDC (TRIUMEQ) was approved for the treatment of HIV-1 infection by the US FDA in August 2014 and by the EMA in September 2014.

Rilpivirine (TMC278) is an NNRTI, with in vitro activity against wild type virus and a broad range of NNRTI-resistant viruses. Rilpivirine combines the convenience of once daily dosing with potent antiviral activity. To date, the efficacy, PK, safety and drug interaction potential of RPV has been evaluated in an extensive program of Phase I to III clinical trials. Rilpivirine dosed at 25 mg once daily in combination with a background regimen consisting of 2 NRTIs was non-inferior to EFV, and was generally safe and well-tolerated. Data are summarized in the Investigator Brochure [RPV IB, 2017]. Rilpivirine was approved for the treatment of HIV-1 infection by the US FDA in May 2011 and by the EMA in November 2011 and is marketed as EDURANT. Rilpivirine is also approved in the US and EU as part of a FDC containing FTC 200 mg and TDF 245 mg (Complera/Eviplera) and as part of a FDC containing FTC 200 mg and TAF 25 mg (Odefsey).

The DTG + RPV regimen currently under development is a 2-drug, “NRTI-sparing” regimen, differing from the current standard of care, which typically includes 2 NRTIs plus a third agent from the PI, NNRTI, or INSTI classes. Prior clinical data using a 2-drug regimen with the similar INSTI cabotegravir combined with RPV provided proof of concept for an NRTI-sparing, 2-drug regimen [Margolis, 2015]. NRTI-based therapies, while highly effective and largely well-tolerated, have associated long-term toxicities, including lactic acidosis risks and bone and kidney changes [Carr, 2003]. As the population with HIV ages, new treatment options with fewer long-term toxicities are needed. Hence, the development of new safe and efficacious drugs continues, with individual profiles being evaluated within the context of combination treatment regimens. The proposed dual regimen consisting of DTG + RPV targets HIV replication at the early and late stages of the virus life cycle, resulting in maintenance of viral suppression of HIV-1 infected adults.

1.1. Current Therapies and Unmet Clinical Needs

A study by the Antiretroviral Therapy Cohort Collaboration [ART-CC, 2013] found that of more than 21,000 patients in a European and North American cohort on their first cART regimen (either PI- or NNRTI-based), 51% modified or interrupted their first cART regimen during a median of 28 months of follow-up with one third of interruptions occurring within the first 6 months of starting therapy. Forty percent of all treatment interruptions were due to the secondary side effects or toxicities of cART, 17% were due to the desire for simplification of the regimen and 14% were due to patient choice. These observations have led to numerous "switch" ART studies, designed to understand the efficacy, safety, and tolerability of switching patients from one regimen to another.

Potential benefit exists from evaluating new FDCs and STRs of existing agents by minimizing the number of components taken and developing more convenient dosing options (e.g., once-daily administration, reduced pill burden, smaller pill size). Study LAI116482 (LATTE) is an ongoing Phase IIb study evaluating the utility of a 2-drug, 2-class combination of cabotegravir + RPV once daily. Data from this study provided proof of principle for RPV combined with an INSTI as an effective 2-drug regimen for the maintenance of virologic suppression [Margolis, 2015]. Additionally, cabotegravir has similar virologic characteristics to DTG and, based on available data, has a similar efficacy, safety, and tolerability profile to DTG, which further supports the clinical investigation of a regimen including DTG + RPV as a 2-drug combination for the treatment of HIV infection.

Fixed-dose combination therapy as a STR is preferred by many patients and has well-recognized benefits. These include the simplification of therapy by combining different products in fixed proportions into a single tablet with the potential to increase patient adherence due to it being a simpler regimen. This also avoids the risk of "partial adherence", where patients take some, but not all, of their medicines. Better compliance with full treatment regimens can decrease the likelihood of virologic failure and subsequent development of resistance. While some STR options are now available, the opportunity to develop new STRs to better address toxicities while concurrently suppressing the emergence of resistance remains.

Data available to date suggest that DTG is a drug that provides good efficacy with a high barrier to the development of resistance in INSTI-naïve subjects and is generally well tolerated [DTG IB, GlaxoSmithKline Document Number RM2007/00683/10]. In addition, RPV represents a favorable therapeutic option when considering the efficacy, safety, and tolerability as well as the convenience of once daily dosing with the potential for FDCs [RPV IB, 2016]. RPV has been assessed in 2 simplification regimens: 2 NRTIs + RPV in SPIRIT and an INSTI + RPV in LAI116482, both of which maintained virologic suppression [Palella, 2014; Margolis, 2015].

Similar efficacy was expected for the DTG/RPV FDC based on the activity of both DTG and RPV as individual agents, and is supported by the lack of antagonism when the anti-HIV activity for DTG + RPV in combination was tested in vitro [GlaxoSmithKline Document Number 2015N229965_00]. These data are further supported by the lack of a DDI between the approved doses of DTG (50 mg) and RPV (25 mg) (Study LAI116181;

GlaxoSmithKline Document Number 2011N130484_00) that are being developed as combination therapy for this HIV-1 infected, virologically suppressed patient population. The data described in this efficacy summary support the use of a DTG + RPV 2-drug regimen as a potential for switching subjects to a well-tolerated ART regimen without an increased risk of virologic failure.

1.2. Overview of the Clinical Development Program

TIVICAY (dolutegravir) and EDURANT (rilpivirine) are currently approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents.

1.2.1. Pivotal Efficacy Studies

To demonstrate the efficacy of the DTG + RPV, data from 2 identical pivotal Phase III studies, 201636 (SWORD-1) and 201637 (SWORD-2), are provided. These studies are ongoing, randomized, parallel group, open-label, 148-week studies, designed to demonstrate non-inferior antiviral activity of switching to DTG 50 mg plus RPV 25 mg once daily compared to continuation of current INSTI-, NNRTI-, or PI-based ARV regimen in HIV-1-infected adults who are virologically suppressed (HIV-1 RNA <50 c/mL). Additional details of study design for these 2 studies are provided in Section 1.5. In addition, a safety study for the assessment of BMD in a subset of subjects in the 201636 and 201637 studies is being conducted. A brief summary of these studies is also provided in Appendix Table 1 and Appendix Table 2.

1.2.2. Supportive Single-Entity Studies for Efficacy

Where no studies have been performed with DTG and RPV, additional previously submitted studies from DTG or RPV SE development programs support this application and are categorized as “key” studies or “supportive” studies:

- **Key SE Studies**: these studies provide data that may be included in labeling, and were conducted during the individual agent development programs. Key clinical studies are described in the module 2 summaries and CSRs for these studies have been previously submitted.
- **Supportive SE Studies**: these studies are not essential for the FDC Benefit Risk assessment, but are considered helpful to the reviewer and supportive on the proposed indication. Supportive studies will be briefly tabulated in the module 2 summaries, but reports will be made available upon request for the convenience of the reviewer. A table of the “supportive” SE studies for efficacy is provided in Appendix Table 3.

All single agent data that are considered not to be relevant to this FDC application, e.g. efficacy data not related to the indication, will not be provided in this FDC submission.

1.2.3. Organization of Data Presentations

In this Summary of Clinical Efficacy, the efficacy data from identical studies 201636 and 201637 were pooled, and therefore are presented either individually in Section 2 or in a side-by-side format with the pooled analyses for comparative purposes in Section 3 when applicable.

Efficacy data are presented under the following headings:

- "Pivotal Efficacy Studies: 201636 and 201637"
- "Supportive SE Studies" (Presentation of "supportive" studies for efficacy is brief and limited to Section 1. Reports for these "supportive" studies will be made available upon request [no hyperlinks to module 5 are provided].)

In this document there are references to 3 types of presentations for tables and figure. The original electronic format, location, and a description of how these tables or figures are referenced throughout this document are summarized in Table 1.

Table 1 Description of the Types of Tables and Figures Presented in this Summary of Clinical Efficacy

Table/Figure Type	Location	How Referenced
In-text	In body of this summary document	Consecutive integers (e.g., Table 1, Table 2, Figure 1, Figure 2)
Statistical Source Tables	Individual CSR and Pooled Data	CSR plus study number plus statistical source table number (e.g., 201636 Table 6.1).
Appendix	In the Appendix section of this summary document (Section 7)	Consecutive integers (e.g., Appendix Table 1, Appendix Table 2)

1.3. Patient Populations in the Pivotal Efficacy Studies Contributing to the DTG + RPV Development Program

The intention of these studies was to enroll a population of subjects who are virologically suppressed (HIV-1 RNA < 50 c/mL) and who are on stable first or second regimen with no evidence of virologic non-response or failure.

Key inclusion criteria for the 2 key efficacy studies included HIV-1 infected men or women ≥18 years of age with plasma HIV-1 RNA <50 c/mL both at Screening and in the 12 months prior to Screening. Subjects were also on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening that included 2 NRTIs plus: INSTI (either the initial or second cART regimen), NNRTI (either the initial or second cART regimen), or boosted PI (or ATV unboosted) (either the initial or second PI-based cART regimen). Any prior switch, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability and/or safety concerns or access to medications, or convenience/simplification.

The main exclusion criteria were any confirmed HIV-1 RNA ≥50 c/mL within the 6 months prior to screening after confirmed suppression to <50 c/mL on the current ART regimen, within the 6- to 12-month window prior to screening and after confirmed suppression to <50 c/mL, any HIV-1 RNA measurement >200 c/mL or 2 or more HIV-1 RNA measurements ≥50 c/mL, women who were pregnant or breastfeeding, subjects

with viral resistance based on the presence of any resistance-associated major PI, INSTI, NRTI, or NNRTI mutation (in any available prior resistance genotype assay results) and INSTI resistance-associated substitution R263K, subjects with any degree of hepatic impairment, subjects who were Hepatitis B positive at Screening, subjects needing Hepatitis C therapy in the Early Switch Phase or interferon-based therapy at any time on study, subjects with a significant suicidality risk, or subjects having a QTc (Bazett) interval >450 msec.

1.3.1. Numbers of Subjects Contributing to the DTG + RPV Development Program

For the pivotal efficacy studies, the numbers of subjects included in each population were similar across treatment groups for the individual studies and for the pooled analyses (Table 2).

Table 2 Summary of Analysis Populations for Studies 201636, 201637, and Pooled Data

	201636		201637		Pooled	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
Intent-to-Treat	254	256	262	256	516	512
Intent-to-Treat Exposed	252	256	261	255	513	511
Per-Protocol	226	239	231	238	457	477

Data Source: 201636/201637 Table 1.010

1.4. Rationale for Dose Selection in the DTG + RPV Clinical Development Program

The proposed indication for DTG 50 mg/RPV 25 mg FDC is for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA <50 c/mL) without known or suspected resistance to either antiretroviral component.

To date, the efficacy, PK, safety, and drug interaction potential of DTG and RPV as single agents have been evaluated in 2 individual extensive clinical development programs of Phase I to III clinical trials. As individual agents, DTG and RPV are both approved and marketed as TIVICAY 50 mg once daily and EDURANT 25 mg once daily, respectively, the doses used in the current studies (201636 and 201637).

Clinical data showed the absence of a drug:drug interaction between DTG and RPV. Study LAI116181 was a Phase I, open-label, crossover study to evaluate the pharmacokinetics and safety of cabotegravir and RPV and DTG and RPV in healthy adult subjects. The study showed that co-administration of RPV with DTG had no clinically meaningful effect on DTG or RPV pharmacokinetics [Ford, 2013]. Co-administration of RPV with DTG had no effect on DTG AUC(0-τ) or Cmax, and a non-clinically significant increase in DTG Cτ by 22%, while co-administration of DTG with RPV had no effect on RPV AUC(0-τ) or Cmax and a non-clinically significant increase in RPV Cτ

by 21%. Hence, based on this data there is no need for a dose adjustment from approved doses when both products are used in combination.

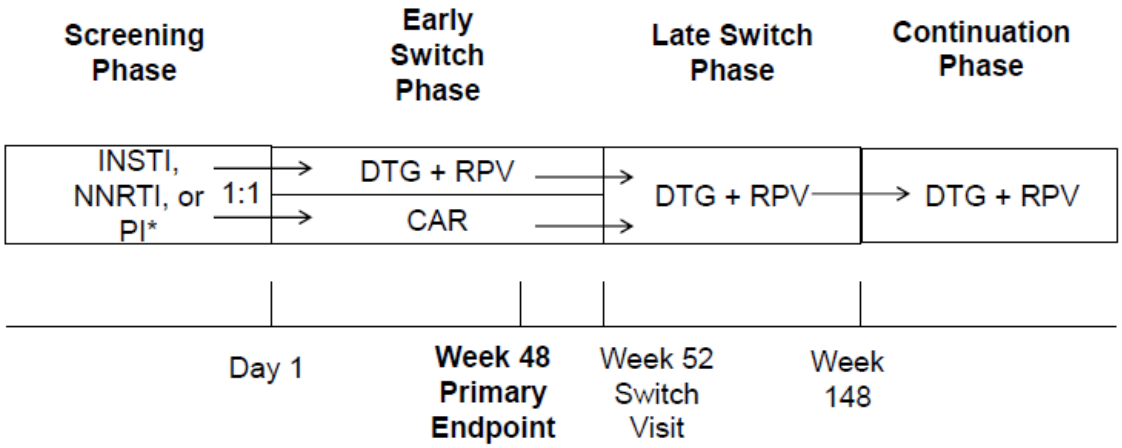
1.5. Design of Pivotal Efficacy Studies: 201636 (SWORD-1) and 201637 (SWORD-2)

These 2 ongoing studies are identical 148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority studies. They are being conducted in 510 (201636) and 518 (201637) adult HIV-1 infected patients who were on stable suppressive cART containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI. Eligible subjects were randomized 1:1 to continue their CAR or be switched to a 2-drug regimen consisting of DTG + RPV given as individual components administered once daily. Individuals who were originally assigned to continue their CAR and remained virologically suppressed at the Week 48 visit (primary endpoint of the studies), switched to DTG + RPV (at Week 52) and are to be followed to Week 148 (Figure 1).

The primary analysis took place after the last subject completed the Week 48 visit. Additional analyses may be conducted after the last subject completes the Week 100 visit, the Week 148 visit, and after the last subject withdraws from the study or transitions to commercial supplies (i.e., complete the Continuation Phase).

The studies include a Screening Phase (up to 28 days), an Early Switch Phase (Day 1 up to Week 52), a Late Switch Phase (Week 52 to Week 148), and a Continuation Phase. No non-protocol defined dose reductions, modifications in dosage, or changes in the frequency of dosing were allowed at any time in this study.

Figure 1 Study Schematic for 201636 (SWORD-1) and 201637 (SWORD-2)



*Plus 2 NRTIs
CAR = current antiretroviral regimen
N=508 (201636) and 516 (201637) randomized 1:1 to each treatment group and stratified by baseline 3rd Agent class, age group (< or ≥50 years old) and planned participation in Study 202094 (DEXA sub-study).

Must be on uninterrupted current regimen (either the initial or second CAR) for at least 6 months prior to Screening.
Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: 1 within the 6 to 12 month window, and 1 within 6 months prior to Screening.
No history of virologic failure.

No evidence of viral resistance based on the presence of any resistance-associated major PI, INSTI, NRTI, or NNRTI mutation and integrase resistance associated substitution R263K from prior resistance genotype assay results.
No current or prior history of etravirine use.

1.6. Efficacy Endpoints in the Pivotal Efficacy Studies: 201636 (SWORD-1) and 201637 (SWORD-2)

The primary efficacy endpoint for the 2 pivotal studies was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E Population.

The secondary efficacy endpoints were:

- Change from Baseline in CD4+ lymphocyte count at Week 24 and Week 48;
- Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 24 using the Snapshot algorithm for the ITT-E population;
- By Baseline third agent treatment class;
  - Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population;
  - Changes from Baseline in CD4+ lymphocyte counts at Week 48.
- Although not specified in the protocol, the proportion of subjects who were classified as Snapshot virological failure at Week 48 was also evaluated.

The relevant exploratory efficacy endpoints for the first 48 weeks of the study included the following:

- Proportion of subjects by patient subgroup(s) (e.g., by age, gender, Baseline CD4+) with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the ITT-E population;
- Change from Baseline in CD4+ lymphocyte counts at Week 48 by patient subgroups;
- Incidence of disease progression (HIV-associated conditions, AIDS, and death) through Week 48.

In addition to the presentation of results of the efficacy endpoints, this summary also includes a summary of Value Evidence and Outcomes results in Section 3.4. The endpoints for this analysis included the following:

- Between and within treatment group comparisons were assessed on change from Baseline in pre-specified treatment symptoms (using the SDM) at Week 48.
- Between and within treatment group comparisons were assessed on change from Baseline treatment satisfaction (using the HIV TSQ) at Week 48.

1.7. Statistical Considerations in the Pivotal Efficacy Studies: 201636 (SWORD-1) and 201637 (SWORD-2)

Details of the statistical analysis methods for the individual studies are found in the RAPs provided in each of the CSRs (201636 CSR and 201637 CSR). The statistical methods described in this section are for the efficacy analyses of data from the 201636 and 201637 CSRs that are included in this module.

1.7.1. Sample Size

For each study (201636 and 201637), non-inferiority could be concluded if the lower bound of the 2-sided 95% CI for the difference in response rates between the 2 treatment arms was greater than -10%. If rg is the response rate on DTG + RPV and rr is the response rate on comparator arm then the hypotheses can be written as follows:

$H0: rg - rr \leq -10\%$ $H1: rg - rr > -10\%$

Assuming a true 87% response rate in each arm, a non-inferiority margin of -10%, and a 2.5% one-sided significance level, each study required 238 subjects per treatment arm. This would provide 90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48. If we observed an 87% response rate for the CAR arm, then non-inferiority would be declared if the observed treatment difference was better than -3.5 percentage points.

Under the same assumptions described above, the pooled data from the 2 key studies provided >90% power to show non-inferiority for the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using a non-inferiority margin of -8%.

Study recruitment was extended beyond the 476 subjects per study to allow for further recruitment into the DEXA sub-study, particularly in underrepresented populations.

1.7.1.1. Rationale for non-inferiority margin

The non-inferiority margin of -10% cannot be justified on a statistical basis due to the large number of comparator regimens in the study and the lack of placebo comparison data for many of the regimens. A non-inferiority margin -10% is a reasonable non-inferiority margin for this study in order to demonstrate adequate preservation of treatment effect. After discussion with a regulatory agency, a pooled analysis of 201636 and 201637 was planned as the studies are identical, and the larger number of subjects allows for analysis with a more stringent non-inferiority margin of -8.0%.

After the protocol was approved, the FDA updated their guidance on the choice of primary endpoint and associated non-inferiority margin for switch trials [FDA, 2015]. Therefore, the RAP included a secondary endpoint comparing the snapshot virological failure response rates between the DTG + RPV and CAR groups assessed using a NI margin of 4%. Given that previous switch studies have shown a snapshot virological failure rate of between 1% and 3%, this NI margin is considered stringent for this endpoint.

1.7.2. Analysis Populations

Efficacy analyses were conducted based on the ITT-E population, which consisted of all randomly assigned subjects who received at least one dose of study drug.

Sensitivity analyses of the primary efficacy endpoint were conducted based on the ITT population (all randomized subjects) and the PP population, defined as subjects in the ITT-E population with the exception of major protocol violators: e.g. violations which could affect the assessment of antiviral activity, or where study drug compliance was known to be less than 90%.

1.7.3. Statistical Analysis Methods

For the primary comparison, adjusted estimates of the difference in the rate of responders between the 2 treatment arms were presented along with 2-sided CIs based on a stratified analysis using CMH weights. All CIs were 2-sided and the analysis was stratified according to the Baseline third agent class (INSTI, NNRTI, PI) and age group (< or ≥50 years old). The CMH estimate of the common difference in rates across strata was calculated as the weighted average of the strata-specific estimates of the difference in response rates between the 2 treatment groups.

The weighted least squares chi-squared statistic [Fleiss, 1981] was used to test for one-way homogeneity across the levels of each categorical variable, with each categorical variable considered separately. Following Lui and Kelly [Lui, 2000], a value of one half was added to each cell in any strata for which the stratum-specific rate estimates of either r_d or r_a were zero, and tests were one-sided. Any heterogeneity found to be statistically significant was to be explored and if necessary results were to be reported for each level

of the categorical variable. Investigation of heterogeneity was confined to the primary endpoint using the Week 48 Snapshot analysis. Tests of homogeneity were assessed at the one-sided 10% level of significance.

Secondary analyses of efficacy data included a repeat of the primary snapshot analysis, as detailed above, at Week 24 conducted at the time of the primary Week 48 analysis and an analysis of the difference in the snapshot virological failures using a 4% non-inferiority margin. Confidence intervals for the difference between the treatment arms in the proportion of subjects with HIV-1 RNA <50 c/mL at Week 48 using a snapshot analysis are also presented by baseline third agent class.

The proportion of subjects without virologic (ERDF) or virologic/tolerability (TRDF) failure was estimated using the Kaplan-Meier nonparametric method based on the time to CVW or treatment related/efficacy related discontinuation (i.e., drug-related AE, protocol defined safety stopping criteria, or lack of efficacy). Subjects who had not met CVW criteria and were ongoing in the study, or who had discontinued for reasons other than those related to treatment/lack of efficacy, were censored. The estimate of the standard error used to derive CIs for the difference in proportions between treatment groups was based on Greenwood's formula [Kalbfleisch, 1980]. The estimated proportion of subjects without CVW and not discontinued due to treatment related/efficacy related reasons at Week 48 was presented by treatment group, along with estimated difference in proportions between treatment groups and its associated 2-sided 95% CI.

2. SUMMARY OF RESULTS OF INDIVIDUAL PIVOTAL EFFICACY STUDIES

Key data are presented here for the individual studies. The data for the individual studies are also included in presentations of combined data in Section 3.1 and Section 3.2, alongside the pooled data.

Details of the study design and key results for the individual studies are also summarized in Appendix Table 1 and Appendix Table 2, respectively.

2.1. Study 201636 (SWORD-1)

A total of 252 subjects were randomized (1:1) and treated with DTG + RPV. Similar proportions of subjects in each treatment group withdrew from the study (DTG + RPV: 5%; CAR: 7%). The most common reasons for withdrawal were withdrew consent (DTG + RPV: 1%; CAR: 3%) and AE (DTG + RPV: 2%; CAR: <1%).

Overall, 95% of subjects in the DTG + RPV group and 96% of subjects in the CAR group achieved the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48. The primary efficacy analysis demonstrated that DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-4.3%) is greater than -10%. This was supported by similar analyses performed for the PP and ITT populations. The number of subjects with snapshot virologic failure was the same in the DTG + RPV and CAR groups (2 subjects each). The secondary endpoints, including plasma HIV-1 RNA at Week 24, further support the results of the primary endpoint with non-inferiority in the primary endpoint supported across demographic subgroups (age, race, and gender), Baseline CD4+ lymphocyte count subgroups and Baseline third agent treatment class.

The proportion of subjects who were classified as snapshot virological failures at Week 48 also demonstrates that the combined use of DTG + RPV is non-inferior to CAR within a non-inferiority margin of 4%. The upper bound of the 95% CI for the adjusted treatment difference (1.6%) is less than 4%.

The data for the 201636 study indicate that the DTG + RPV 2-drug regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure.

2.2. Study 201637 (SWORD-2)

A total of 261 subjects were randomized (1:1) and treatment with DTG + RPV. The same number of subjects in each treatment group withdrew from the study (6%). The most common reasons for withdrawal were AEs (DTG + RPV: 4%; CAR: <1%) and withdrew consent (DTG + RPV: <1%; CAR: 3%).

Overall, 94% of subjects in both the DTG + RPV and CAR groups achieved the primary efficacy endpoint of plasma HIV-1 RNA <50 c/mL at Week 48. The primary efficacy analysis demonstrated that DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.9%) is greater than -10%. This was supported by similar analyses performed for the PP and ITT populations. There was 1 subject in the DTG + RPV group and 4 subjects in the CAR group with snapshot virologic failure. The secondary endpoints, including plasma HIV-1 RNA at Week 24, further support the results of the primary endpoint with non-inferiority in the primary endpoint supported across demographic subgroups (age, race, and gender), Baseline CD4+ lymphocyte count subgroups and Baseline third agent treatment class.

The proportion of subjects who were classified as snapshot virological failures at Week 48 also demonstrates that the combined use of DTG + RPV is non-inferior to CAR

within a non-inferiority margin of 4%. The upper bound of the 95% CI for the adjusted treatment difference (0.6%) is less than 4%.

The data for the 201637 study indicate that the DTG + RPV 2-drug regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS PIVOTAL EFFICACY STUDIES

3.1. Study Populations in Pivotal Efficacy Studies

3.1.1. Subject Disposition

For both studies combined, a total of 513 subjects were randomized (1:1) to receive DTG + RPV and 511 subjects remained on their CAR. Similar proportions of subjects in each treatment group withdrew from the study (6% compared to 7%; Table 3). The most common reason for withdrawal was adverse events (DTG + RPV: 3%; CAR: <1%). Less than 1% of subjects from both groups were withdrawn from the study due to investigator's assessment of lack of efficacy.

Table 3 Summary of Subject Disposition for Studies 201636 and 201637 Pooled Data (ITT-E Population)

Number of subjects, n (%)	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
Randomized and treated	252	256	261	255	513	511
Ongoing[a]	239 (95)	238 (93)	245 (94)	239 (94)	484 (94)	477 (93)
Premature Withdrawal	13 (5)	18 (7)	16 (6)	16 (6)	29 (6)	34 (7)
Primary reason for withdrawal						
Adverse Event	6 (2)	2 (<1)	11 (4)	1 (<1)	17 (3)	3 (<1)
Investigator Discretion	0	2 (<1)	0	1 (<1)	0	3 (<1)
Lack of Efficacy	2 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)	3 (<1)
Lost to Follow-up	1 (<1)	2 (<1)	1 (<1)	1 (<1)	2 (<1)	3 (<1)
Protocol Deviation	1 (<1)	4 (2)	0	3 (1)	1 (<1)	7 (1)
Subject reached Protocol-defined stopping criteria	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Withdrew Consent	3 (1)	7 (3)	2 (<1)	7 (3)	5 (<1)	14 (3)

Data Source: 201636/201637 Table 1.050

a. 'Ongoing' includes all subjects who completed the Early Switch Phase and entered the Late Switch Phase. As per the protocol definition, subjects were not considered to have completed the study until they had reached the end of the Late Switch Phase.

3.1.2. Demographic and Baseline Characteristics

3.1.2.1. Demographic Characteristics

Demographic characteristics were well balanced across treatment groups (Table 4). Of note, >20% of subjects were women for both studies pooled (DTG + RPV: 23%; CAR: 21%) and 29% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older.

Table 4 Summary of Demographic Characteristics for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Age (y), median (range)	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-6[redacted])	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-7[redacted])
Age group (y), n (%)						
<35	53 (21)	60 (23)	64 (25)	55 (22)	117 (23)	115 (23)
35-<50	130 (52)	125 (49)	119 (46)	129 (51)	249 (49)	254 (50)
≥50	69 (27)	71 (28)	78 (30)	71 (28)	147 (29)	142 (28)
Sex, n (%)						
Female	58 (23)	51 (20)	62 (24)	57 (22)	120 (23)	108 (21)
Male	194 (77)	205 (80)	199 (76)	198 (78)	393 (77)	403 (79)
Ethnicity, n (%)						
Hispanic/Latino	30 (12)	34 (13)	37 (14)	48 (19)	67 (13)	82 (16)
Not Hispanic/Latino	222 (88)	222 (87)	224 (86)	207 (81)	446 (87)	429 (84)
Race, n (%)						
American Indian or Alaska Native	3 (1)	6 (2)	11 (4)	8 (3)	14 (3)	14 (3)
Asian	25 (10)	34 (13)	13 (5)	16 (6)	38 (7)	50 (10)
Central/South Asian Heritage	0	0	0	1 (<1)	0	1 (<1)
Japanese/East Asian Heritage/South East Asian Heritage	25 (10)	34 (13)	13 (5)	15 (6)	38 (7)	49 (10)
Black/African American	24 (10)	27 (11)	13 (5)	20 (8)	37 (7)	47 (9)
Native Hawaiian or other Pacific Islander	1 (<1)	0	1 (<1)	0	2 (<1)	0
White	198 (79)	188 (73)	223 (85)	210 (82)	421 (82)	398 (78)
White & African American/African Heritage	0	0	0	1 (<1)	0	1 (<1)
White and American Indian or Alaska Native	0	1 (<1)	0	0	0	1 (<1)
Asian and African American/African Heritage	1 (<1)	0	0	0	1 (<1)	0

Data Source: 201636/201637 Table 1.150, Table 1.171, Table 1.172, and Table 1.173.

3.1.2.2. Baseline Characteristics

Baseline characteristics were also well balanced across the treatment groups (Table 5). Overall, most subjects had negative test results at screening for HCV infection (DTG + RPV: 94%; CAR: 92%) and were in CDC Class A (DTG + RPV: 78%; CAR: 75%).

Table 5 Summary of Baseline Characteristics for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
Baseline HIV-1 RNA (c/mL)						
<50 c/mL	247(98)	253 (99)	259 (99)	251 (98)	506 (99)	504 (99)
≥50 c/mL	5 (2)	3 (1)	2 (1)	4 (2)	7 (1)	7 (1)
Baseline CD4+ (log_{10} cells/mm^3)						
Median	2.786	2.805	2.785	2.798	2.786	2.805
Min., Max.	1.57, 3.18	1.98, 3.18	2.06, 3.25	2.03, 3.22	1.57, 3.25	1.98, 3.22
Hepatitis B & C Test Results						
B only	0	1 (<1)	0	1 (<1)	0	2 (<1)
C only	15 (6)	19 (7)	13 (5)	21 (8)	28 (5)	40 (8)
B and C	0	0	0	0	0	0
Borderline C only	0	0	1 (<1)	0	1 (<1)	0
Neither	237 (94)	236 (92)	247 (95)	233 (91)	484 (94)	469 (92)
CDC Category						
A: Asymptomatic or Lymphadenopathy or Acute HIV	203 (81)	198 (77)	197 (75)	187 (73)	400 (78)	385 (75)
B: Symptomatic, not AIDS	20 (8)	35 (14)	35 (13)	33 (13)	55 (11)	68 (13)
C: AIDS	29 (12%)	23 (9%)	29 (11%)	34 (13%)	58 (11%)	57 (11%)
Missing	0	0	0	1 (<1)	0	1 (<1)

Data Source: 201636/201637 Table 1.210, Table 1.230, Table 2.111, Table 2.112, Table 2.113, and Table 1.200

3.1.2.3. Antiretroviral Therapy at Screening by Individual Component

As per the protocol for these studies, all subjects (100%) were receiving NRTIs as part of their ART regimen at screening (Table 6). The most commonly reported individual NRTIs were TDF (DTG + RPV: 73%; CAR: 70%) and FTC (DTG + RPV: 69%; CAR: 67%).

In addition, 54% of subjects in both groups were receiving NNRTIs, 26% of subjects in the DTG + RPV group and 27% of subjects in the CAR group were receiving PIs, and 20% in the DTG + RPV group and 19% of subjects in the CAR group were receiving INSTIs at screening.

Table 6 Summary of Antiretroviral Therapy at Screening for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Any medication, n (%)	252 (100)	256 (100)	261 (100)	255 (100)	513 (100)	511 (100)
NRTI						
Any medication	252 (100)	256 (100)	261 (100)	255 (100)	513 (100)	511 (100)
Tenofovir	184 (73)	172 (67)	190 (73)	187 (73)	374 (73)	359 (70)
Emtricitabine	166 (66)	156 (61)	186 (71)	185 (73)	352 (69)	341 (67)
Lamivudine	85 (34)	100 (39)	75 (29)	70 (27)	160 (31)	170 (33)
Abacavir	56 (22)	66 (26)	48 (18)	55 (22)	104 (20)	121 (24)
Zidovudine	11 (4)	17 (7)	21 (8)	10 (4)	32 (6)	27 (5)
Didanosine	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)
Phosphazide	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Stavudine	1 (<1)	0	0	0	1 (<1)	0
NNRTI						
Any medication	131 (52)	134 (52)	144 (55)	144 (56)	275 (54)	278 (54)
Efavirenz	83 (33)	86 (34)	102 (39)	103 (40)	185 (36)	189 (37)
Nevirapine	29 (12)	31 (12)	27 (10)	18 (7)	56 (11)	49 (10)
Rilpivirine	18 (7)	17 (7)	15 (6)	22 (9)	33 (6)	39 (8)
Etravirine	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
PI						
Any medication	75 (30)	74 (29)	58 (22)	62 (24)	133 (26)	136 (27)
Darunavir-Ritonavir	31 (12)	19 (7)	27 (10)	21 (8)	58 (11)	40 (8)
Atazanavir-Ritonavir	24 (10)	23 (9)	15 (6)	18 (7)	39 (8)	41 (8)
Lopinavir	7 (3)	7 (3)	10 (4)	18 (7)	17 (3)	25 (5)
Ritonavir	7 (3)	7 (3)	10 (4)	20 (8)	17 (3)	27 (5)
Atazanavir	10 (4)	22 (9)	4 (2)	4 (2)	14 (3)	26 (5)
Lopinavir-Ritonavir	10 (4)	10 (4)	10 (4)	18 (7)	20 (4)	28 (5)
Darunavir	0	0	1 (<1)	0	1 (<1)	0
Fosamprenavir-Ritonavir	0	0	1 (<1)	0	1 (<1)	0
Nelfinavir	0	0	0	1 (<1)	0	1 (<1)
INSTI						
Any medication	46 (18)	48 (19)	59 (23)	49 (19)	105 (20)	97 (19)
Raltegravir	13 (5)	22 (9)	30 (11)	22 (9)	43 (8)	44 (9)
Dolutegravir	16 (6)	17 (7)	17 (7)	16 (6)	33 (6)	33 (6)
Elvitegravir-Cobicistat	17 (7)	9 (4)	12 (5)	11 (4)	29 (6)	20 (4)
Other ART						
Any medication	15 (6)	9 (4)	12 (5)	11 (4)	27 (5)	20 (4)
Cobicistat	15 (6)	9 (4)	12 (5)	11 (4)	27 (5)	20 (4)

Data Source: 201636/201637 Table 1.400

3.1.2.4. Antiretroviral Therapy at Screening by Regimen

Antiretroviral therapies received by study participants at Screening constituted the CAR for subjects randomized to this group on Day 1. The most commonly-reported ARV backbone treatment at Screening was FTC and TDF followed by ABC and 3TC (Table 7). Approximately 69% of subjects in the DTG + RPV group and 68% of subjects in the CAR group were receiving FTC + TDF backbone regimens. Approximately 22% of subjects in the DTG + RPV group and 25% of subjects in the CAR group were receiving ABC + 3TC backbone regimens.

Table 7 Summary of Antiretroviral Therapy at Screening by Regimen for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
Any medication, n (%)	252 (100)	256 (100)	261 (100)	255 (100)	513 (100)	511 (100)
FTC,TDF / FTC+TDF backbone						
EFV+FTC+TDF	60 (24)	64 (25)	70 (27)	78 (31)	130 (25)	142 (28)
EFV, FTC+TDF	1 (<1)	0	9 (3)	7 (3)	10 (2)	7 (1)
EFV, FTC, TDF	1 (<1)	1 (<1)	5 (2)	3 (1)	6 (1)	4 (<1)
RPV+FTC+ TDF	16 (6)	15 (6)	13 (5)	19 (7)	29 (6)	34 (7)
ETR, FTC+TDF	1 (<1)	0	0	0	1 (<1)	0
NVP, FTC+TDF	13 (5)	12 (5)	8 (3)	10 (4)	21 (4)	22 (4)
DRV-RTV, FTC+TDF, RTV	0	0	0	1 (<1)	0	1 (<1)
DRV-RTV, FTC+TDF	24 (10)	14 (5)	21 (8)	17 (7)	45 (9)	31 (6)
DRV, FTC+TDF	0	0	1 (<1)	0	1 (<1)	0
DRV-RTV, FTC, TDF	2 (<1)	0	3 (1)	2 (<1)	5 (<1)	2 (<1)
ATV-RTV, FTC+TDF	19 (8)	21 (8)	13 (5)	12 (5)	32 (6)	33 (6)
ATV-RTV, FTC, TDF	1 (<1)	0	1 (<1)	0	2 (<1)	0
ATV+RTV, FTC+TDF	0	0	0	1 (<1)	0	1 (<1)
LPV+RTV, FTC+TDF	1 (<1)	2 (<1)	4 (2)	6 (2)	5 (<1)	8 (2)
FPV-RTV, FTC+TDF	0	0	1 (<1)	0	1 (<1)	0
EVG-COBI, FTC, TDF	2 (<1)	0	0	0	2 (<1)	0
COBI+EVG+FTC+TDF	15 (6)	9 (4)	12 (5)	11 (4)	27 (5)	20 (4)
RAL, FTC+TDF	9 (4)	11 (4)	20 (8)	17 (7)	29 (6)	28 (5)
RAL, FTC, TDF	0	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)
DTG, FTC, TDF	0	0	1 (<1)	0	1 (<1)	0
DTG, FTC+TDF	1 (<1)	5 (2)	3 (1)	1 (<1)	4 (<1)	6 (1)

	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
ABC,3TC / ABC+3TC backbone						
EFV, ABC+3TC	7 (3)	12 (5)	8 (3)	8 (3)	15 (3)	20 (4)
EFV, ABC, 3TC	0	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)
RPV, ABC+3TC	2 (<1)	2 (<1)	2 (<1)	2 (<1)	4 (<1)	4 (<1)
RPV, ABC, 3TC	0	0	0	1 (<1)	0	1 (<1)
ETR, ABC+3TC	0	0	0	1 (<1)	0	1 (<1)
NVP, ABC+3TC	6 (2)	12 (5)	7 (3)	4 (2)	13 (3)	16 (3)
NVP, 3TC, TDF	7 (3)	5 (2)	3 (1)	1 (<1)	10 (2)	6 (1)
DRV-RTV, ABC+3TC	5 (2)	4 (2)	3 (1)	1 (<1)	8 (2)	5 (<1)
ATV, ABC+3TC	8 (3)	11 (4)	3 (1)	3 (1)	11 (2)	14 (3)
ATV, ABC, 3TC	0	3 (1)	0	0	0	3 (<1)
ATV-RTV, ABC, 3TC	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
ATV-RTV, ABC+3TC	3 (1)	1 (<1)	0	5 (2)	3 (<1)	6 (1)
LPV+RTV, ABC+3TC	0	0	0	1 (<1)	0	1 (<1)
LPV-RTV, ABC, 3TC	1 (<1)	0	0	0	1 (<1)	0
LPV+RTV, ABC, 3TC	1 (<1)	0	1 (<1)	0	2 (<1)	0
LPV+RTV, ABC+3TC	2 (<1)	0	1 (<1)	8 (3)	3 (<1)	8 (2)
RAL, ABC, 3TC	1 (<1)	3 (1)	0	0	1 (<1)	3 (<1)
RAL, ABC+3TC	3 (1)	3 (1)	8 (3)	4 (2)	11 (2)	7 (1)
DTG+ABC+3TC	11 (4)	8 (3)	4 (2)	5 (2)	15 (3)	13 (3)
DTG, ABC+3TC	4 (2)	4 (2)	9 (3)	10 (4)	13 (3)	14 (3)
3TC,AZT / 3TC+AZT backbone						
EFV, 3TC+AZT	2 (<1)	0	4 (2)	1 (<1)	6 (1)	1 (<1)
EFV, 3TC, AZT	3 (1)	1 (<1)	3 (1)	2 (<1)	6 (1)	3 (<1)
NFV, 3TC+AZT,	0	0	0	1 (<1)	0	1 (<1)
NVP, 3TC, AZT	1 (<1)	0	4 (2)	0	5 (<1)	0
NVP, 3TC+AZT,	2 (<1)	2 (<1)	5 (2)	2 (<1)	7 (1)	4 (<1)
DRV-RTV, 3TC+AZT	0	1 (<1)	0	0	0	1 (<1)
ATV-RTV, 3TC+AZT	0	0	1 (<1)	0	1 (<1)	0
ATV, 3TC+AZT	0	1 (<1)	0	0	0	1 (<1)
ATV, 3TC, AZT	0	2 (<1)	0	0	0	2 (<1)
LPV-RTV, 3TC, AZT	2 (<1)	3 (1)	0	0	2 (<1)	3 (<1)
LPV+RTV, 3TC, AZT	0	0	1 (<1)	0	1 (<1)	0
RAL, 3TC+AZT	0	3 (1)	0	1 (<1)	0	4 (<1)
RAL, 3TC, AZT	0	0	1 (<1)	0	1 (<1)	0
3TC,TDF / 3TC+TDF backbone						
EFV+3TC+TDF	4 (2)	4 (2)	0	0	4 (<1)	4 (<1)
EFV, 3TC, TDF	4 (2)	2 (<1)	0	0	4 (<1)	2 (<1)
EFV, 3TC+TDF	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
ATV, 3TC, TDF	1 (<1)	4 (2)	0	0	1 (<1)	4 (<1)
LPV+RTV, 3TC, TDF	2 (<1)	1 (<1)	0	0	2 (<1)	1 (<1)
Other backbone						
EFV, ddl, 3TC	0	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)

	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
ATV, ddl, 3TC	0	1 (<1)	0	0	0	1 (<1)
EFV, ddl, ABC	1 (<1)	0	0	0	1 (<1)	0
ATV, 3TC, d4T	1 (<1)	0	0	0	1 (<1)	0
LPV+RTV, 3TC, Phosphazide	0	0	1 (<1)	0	1 (<1)	0
ATV, 3TC, Phosphazide	0	0	0	1 (<1)	0	1 (<1)

Data Source: 201636/201637 Table 1.470
Multi-ingredient products are labeled according to the sum of their ingredients with the symbol '+'.
Boosted drugs are presented on the same line separated with a '-'.

3.1.3. Extent of Exposure

The median time of exposure to DTG + RPV and CAR was 364 days (52 weeks) for both studies and for the pooled data (Table 8). There were 2 subjects in the CAR group for whom study treatment was interrupted more than 10% of total time in the Early Switch Phase and this subject was not included in the PP Population (201636 CSR Section 5.2; 201637 CSR Section 5.2).

For those subjects randomized to DTG + RPV in the Early Switch Phase, there was no schedule to switch treatment (and no Week 52 assessment visit). As a result, their exposure within the Early Switch Phase was considered to be 52 weeks (364 days) unless they withdrew earlier in the study.

Extent of exposure for CAR is calculated using medication start and stop dates. The late switch from CAR to DTG + RPV takes place at the Week 52 visit but there is variability in the actual day that subjects attend the clinic. As a result, in contrast with the DTG + RPV group, there were some subjects with less than 52 weeks of treatment and others with at least 52 weeks of treatment.

In the Early Switch Phase, exposure was comparable between DTG + RPV and CAR.

Table 8 Summary of Extent of Exposure during the Early Switch Phase in Studies 201636, 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Exposure (Weeks) n (%)						
<2 weeks	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
2 to <4 weeks	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
4 to <8 weeks	2 (<1)	2 (<1)	0	1 (<1)	2 (<1)	3 (<1)
8 to <12 weeks	1 (<1)	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)
12 to <16 weeks	1 (<1)	0	2 (<1)	1 (<1)	3 (<1)	1 (<1)
16 to <20 weeks	1 (<1)	0	1 (<1)	0	2 (<1)	0
20 to <24 weeks	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
24 to <28 weeks	1 (<1)	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)
28 to <32 weeks	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)	3 (<1)
32 to <36 weeks	0	2 (<1)	3 (<1)	0	3 (<1)	2 (<1)
36 to <40 weeks	2 (<1)	0	1 (<1)	3 (1)	3 (<1)	3 (<1)
40 to <44 weeks	2 (<1)	0	0	1 (<1)	2 (<1)	1 (<1)
44 to <48 weeks	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
48 to <52 weeks	0	93 (36)	1 (<1)	103 (40)	1 (<1)	196 (38)
≥52 weeks[b]	239 (95)	152 (59)	244 (93)	141 (55)	483 (94)	293 (57)
Exposure (Days)						
Mean (SD)	354.3 (47.01)	354.8 (50.08)	350.6 (57.96)	356.3 (40.58)	352.4 (52.85)	355.5 (45.55)
Median (IQR)	364.0 (364.0 - 364.0)	364.0 (362.0 - 365.0)	364.0 (364.0 - 364.0)	364.0 (361.0 - 364.0)	364.0 (364.0 - 364.0)	364.0 (362.0 - 365.0)
Duration of dosing in subject years[a]	244.4	248.6	250.5	248.8	495.0	497.4

Data Source: 201636/201637 Table 3.010.
Note: Dose interruptions are not excluded.
a. Cumulative sum across subjects of (treatment stop date - treatment start date + 1) divided by 365.25
b. For CAR subjects, exposure in the Early Switch Phase is calculated to the day prior to switching to DTG + RPV or to withdrawal where withdrawal took place sooner. For DTG + RPV subjects, exposure in the Early Switch Phase is calculated as 52 weeks (364 days) or to withdrawal if withdrawal took place sooner.

3.2. Comparison of Efficacy Results in Pivotal Efficacy Studies

3.2.1. Primary Efficacy Results: Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot Analysis)

The primary endpoint for this study was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm for the Intent-to-Treat Exposed (ITT-E) population.

In the pooled analysis, the same proportion of subjects in the DTG + RPV and CAR groups (95% of subjects; 95% CI: 93%, 97%) achieved the primary efficacy response (Table 9) and thus response to treatment has been maintained with viral suppression greater than 90% at Week 48. The analysis demonstrated that DTG + RPV is non-

inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.0%) is greater than -8% for the combined studies.

The primary efficacy endpoint was also achieved within each of the individual studies with the lower bound of the 95% CI for the adjusted treatment difference greater than -10%.

The results from the PP population were consistent with those from the ITT-E (primary) population (Table 10).

Table 9 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population)

Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion, % (95% CI)[a]	Adjusted Difference in Proportion, % (95% CI)[b]
201636				
DTG + RPV	252	240 / 252 (95%)	-0.5 (-4.1, 3.2)	-0.6 (-4.3, 3.0)
CAR	256	245 / 256 (96%)		
201637				
DTG + RPV	261	246 / 261 (94%)	0.1 (-3.9, 4.2)	0.2 (-3.9, 4.2)
CAR	255	240 / 255 (94%)		
Pooled Data				
DTG + RPV	513	486 / 513 (95%)	-0.2 (-2.9, 2.5)	-0.2 (-3.0, 2.5)
CAR	511	485 / 511 (95%)		

Data Source: 201636/201637 Table 2.011, Table 2.012, and Table 2.013.

a. Difference: Proportion on (DTG + RPV) – Proportion on CAR.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: age (< vs. ≥ 50 years old) and Baseline third agent (PI, NNRTI, INSTI).

Table 10 Summary of Analysis for Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (PP Population)

Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion (95% CI)[a]	Adjusted Difference in Proportion (95% CI)[b]
201636				
DTG + RPV	226	217 / 226 (96%)	-0.6 (-4.1, 2.8)	-0.8 (-4.2, 2.7)
CAR	239	231 / 239 (97%)		
201637				
DTG + RPV	231	220 / 231 (95%)	-0.6 (-4.3, 3.2)	-0.6 (-4.4, 3.2)
CAR	238	228 / 238 (96%)		
Pooled Data				
DTG + RPV	457	437 / 457 (96%)	-0.6 (-3.1, 1.9)	-0.7 (-3.3, 1.8)
CAR	477	459 / 477 (96%)		

Data Source: 201636/201637 Table 2.021, Table 2.022, and Table 2.023.

The Week 48 window was up to the end of on-treatment early switch phase.

a. Difference: Proportion on (DTG + RPV) – Proportion on CAR.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: age (< vs. ≥ 50 years old) and Baseline third agent (PI, NNRTI, INSTI).

3.2.2. Secondary Efficacy Results

3.2.2.1. Study Outcomes at Week 48: Plasma HIV-1 RNA <50 c/mL (Snapshot Analysis)

Virologic response rates were the same between the DTG + RPV and CAR treatment groups (95%) (Table 11).

For subjects in the Snapshot category of 'No virologic data', as would be expected in open-label switch studies, there were fewer discontinuations due to AEs or death in the CAR group (3 subjects) where subjects have already taken at least 6 months of stable treatment, compared to the DTG + RPV group (17 subjects). In contrast there were fewer disconnections due for 'Other' reasons in the DTG + RPV group (7 subjects) compared with the CAR group (16 subjects). Of the 16 'Other reasons' for discontinuation in the CAR group, 5 withdrew consent, 6 had protocol deviations, 2 were lost to follow-up, 2 relocated, and 1 cited burden of travel (Data Source: 201636/201637 Listing 4 and Listing 14). Of the 7 'Other reasons' for discontinuation in the DTG + RPV group, 3 withdrew consent, 2 relocated, 1 was lost to follow-up, and 1 became pregnant. Adverse events leading to withdrawal from the study are summarized in m2.7.4 Section 2.1.5.1. One subject in the CAR group died during Study 201636 and one subject in the DTG + RPV group died during Study 201637 (m2.7.4 Section 2.1.2).

Table 11 Summary of Study Outcomes (Plasma HIV-1 RNA <50 c/mL) at Week 48 – Snapshot Analysis in Studies 201636, 201637, and Pooled Data (ITT-E Population)

Outcome n (%)	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Virologic Success	240 (95)	245 (96)	246 (94)	240 (94)	486 (95)	485 (95)
Virologic Failure	2 (<1)	2 (<1)	1 (<1)	4 (2)	3 (<1)	6 (1)
Data in window not below threshold	0	1 (<1)	0	1 (<1)	0	2 (<1)
Discontinued for lack of efficacy	2 (<1)	0	0	2 (<1)	2 (<1)	2 (<1)
Discontinued for other reason while not below threshold	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Change in ART	0	0	0	1 (<1)	0	1 (<1)
No Virologic Data	10 (4)	9 (4)	14 (5)	11 (4)	24 (5)	20 (4)
Discontinued study due to AE or Death	5 (2)	2 (<1)	12 (5)	1 (<1)	17 (3)	3 (<1)
Discontinued study for Other Reasons	5 (2)	7 (3)	2 (<1)	9 (4)	7 (1)	16 (3)
Missing data during window but on study	0	0	0	1 (<1)	0	1 (<1)

Data Source: 201636/201637 Table 2.040

3.2.2.2. Subjects with Plasma HIV-1 RNA <50 c/mL at Week 24 (Snapshot Analysis)

At Week 24, the same proportion of subjects in the DTG + RPV group (97%) achieved this efficacy endpoint compared with the CAR group (97%) (Data Source: 201636/201637 Table 2.713).

3.2.2.3. Proportion of Subjects Classified as Snapshot Virological Failures at Week 48

The proportion of subjects who were classified as Snapshot virological failures at Week 48 is summarized in Table 12. These results indicate that the combined use of DTG + RPV is non-inferior to CAR based on snapshot virologic failure with a non-inferiority margin of 4%. The upper bound of the 95% CI for the adjusted treatment difference (0.6%) is less than 4%.

Table 12 Analysis of Proportion of Subjects Classified as Virological Failures[a] at Week 48 – Snapshot Analysis for Studies 201636, 201637, and Pooled Data (ITT-E Population)

Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion (95% CI)[b]	Adjusted Difference in Proportion (95% CI)[c]
201636				
DTG + RPV	252	2 / 252 (<1%)	0.0 (-1.5, 1.5)	0.1 (-1.5, 1.6)
CAR	256	2 / 256 (<1%)		
201637				
DTG + RPV	261	1 / 261 (<1%)	-1.2 (-2.9, 0.5)	-1.1 (-2.8, 0.6)
CAR	255	4 / 255 (2%)		
Pooled Data				
DTG + RPV	513	3 / 513 (<1%)	-0.6 (-1.7, 0.6)	-0.6 (-1.7, 0.6)
CAR	511	6 / 511 (1%)		

Data Source: 201636/201637 Table 2.181, Table 2.182, and Table 2.183.

a. Virologic failures include subjects who had plasma HIV-1 RNA ≥ 50 c/mL at Week 48, who discontinued due to lack of efficacy, who discontinued for other reasons while not <50 c/mL, and who changed in ART.
b. Difference: Proportion on DTG - Proportion on Current ART Regimen
c. Based on Cochran-Mantel Haenszel stratified analysis adjusting for age (<50, ≥ 50 years old) and Baseline third agent class (PI, NNRTI, INSTI).

Note: Week 48 window is up to the end of on-treatment Early Switch Phase.

3.2.2.4. Treatment/Efficacy-Related Discontinuations

Kaplan-Meier estimates of the proportion of subjects without TRDF by Week 48 were high and similar between treatment groups (DTG + RPV: 96.8%; CAR: 99.0%) (Table 13), and the proportion of subjects without ERDF was the same for both treatment groups (99.4%) (Table 14). For TRDF, the 95% CI for the difference in proportions excludes zero but with a lower bound of only -3.9% it is supportive of the primary endpoint conclusion of non-inferiority.

Table 13 Summary of Kaplan-Meier Estimates of Proportion of Subjects Not Meeting CVW Criteria or Discontinuing for Reasons Related to Treatment by end of Early Switch Phase – *Treatment Related Discontinuation* = *Failure* – in Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Number of Subjects, n/N (%)						
Protocol-Defined CVW or discontinuation due to treatment-related reasons by the end of Early Switch Phase	6/252 (2)	1/256 (<1)	10/261 (4)	4/255 (2)	16/513 (3)	5/511 (<1)
Censored[a]	246/252 (98)	255/256 (>99)	251/261 (96)	251/255 (98)	497/513 (97)	506/511 (>99)
Proportion of Subjects Without Protocol-Defined CVW or not discontinued due to treatment-related reasons by the end of Early Switch Phase						
Estimate (%)	97.6	99.6	96.1	98.4	96.8	99.0
95% CI (%)	94.7, 98.9	97.0, 99.9	92.9, 97.9	95.8, 99.4	94.9, 98.0	97.6, 99.6
Difference in Proportions[b]						
Estimated Difference (%)	-2.0		-2.3		-2.2	
95% CI[c] (%)	-4.1, 0.1		-5.1, 0.5		-3.9, -0.4	

Data Source: 201636/201637 Table 2.081, Table 2.082, and Table 2.083.

a. Subjects who have not met the protocol defined CVW criteria and are ongoing in the study, or who have discontinued for non-treatment related reasons up to the end of the Early Switch Phase are censored.
b. Difference: Proportion on DTG + RPV – Proportion on CAR.
c. Based on Greenwood's formula.

Table 14 Summary of Kaplan-Meier Estimates of Proportion of Subjects Not Meeting CVW Criteria or Discontinuing for Reasons Related to Efficacy by End of Early Switch Phase - *Efficacy Related Discontinuation = Failure* – in Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Number of Subjects, n/N (%)						
Protocol-Defined CVW or discontinuation due to efficacy-related reasons by the end of Early Switch Phase	2/252 (<1)	1/256 (<1)	1/261 (<1)	2/255 (<1)	3/513 (<1)	3/511 (<1)
Censored[a]	250/252 (>99)	255/256 (>99)	260/261 (>99)	253/255 (>99)	510/513 (>99)	508/511 (>99)
Proportion of Subjects Without Protocol-Defined CVW or not discontinued due to efficacy-related reasons by the end of Early Switch Phase						
Estimate (%)	99.2	99.6	99.6	99.2	99.4	99.4
95% CI (%)	96.8, 99.8	97.0, 99.9	97.1, 99.9	96.9, 99.8	98.1, 99.8	98.1, 99.8
Difference in Proportions[b]						
Estimated Difference (%)	-0.4		0.4		0.0	
95% CI[c] (%)	-1.8, 1.0		-1.0, 1.7		-1.0, 1.0	

Data Source: 201636/201637 Table 2.091, Table 2.092, and Table 2.093.

a. Subjects who have not met the CVW criteria and are ongoing in the study, or who have discontinued for reasons other than lack of efficacy up to the end of the Early Switch Phase are censored.
b. Difference: Proportion on DTG + RPV – Proportion on CAR.
c. Based on Greenwood's formula.

3.2.2.5. Subjects Who Met CVW Criteria Through Week 48

The numbers of subjects who met the confirmed virologic withdrawal criteria were very low in each treatment group, with 2 subjects in each treatment group meeting these criteria at any time during the Early Switch Phase for the pooled data (Table 15).

Table 15 Proportion of Subjects Meeting Confirmed Virologic Withdrawal Criteria by Visit, Studies 201636, 201637, and Pooled Data (ITT-E Population)

Time Point n (%)	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Any time	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
Week 24	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Week 36	0	0	1 (<1)	0	1 (<1)	0
Week 48	0	1 (<1)	0	0	0	1 (<1)

Data Source: 201636/201637 Table 2.120

Observed Drug Class Mutations for Subjects Meeting CVW through Week 48

Of the 4 subjects who met CVW criteria, only 1 subject in the DTG + RPV arm who was noted as non-adherent had genotypic substitution K101K/E mixture in RT, no decrease in RPV susceptibility, and a greater than 3-log decrease in HIV-1 viral load on resumption of their DTG + RPV regimen (from 1,059,771 c/mL at suspected virologic withdrawal visit to 1,018 c/mL at the confirmatory visit, and decreased further to <50 c/mL at the withdrawal visit).

3.2.2.6. Change from Baseline in CD4+ Lymphocyte Count

CD4+ cell counts were maintained overall in both treatment groups (Table 16). The median change from Baseline in CD4+ cell counts was 28.0 cells/mm^3 in the DTG + RPV group and 22.0 cells/mm^3 in the CAR group.

Table 16 Summary of Change from Baseline in CD4+ Lymphocyte Count (cells/mm^3) by Visit in Studies 201636, 201637, and Pooled Data (ITT-E Population)

Median (IQR)	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252)	(N=256)	(N=261)	(N=255)	(N=513)	(N=511)
Baseline	611.5 (442, 800)	638.0 (459.5,846.0)	609.0 (467.0, 814.0)	628.0 (481.0, 824.0)	611.0 (459, 809)	638.0 (470.0, 829.0)
Week 12	24.5 (-48.5, 129.5)	49.0 (-40.0, 136.0)	34.0 (-39.0, 112)	31.0 (-62.0, 109.0)	32.0 (-42.0, 117.0)	38.0 (-49.0, 124.0)
Week 24	22.0 (-67.0, 103.0)	33.0 (-45.0, 129.0)	30.0 (-44.0, 140)	29.5 (-48.0, 123.0)	26.5 (-58.0, 126.0)	31.0 (-48.0, 126.0)
Week 48	25.0 (-68, 119)	35.0 (-37.0, 104.0)	29.0 (-47.0, 108.0)	13.0 (-59.0, 108.0)	28.0 (-55.0, 112.5)	22.0 (-46.0, 108.0)

Data Source: 201636/201637 Table 2.141, Table 2.142, and Table 2.143
Note: Baseline values are actual CD4+ lymphocyte count (cells/mm^3) values.

3.2.2.7. Incidence of HIV-1 Disease Progression (HIV-associated Conditions, AIDS, and Death)

For the pooled data, a total of 3 subjects in the RPV + DTG group and 1 subject in the CAR group experienced HIV-1 disease progression to CDC Class C clinical conditions or death during the Early Switch Phase (Table 17). Of these, 2 subjects in the DTG + RPV group progressed to Class C, and the other 2 subjects died (1 DTG + RPV; 1 CAR).

Overall, few subjects had HIV-1 associated conditions during the Early Switch Phase (Table 18). A total of 11 subjects in the DTG + RPV group and 0 subjects in the CAR group were reported to have experienced HIV-1 associated conditions including recurrences. Eight subjects in the DTG + RPV group experienced HIV-1 associated conditions when recurrences were not included.

Of the 11 subjects in the DTG + RPV group who were reported to have experienced HIV-1 associated conditions including recurrences (Table 18), these conditions were reported by the investigator for the following 5 subjects in error.

- Subject [redacted] had peripheral neuropathy reported as a Post-Baseline event and progression from Class A to Class B but the neuropathy was pre-existing and related to prior treatment with stavudine and did not progress.
- Subjects [redacted], [redacted], and [redacted] had diarrhea reported as a constitutional symptom lasting for >1 month and progression from Class A to Class B, but the diarrhea was due to a change in diet, an adverse reaction to study drug, and use of a protein supplement, respectively.
- Subject [redacted] had oropharyngeal candidiasis reported with no progression but this condition pre-dated enrolment.

Table 17 Summary of Post-Baseline HIV-1 Disease Progressions in the Early Switch Phase for Studies 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
	(N=252) n (%)	(N=256) n (%)	(N=261) n (%)	(N=255) n (%)	(N=513) n (%)	(N=511) n (%)
Did subject experience disease progression to CDC Class C or death?						
N	252	256	261	255	513	511
Yes	2 (<1)	1 (<1)	1 (<1)	0	3 (<1)	1 (<1)
No	250 (>99)	255 (>99)	260 (>99)	255 (100)	510 (>99)	510 (>99)
Progression						
N	3	1	5	0	8	1
from CDC Class A to CDC Class B	1 (<1)	0	4 (2)	0	5 (<1)	0
from CDC Class A to CDC Class C	1 (<1)	0	0	0	1 (<1)	0
from CDC Class B to CDC Class C	1 (<1)	0	0	0	1 (<1)	0
from CDC Class C to new CDC Class C	0	0	0	0	0	0
from CDC Class A, B or C to Death	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)

Data Source: 201636/201637 Table 2.171, Table 2.172, and Table 2.173.
Note: Subject [redacted] (CAR) stopped treatment a* and died b* .
Note: Subject [redacted] (DTG + RPV) stopped treatment c* and died d* .

a*: the Day 198
b*: after 41 days
c*: the Day 214
d*: the next day

* 新薬承認情報提供時に置き換え

Table 18 Summary of Post-Baseline HIV-1 Associated Conditions in the Early Switch Phase for 201636, 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV (N=252) n (%)	CAR (N=256) n (%)	DTG + RPV (N=261) n (%)	CAR (N=255) n (%)	DTG + RPV (N=513) n (%)	CAR (N=511) n (%)
Including Recurrences[a]						
Any Category	4 (2)	0	7 (3)	0	11 (2)	0
Category B						
Any Condition	2 (<1)	0	6 (2)	0	8 (2)	0
Peripheral neuropathy	2 (<1)	0	0	0	2 (<1)	0
Candidiasis, oropharyngeal	0	0	2 (<1)	0	2 (<1)	0
Constitutional symptoms last >1 month	0	0	4 (2)	0	4 (<1)	0
Category C						
Any Condition	2 (<1)	0	1 (<1)	0	3 (<1)	0
Herpes simplex	1 (<1)	0	0	0	1 (<1)	0
Lymphoma, immunoblastic	1 (<1)	0	0	0	1 (<1)	0
Kaposi's sarcoma	0	0	1 (<1)	0	1 (<1)	0
Excluding Recurrences						
Any Category	2 (<1)	0	6 (2)	0	8 (2)	0
Category B						
Any Condition	1 (<1)	0	5 (2)	0	6 (1)	0
Peripheral neuropathy	1 (<1)	0	0	0	1 (<1)	0
Candidiasis, oropharyngeal	0	0	2 (<1)	0	2 (<1)	0
Constitutional symptoms last >1 month	0	0	3 (1)	0	3 (<1)	0
Category C						
Any Condition	1 (<1)	0	1 (<1)	0	2 (<1)	0
Lymphoma, immunoblastic	1 (<1)	0	0	0	1 (<1)	0
Kaposi's sarcoma	0	0	1 (<1)	0	1 (<1)	0

Data Source: 201636/201637 Table 2.151, Table 2.152, Table 2.153, Table 2.161, Table 2.162, and Table 2.163.
Subjects may have more than one HIV-associated condition and recurrences are included.

3.3. Comparison of Results in Sub-Populations in Pivotal Efficacy Studies

To assess the generalizability of the primary analysis results, consistency of the treatment difference was explored within subgroups. One-way homogeneity across the levels of each variable used to stratify randomization (age group [< or ≥ 50 years old] and Baseline third agent class) was tested. One-way homogeneity across the levels of gender and two categorizations of Race (White vs. non-White, African American/African Heritage vs.

non-African American/African Heritage) was also tested. In addition, potential treatment-by-subgroup interactions were considered via the assessment of summaries of the treatment differences across subgroups.

Evidence of heterogeneity was observed for age group in the pooled analysis and by race group (White vs. non-White only) both in Study 201637 and in the pooled analysis. However, further exploration of the reasons for this finding did not reveal any pattern and was limited by the small number of snapshot non-responders. Regardless, treatment differences across age, Baseline third agent, race, and gender are consistent with primary endpoint conclusion of non-inferiority.

3.3.1. Baseline Third Agent Treatment Subgroup Analyses

3.3.1.1. Plasma HIV-1 RNA <50 c/mL at Week 48 by Baseline Third Agent Treatment Class (Snapshot Analysis)

Treatment differences across Baseline third agent treatment class support the primary endpoint. In both treatment groups the response rate was similar in each of the Baseline third agent class groups (Table 19, Data Source: 201636/201637 Table 2.053 and Figure 2). The test for evidence against homogeneity of the treatment difference across baseline third agent class was not statistically significant (p=0.930). The clinical pharmacology data addressing the NNRTI sub-set supports the efficacy data observed for subjects switching to DTG + RPV from NNRTI-based regimens (m2.7.2 Section 2.2.2).

Table 19 Treatment by Strata Tests of Homogeneity for the Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 in the Pooled Data - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion (95% CI)[a]
Baseline Third Agent	PI	CAR	136	128/136 (94)	-0.9 (-6.7, 4.9)
		DTG + RPV	133	124/133 (93)	
	NNRTI	CAR	278	265/278 (95)	0.3 (-3.1, 3.8)
		DTG + RPV	275	263/275 (96)	
	INSTI	CAR	97	92/ 97 (95)	-0.6 (-6.8, 5.7)
		DTG + RPV	105	99/105 (94)	
	p-value for Test of Homogeneity[b]				0.930

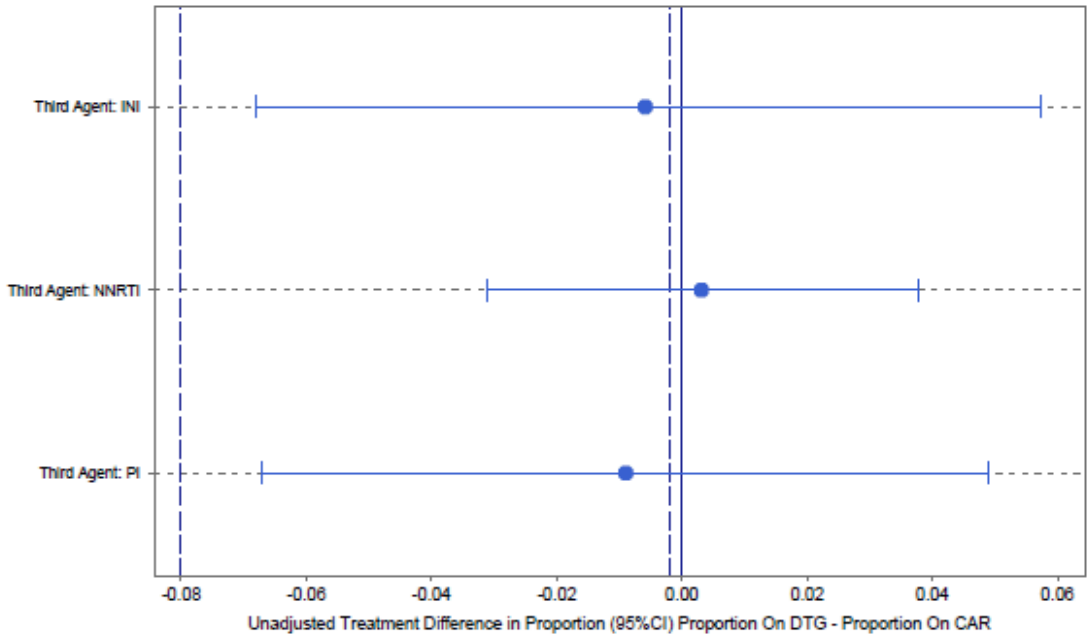
Data Source: 201636/201637 Table 2.053.

Note: Week 48 window is up to the end of on-treatment Early Switch Phase.

a. Difference = Proportion on DTG – Proportion on CAR (unadjusted).

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

Figure 2 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week 48 by Baseline Third Agent in the Pooled Data – Snapshot Analysis (ITT-E Population)



Data Source: 201636/201637 Figure 2.023
Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV – CAR).

3.3.1.2. Change from Baseline CD4+ Lymphocyte Counts by Baseline Third Agent

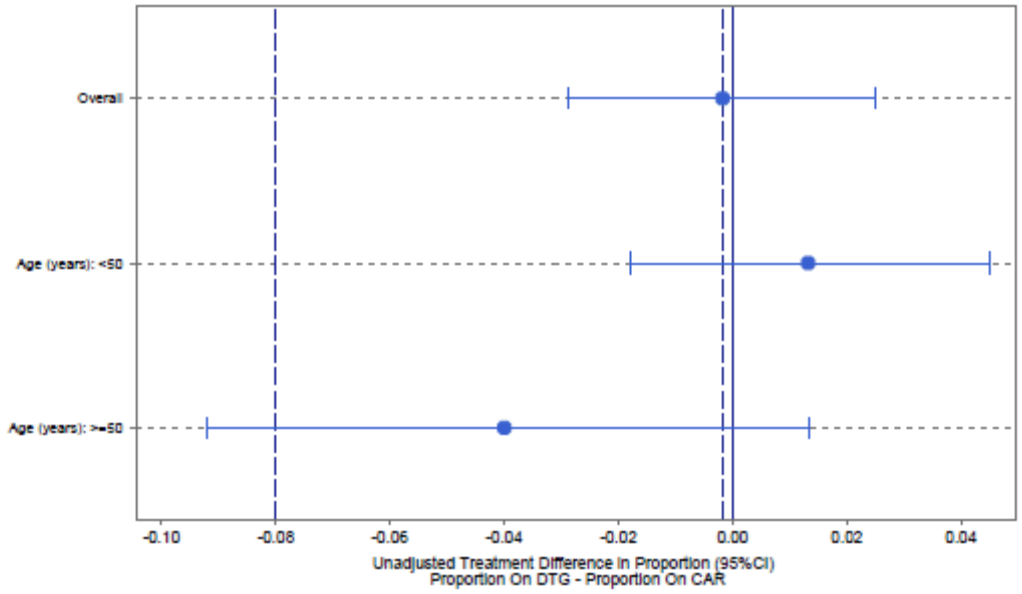
For the pooled data, CD4+ cell counts were maintained overall in both treatment groups with similar increases across the Baseline third agent class (Data Source: 201636/201637 Table 2.721, Table 2.722, and Table 2.723).

3.3.2. Age Subgroup Analyses

3.3.2.1. Plasma HIV-1 RNA <50 c/mL at Week 48 by Age Subgroups (Snapshot Analysis)

Treatment differences across age subgroups support the primary endpoint (Figure 3 and Table 20). The test for heterogeneity for an effect of age on the proportion of subjects with HIV-1 RNA <50 c/mL was statistically significant (p=0.091).

Figure 3 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week 48 by Age Subgroups for the Pooled Data – Snapshot Analysis



Data Source: 201636/201637 Figure 2.023
Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV – CAR).

Table 20 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Age Subgroups in the Pooled Data - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion % (95% CI)[a]
Age (years)	<50	CAR	369	348/369 (94)	1.3 (-1.8, 4.5)
		DTG + RPV	366	350/366 (96)	
	≥50	CAR	142	137/142 (96)	-4.0 (-9.2, 1.3)
		DTG + RPV	147	136/147 (93)	
				p-value for Test of Homogeneity[b]	0.091

Data Source: 201636/201637 Table 2.063.
a. Proportion on DTG – Proportion on CAR (unadjusted).
b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

3.3.2.2. Study Outcomes Subgroup Analyses by Age

The test for heterogeneity for an effect of age on the proportion of subjects with HIV-1 RNA <50 c/mL was statistically significant in the pooled data (p=0.091; Table 20).

This difference was driven by higher numbers of subjects in the "No Virologic Data at Week 48" category, which includes subjects who were withdrawn due to both the subgroupings of "other reasons" and "AEs leading to discontinuation" in the <50 years of age subgroup compared to the ≥50 years of age subgroup. This was not driven by a difference in virologic failure between the age groups (Table 21). The proportion of subjects who were Snapshot virological failures remains constant at ≤1% across treatment groups and within each age group and differences of only 2% were observed between the age groups within each treatment arm for subjects with no virologic data. Of note, the test for heterogeneity of age group was not significant within either of the individual studies.

The result within each age category remains consistent with an overall conclusion of the non-inferiority of DTG + RPV compared to CAR at Week 48.

Table 21 Summary of Study Outcomes (<50 c/mL) at Week 48 Snapshot Analysis by Age Subgroup in the Pooled Data - Snapshot Analysis (ITT-E Population)

n (%)	<50 years		≥50 years		All Pooled Data	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
n	**366**	**369**	**147**	**142**	**513**	**511**
Virologic Success	350 (96)	348 (94)	136 (93)	137 (96)	486 (95)	485 (95)
Virologic Failure	1 (<1)	5 (1.4)	2 (1)	1 (<1)	3 (<1)	6 (1)
Data in window not below threshold	0	1 (<1)	0	1 (<1)	0	2 (<1)
Discontinued for lack of efficacy	0	2 (<1)	2 (1)	0	2 (<1)	2 (<1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Change in ART	0	1 (<1)	0	0	0	1 (<1)
No Virologic Data	15 (4)	16 (5)	9 (6)	4 (3)	24 (5)	20 (4)
Discontinued study due to AE or Death	11 (3)	2 (<1)	6 (4)	1 (<1)	17 (3)	3 (<1)
Discontinued study for Other Reasons	4 (1)	13 (4)	3 (2)	3 (2)	7 (1)	16 (3)
Missing data during window but on study	0	1 (<1)	0	0	0	1 (<1)

Data Source: 201636/201637 Table 2.040 and Table 2.073

3.3.2.3. Change from Baseline in CD4+ Lymphocyte Counts at Week 48 by Age Subgroups

CD4+ cell counts were maintained overall in both treatment groups for subjects in all 3 age subgroups (Data Source: 201636/201637 Table 2.721, Table 2.722, and Table 2.723).

3.3.3. Race Subgroup Analyses

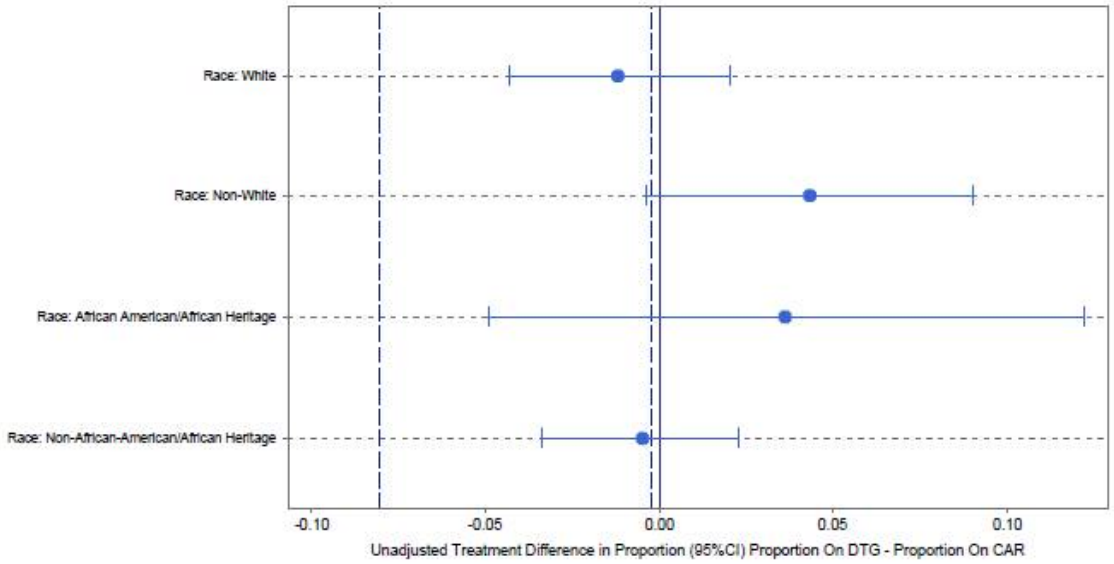
3.3.3.1. Plasma HIV-1 RNA <50 c/mL at Week 48 by Race (Snapshot Analysis)

Treatment differences across race subgroup categories support the primary endpoint (Figure 4 and Table 22).

The test for heterogeneity for an effect of race for White versus Non-White subjects for the proportion of subjects with HIV-1 RNA <50 c/mL was statistically significant for the pooled analysis (p=0.058). This difference was also statistically significant for the 201637 study (p=0.06), but not for the 201636 study (p=0.592).

The test for heterogeneity for an effect of race for African American/African versus Non-African American/African subjects for the proportion of subjects with HIV-1 RNA <50 c/mL was not statistically significant for the pooled analysis (p=0.374). This difference was also not statistically significant for the individual studies.

Figure 4 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week 48 by Race Subgroups for the Pooled Data – Snapshot Analysis



Data Source: 201636/201637 Figure 2.023
Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV – CAR).

Table 22 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Race Subgroups in the Pooled Data - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion % (95% CI)[a]
Race	White	CAR	400	380 / 400 (95)	-1.2 (-4.3, 2.0)
		DTG + RPV	421	395 / 421 (94)	
	Non-White	CAR	111	105 / 111 (95)	4.3 (-0.4, 9.0)
		DTG + RPV	92	91 / 92 (99)	
	p-value for Test of Homogeneity[b]				0.058
Race	African American/ African Heritage	CAR	48	45 / 48 (94)	3.6 (-4.9, 12.2)
		DTG + RPV	38	37 / 38 (97)	
	Non-African-American/African Heritage	CAR	463	440 / 463 (95)	-0.5 (-3.4, 2.3)
		DTG + RPV	475	449 / 475 (95)	
	p-value for Test of Homogeneity[b]				0.374

Data Source: 201636/201637 Table 2.063.

a. Proportion on DTG – Proportion on CAR (unadjusted).

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

3.3.3.2. Study Outcomes Subgroup Analyses by Race

The test for heterogeneity for an effect of race for White versus Non-White subjects for the proportion of subjects with HIV-1 RNA <50 c/mL was statistically significant for the pooled analysis (p=0.058; Table 22).

This difference is driven by the 99% response rate in the Non-White race subgroup within the DTG + RPV treatment group (Table 23). It is difficult to make a meaningful interpretation of this result due to the small sample size in this subgroup; if just 3 additional subjects had been snapshot non-responders then the overall response rate would have been 96%. Of note, the test for heterogeneity for this race group was only significant in study 201637 and the tests for heterogeneity for the other race categorization (African American/African Heritage vs. Non-African American/African Heritage) were not significant in either study or in the pooled analysis.

In addition, the result within each race category remains consistent with an overall conclusion of the non-inferiority of DTG+RPV compared to CAR at Week 48.

Table 23 Summary of Study Outcomes (<50 c/mL) at Week 48 Snapshot Analysis by Race Subgroup in the Pooled Data - Snapshot Analysis (ITT-E Population)

n (%)	White		Non-White		All Pooled Data	
	DTG + RPV	CAR	DTG + RPV	CAR	DTG + RPV	CAR
n	**421**	**400**	**92**	**111**	**513**	**511**
Virologic Success	**395 (94)**	**380 (95)**	**91 (99)**	**105 (95)**	**486 (95)**	**485 (95)**
Virologic Failure	**3 (<1)**	**3 (<1)**	**0**	**3 (3)**	**3 (<1)**	**6 (1)**
Data in window not below threshold	0	1 (<1)	0	1 (<1)	0	2 (<1)
Discontinued for lack of efficacy	2 (<1)	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)
Discontinued for other reason while not below threshold	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Change in ART	0	0	0	1 (<1)	0	1 (<1)
No Virologic Data	**23 (5)**	**17 (4)**	**1 (1)**	**3 (3)**	**24 (5)**	**20 (4)**
Discontinued study due to AE or Death	17 (4)	2 (<1)	0	1 (<1)	17 (3)	3 (<1)
Discontinued study for Other Reasons	6 (1)	14 (4)	1 (1%)	2 (2)	7 (1)	16 (3)
Missing data during window but on study	0	1 (<1)	0	0	0	1 (<1)

Data Source: 201636/201637 Table 2.040 and Table 2.073

3.3.3.3. Change from Baseline in CD4+ Lymphocyte Counts at Week 48 by Race

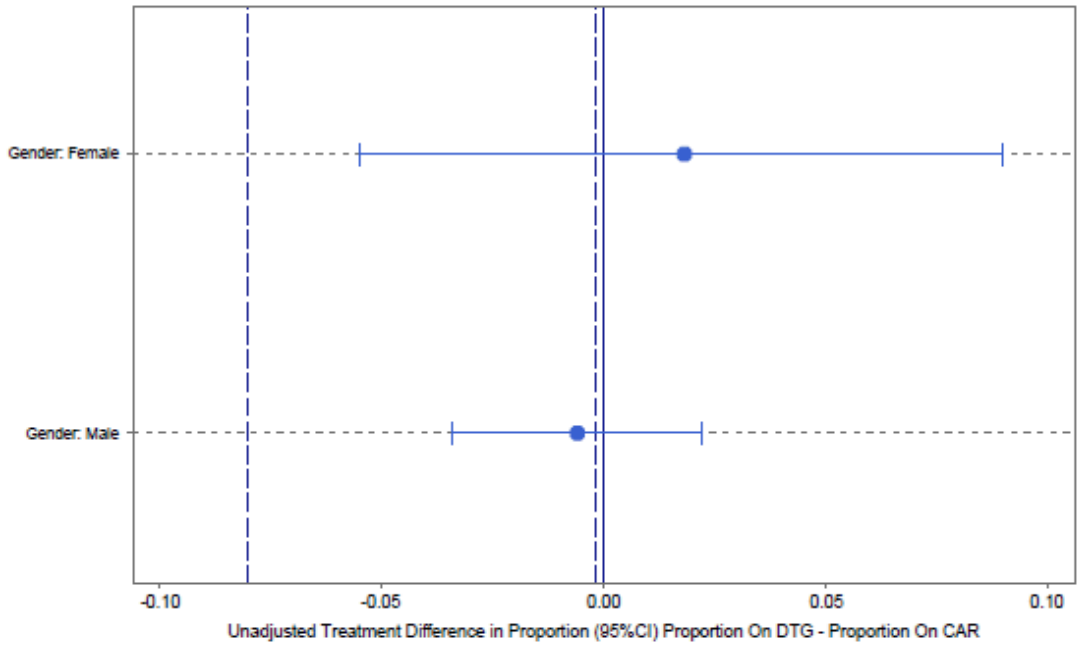
CD4+ cell counts were maintained overall in both treatment groups for all race subgroups (Data Source: 201636/201637 Table 2.721, Table 2.722, and Table 2.723).

3.3.4. Gender Subgroup Analyses

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

Treatment differences across gender subgroup categories support the primary endpoint (Figure 5 and Table 24). The participants were over 20% female, which was an intended goal of the studies in order to provide substantial comparative data in this demographic. The test for heterogeneity for an effect of gender on the proportion of subjects with HIV-1 RNA <50 c/mL was not statistically significant (p=0.550).

Figure 5 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week 48 by Gender Subgroups for the Pooled Data – Snapshot Analysis



Data Source: 201636/201637 Figure 2.023
Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV – CAR).

Table 24 Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by Gender Subgroups in the Pooled Data - Snapshot Analysis (ITT-E Population)

Analysis Strata		Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion % (95% CI)[a]
Gender	Female	CAR	108	98 / 108 (91)	1.8 (-5.5, 9.0)
		DTG + RPV	120	111 / 120 (93)	
	Male	CAR	403	387 / 403 (96)	-0.6 (-3.4, 2.2)
		DTG + RPV	393	375 / 393 (95)	
	p-value for Test of Homogeneity[b]				0.550

Data Source: 201636/201637 Table 2.063.

a. Proportion on DTG – Proportion on CAR (unadjusted).

b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

3.3.4.2. Change from Baseline in CD4+ Lymphocyte Counts at Week 48 by Gender

CD4+ cell counts were maintained overall in both treatment groups for male and female subgroups (Data Source: 201636/201637 Table 2.721, Table 2.722, and Table 2.723).

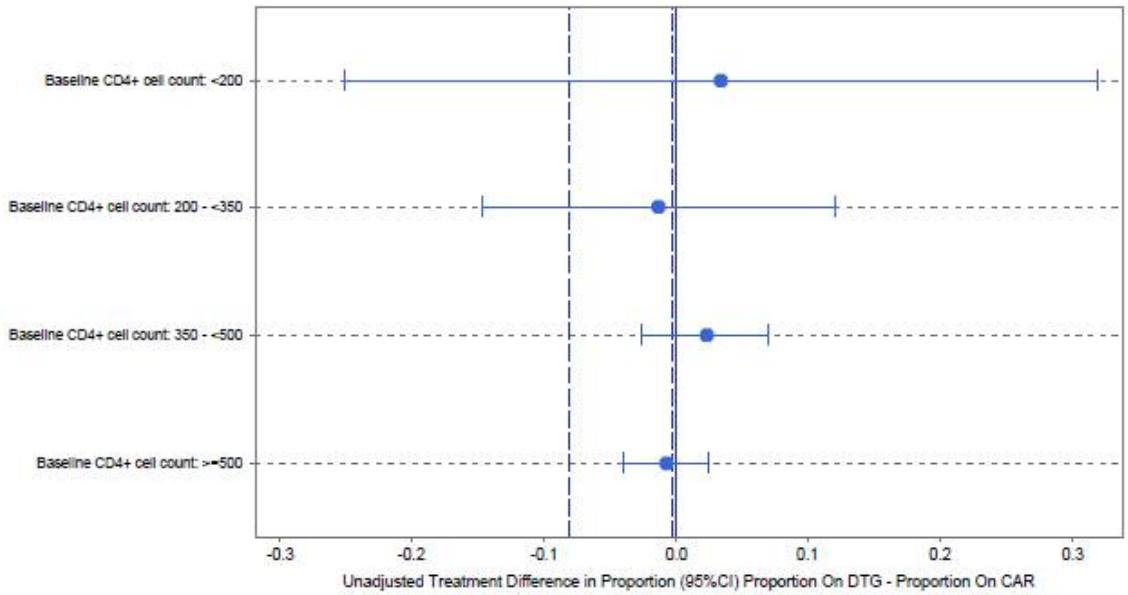
3.3.5. Other Demographic Subgroup Analyses

Additional subgroup analyses of the primary endpoint and study outcomes were performed by country and Baseline CDC category and are presented in Data Source: 201636/201637 Table 2.063 and Table 2.073. No statistically significant differences were observed for plasma HIV-1 RNA <50 c/mL at 48 weeks between treatment groups by country or Baseline CDC category. However, numbers of subjects per country were small.

3.3.6. Plasma HIV-1 RNA <50 c/mL at Week 48 by CD4+ Lymphocyte Count Subgroup

The proportions of subjects with plasma HIV-1 RNA <50 c/mL were assessed by Baseline CD4+ lymphocyte count group (Figure 6 and Table 25) and support the primary endpoint. The majority of the subjects, being on at least 6 months of effective ART, had Baseline CD4+ lymphocyte counts above 350 cells/mm^3.

Figure 6 Unadjusted Treatment Difference in Proportion (95% CI) of Subjects with HIV-1 RNA <50 c/mL at Week 48 by CD4+ Lymphocyte Count Subgroups in the Pooled Data – Snapshot Analysis (ITT-E Population)



Data Source: 201636/201637 Figure 2.023
Note: The dashed reference line on the left at -0.08 represents the non-inferiority margin.
The dashed reference line on the right represents the overall difference in proportion (DTG + RPV – CAR).

Table 25 Summary of Proportion of Subjects with Plasma HIV-1 RNA <50 c/mL at Week 48 by CD4+ Lymphocyte Count Subgroup in the Pooled Data - Snapshot Analysis (ITT-E Population)

Treatment	N	Number Responded/ Total Assessed (%)	Difference in Proportion, % (95% CI)[a]
<200			
DTG + RPV	11	10/ 11 (91)	3.4 (-25.1, 31.9)
CAR	8	7/ 8 (88)	
200 - <350			
DTG + RPV	47	41/ 47 (87)	-1.4 (-14.8, 12.0)
CAR	44	39/ 44 (89)	
350 - <500			
DTG + RPV	107	105/107 (98)	2.3 (-2.5, 7.0)
CAR	97	93/ 97 (96)	
≥500			
DTG + RPV	348	330/348 (95)	-0.8 (-3.9, 2.4)
CAR	362	346/362 (96)	

Data Source: 201636/201637 Table 2.061, Table 2.062, and Table 2.063
Note: Week 48 window is up to the end of on-treatment Early Switch.
a. Difference: Proportion on (DTG + RPV) – Proportion on CAR.
b. One-sided p-value from weighted least squares chi-squared statistic. A p-value ≤0.10 was used to indicate statistically significant evidence of heterogeneity in the difference in proportions across levels of each analysis strata.

3.4. Comparison of Patient Reported Outcomes Results in Pivotal Efficacy Studies

Change in patient reported symptoms were assessed using the HIV SDM which measures the presence and level of symptom bother for 20 pre-defined symptoms. Total symptom bother scores range from 0 if no symptoms are present to a maximum bother score of 80.

Change in overall patient reported treatment satisfaction was assessed using the 10-item HIV TSQ - status version. Scores can range from 0 – 60 with higher scores indicating greater level of satisfaction with current therapy.

3.4.1. Symptom Bother Score

In the pooled analysis, the mean (SD) baseline symptom bother scores were 9.6 (10.0) and 11.0 (11.2) in the DTG + RPV and CAR respectively (Data Source: 201636/201637 Table 6.093). Despite numerically lower baseline scores, the DTG + RPV arm had a small but statistically significant reduction in Symptom Bother score from baseline compared to the CAR group at Week 4 and Week 48 (Table 26). Neither symptom count nor symptom bother scores worsened from baseline at any time point suggesting that stable subjects receiving CAR were able to switch to DTG + RPV with no associated introduction or exacerbation of bothersome symptoms reported by subjects.

Table 26 Statistical Analysis of Symptom Bother Score Change from Baseline in SDM (LOCF Dataset) for Studies 201363, 201637, and Pooled Data (ITT-E Population)

Visit	Treatment	N	n[a]	Adjusted Mean (SE)	Difference vs CAR	95% CI for Treatment Difference	P-Value
201636							
Week 4	**DTG + RPV**	252	212	-3.320 (0.4691)	-2.924	-4.260, -1.588	<0.001
	CAR	256	197	-0.396 (0.4868)			
Week 24	**DTG + RPV**	252	214	-2.079 (0.5154)	-1.192	-2.656, 0.271	0.110
	CAR	256	201	-0.886 (0.5320)			
Week 48	**DTG + RPV**	252	214	-1.806 (0.5208)	-1.569	-3.048, -0.090	0.038
	CAR	256	201	-0.237 (0.5376)			
201637							
Week 4	**DTG + RPV**	261	224	-2.893 (0.4238)	-1.239	-2.414, -0.064	0.039
	CAR	255	229	-1.655 (0. 4191)			
Week 24	**DTG + RPV**	261	228	-2.053 (0.4931)	-0.528	-1.896, 0.840	0.448
	CAR	255	232	-1.525 (0.4888)			
Week 48	**DTG + RPV**	261	228	-1.594 (0.5269)	-1.037	-2.501, 0.426	0.164
	CAR	255	231	-0.557 (0.5234)			
Pooled							
Week 4	**DTG + RPV**	513	436	-3.103 (0.3157)	-2.032	-2.915, -1.148	<0.001
	CAR	511	426	-1.071 (0.3194)			
Week 24	**DTG + RPV**	513	442	-2.081 (0.3564)	-0.868	-1.865, 0.129	0.088
	CAR	511	433	-1.213 (0.3601)			
Week 48	**DTG + RPV**	513	442	-1.701 (0.3707)	-1.298	-2.336, -0.261	0.014
	CAR	511	432	-0.403 (0.3750)			

Data Source: 201636/201637 Table 6.121; Table 6.122; Table 6.123.
Note: The symptom bother score is based on the score for each symptom present ranging from 1 (it doesn't bother me) to 4 (it bothers me a lot). The symptom bother score ranges from 0 to 80.
a. Number of subjects with a value at baseline and time point (after LOCF). Changes from baseline are analysed using an ANCOVA model adjusting for age, baseline third agent, gender, race and baseline Symptom Bother score.

3.4.2. HIV Treatment Satisfaction

In the pooled analysis, subjects reported a high degree of satisfaction at baseline with their current regimen. The DTG + RPV arm had a small but statistically significant improvement from baseline in the TSQs total score at each assessed time point (Table 27). Overall patient reported treatment satisfaction did not worsen at any time point in these studies for patients in the DTG + RPV arm compared to the CAR arm.

Table 27 Statistical Analysis of HIVTSQs Total Score Change from Baseline (LOCF Dataset) for Studies 201363, 201637, and Pooled Data (ITT-E Population)

Treatment	N	Visit	N	Mean (SD)	Median	IQR	Range	P-Value[a]
201636								
DTG+RPV	**252**	**Baseline**	252	53.9 (6.64)	56.0	50.0, 60.0	27, 60	0.839
		Week 4	250	2.0 (6.01)	0.0	0.0, 4.0	-16, 33	0.002
		Week 24	252	2.3 (6.18)	1.0	0.0, 5.0	-18, 33	<0.001
		Week 48	252	1.8 (7.30)	0.5	0.0, 5.0	-24, 33	0.024
CAR	**256**	**Baseline**	255	54.0 (6.48)	56.0	50.0, 60.0	29, 60	NA
		Week 4	249	0.4 (5.02)	0.0	-1.0, 2.0	-25, 21	NA
		Week 24	254	0.3 (5.68)	0.0	-2.0, 2.0	-28, 28	NA
		Week 48	254	0.8 (5.55)	0.0	-2.0, 3.0	-28, 20	NA
201637								
DTG+RPV	**261**	**Baseline**	261	54.8 (6.18)	57.0	52.0, 60.0	23, 60	0.089
		Week 4	253	0.7 (6.09)	0.0	-1.0, 3.0	-21, 23	0.037
		Week 24	257	1.2 (6.62)	0.0	-1.0, 4.0	-27, 23	0.101
		Week 48	257	1.2 (6.64)	0.0	-1.0, 4.0	-27, 25	0.042
CAR	**255**	**Baseline**	252	53.8 (6.67)	56.0	50.5, 59.0	27, 60	NA
		Week 4	250	-0.2 (5.22)	0.0	-2.0, 2.0	-22, 22	NA
		Week 24	252	0.1 (6.24)	0.0	-2.0, 2.0	-24, 24	NA
		Week 48	251	0.0 (6.49)	0.0	-2.0, 3.0	-50, 23	NA
Pooled								
DTG+RPV	**513**	**Baseline**	513	54.4 (6.42)	57.0	51.0, 60.0	23, 60	0.177
		Week 4	503	1.3 (6.08)	0.0	-1.0, 4.0	-21, 33	<0.001
		Week 24	509	1.8 (6.42)	0.0	0.0, 5.0	-27, 33	<0.001
		Week 48	509	1.5 (6.97)	0.0	-1.0, 5.0	-27, 33	0.002
CAR	**511**	**Baseline**	507	53.9 (6.57)	56.0	50.0, 59.0	27, 60	NA
		Week 4	499	0.1 (5.12)	0.0	-2.0, 2.0	-25, 22	NA
		Week 24	506	0.2 (5.96)	0.0	-2.0, 2.0	-28, 28	NA
		Week 48	505	0.4 (6.04)	0.0	-2.0, 3.0	-50, 23	NA

Data Source: 201636/201637 Table 6.231; Table 6.232; Table 2.233
Note: Actual values shown at Baseline visit.
a. DTG+RPV vs. CAR *p*-value at each time point is based on a Wilcoxon rank sum test.

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The dosing for the DTG/RPV FDC tablet of DTG 50 mg and RPV 25 mg given once daily with a meal is based on the approved doses of the individual components DTG (TIVICAY) and RPV (EDURANT) and the absence of a drug-drug interaction between these components. The efficacy of the currently approved DTG 50 mg and RPV 25 mg once daily dosing was demonstrated in the studies included in this submission, and this dosing is indicated in current product labeling [TIVICAY Prescribing Information, 2016,

EDURANT Prescribing Information, 2015]. Thus, a reanalysis of data supporting the approved DTG 50 mg or RPV 25 mg components is not provided here.

Study LAI116181 was a Phase I, open-label, crossover study to evaluate the pharmacokinetics and safety of cabotegravir and RPV and DTG and RPV in healthy adult subjects. The study showed that co-administration of RPV with DTG had no clinically meaningful effect on DTG or RPV pharmacokinetics [Ford, 2013]. Co-administration of RPV with DTG had no effect on DTG AUC(0-τ) or Cmax, and a non-clinically significant increase in DTG Cτ by 22%, while co-administration of DTG with RPV had no effect on RPV AUC(0-τ) or Cmax and a non-clinically significant increase in RPV Cτ by 21%. Hence, based on this data there is no need for a dose adjustment from approved doses when both products are used in combination.

A potential for a lingering enzyme induction effect on DTG and RPV exposure due to long half life of other NNRTI class drugs was evaluated in the 201636 and 201637 studies. Pre-dose plasma concentrations were analyzed for all early switch subjects at Week 4, 24 and 48, and also and also for a smaller NNRTI subset with extra sampling Weeks 2 and 8. The results from the NNRTI subset with extra sampling show that the DTG and RPV C0 increased from Week 2 through Week 4 post-switch and remained relatively constant from Week 4 to Week 48 following treatment with DTG + RPV. Residual concentrations of EFV and NVP decreased over the 4-week post-switch period. The DTG and RPV C0 from Week 4 to Week 48 in the NNRTI Subset with extra sampling were comparable to the DTG and RPV C0 at Week 4, 24, and 48 in the larger NNRTI subset of all patients who switched from CAR (201636 CSR, 201637 CSR). These exposure data, combined the clinical efficacy in the NNRTI subset, further support the DTG 50 mg and RPV 25 mg dose regimen for switching in subjects who are stably suppressed on a 3 drug ART regimen.

Overall, the PK, PD, and drug interaction profile support the dose recommendation for a FDC of DTG/RPV 50 mg/25 mg (GSK3365791) with a proposed indication for the treatment of HIV-1 infection in virologically-suppressed (HIV-1 RNA <50 c/mL) adults without known or suspected resistance to either ARV component (m2.7.2 Section 3.6).

5. PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

The current submission includes 48-week efficacy data for subjects receiving DTG + RPV in 2 ongoing Phase III clinical studies. These studies will continue for 148 weeks and thus longer-term data on this combination will become available. At this time, longer term data are only available for each of the components from single entity studies.

HIV antiretroviral drugs are not associated with pharmacological tolerance; however, as HIV-1 is highly mutable, it can develop mutations that confer decreased susceptibility of the virus to one or more ARTs. A detailed summary of virologic resistance to DTG and RPV is presented in m2.7.2.4 (Special Studies, Virology), and thus is not repeated here.

Study LAI116482 (LATTE) is an ongoing Phase IIb study evaluating the utility of a 2-drug, 2-class combination of cabotegravir + RPV once daily. Data from this study

provided proof of principle for RPV combined with an INSTI as an effective 2-drug regimen for the maintenance of virologic suppression [Margolis, 2015]. A rapid and sustained response was observed across all CAB treatment arms, with ≥80% of subjects achieving the primary endpoint of plasma HIV-1 RNA <50 c/mL by Week 48 [GSK Document Number RH2009/00003/06]. In addition, data at Week 96 (72 weeks on 2-drug therapy) showed that more subjects on CAB + RPV remained suppressed (HIV-1 RNA <50 c/mL) compared to EFV +2 NRTI drugs (CAB Subtotal: 76%; EFV: 63%). While the virologic response in the CAB 60 mg arm was numerically higher than the 10 mg and 30 mg arms, the difference was driven primarily by low level viremia (data in window not below threshold) and non-virologic discontinuations (discontinuations for other reasons). Furthermore, there were fewer virologic non-responders using the Snapshot algorithm through Week 96 in the CAB arm compared to the EFV arm. These data indicate that a 2-drug regimen of RPV, in combination with an INSTI, can provide long-term efficacy.

6. EFFICACY CONCLUSIONS

The primary efficacy endpoint for the 2 pivotal studies was the proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 using the Snapshot algorithm. In individual and pooled analyses, a switch to a novel, once daily 2-drug regimen of DTG + RPV demonstrated high efficacy and was non-inferior to the continuation of CAR in virologically suppressed HIV-1-infected adults. This 2-drug regimen was able to maintain HIV-1 suppression through the 48 Week primary endpoint as well as the 3-drug ART regimens.

DTG + RPV offers the option to switch subjects to a well-tolerated 2-drug ART regimen, without an increased risk of virologic failure. The following conclusions can be made with regard to the pooled data:

- The pooled primary analysis demonstrated that DTG + RPV and CAR provided good clinical efficacy, with 95% of subjects in both treatment groups achieving the primary endpoint of plasma HIV-1 RNA <50 c/mL at Week 48 based on the Snapshot algorithm for the ITT E Population. The pooled analysis demonstrated that DTG + RPV met the predefined statistical conclusion of non-inferiority to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.0%) was greater than -8%. The predefined non-inferiority margins of -10% were also reached for each individual study (Studies 201636 and 201637).
- Evidence of heterogeneity was observed for age subgroup in the pooled analysis and by race subgroup (White vs. non-White only) both in Study 201637 and in the pooled analysis. However, further exploration of the reasons for this finding did not reveal any pattern and was limited by the small number of snapshot non-responders within subgroups. Regardless, treatment differences across age, Baseline third agent, race, and gender are consistent with primary endpoint conclusion of non-inferiority
- The efficacy and virology results were consistent across the baseline third agent classes (PI, INI, and NNRTI). -In the NNRTI subgroup, PK and clinical data demonstrate that the plasma concentrations of DTG and RPV during the immediate post-NNRTI switch period were sufficient to maintain virologic response.

- A dedicated analysis was performed on the rates of Snapshot virologic failure. The proportion of subjects who were classified as Snapshot virological failures at Week 48 demonstrates that the combined use of DTG + RPV is non-inferior to CAR for this endpoint with a non-inferiority margin of 4%. The 2-drug regimen effectively maintained virologic suppression, with few Snapshot virologic failures and no increased risk of resistance identified through 48 Weeks.
- Of the 4 subjects who met CVW criteria, 1 subject in the DTG+ RPV arm of Study 201637 was noted as non-adherent and had genotypic substitution K101K/E mixture in RT, with no decrease in RPV susceptibility, and a greater than 3-log decrease in HIV-1 viral load on resumption of their DTG + RPV regimen. The other 3 subjects had no observed resistance on study.
- Results were similar across the 2 studies (201636 and 201637) indicating reproducibility of the data.

Taken together, these 48-week results indicate that the DTG + RPV 2-drug regimen is effective in the maintenance of plasma HIV-1 RNA <50 c/mL across a diverse spectrum of subjects and regardless of current third agent class. This simplified regimen is non-inferior to CAR without an increased risk of virologic failure.

7. APPENDIX

Appendix Table 1 Description of Pivotal Efficacy and Safety Studies

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)
201636 (SWORD-1)	69 centers: Spain: 16, US: 14, Canada: 6, France: 5, Germany: 5, Russia: 5, Belgium: 4, Italy: 4, Taiwan: 3, Australia: 2, Netherlands: 2, UK: 2, Argentina: 1	14 April 2015 Ongoing LSLV for Week 48: 16 September 2016. Data cut-off for Week 48: [redacted]	Non-inferior antiviral activity of switching to DTG + RPV once daily compared to continuation of CAR over 48 weeks in HIV-1 infected ART-experienced subjects	148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1 infected adults with plasma HIV-1 RNA <50 c/mL. CAR for at least 6 months prior to Screening with 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	DTG 50 mg + RPV 25 mg oral tablets once daily with a meal or CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	ITT-E Population: DTG + RPV: 252 CAR: 256	DTG + RPV: 58F; 194M; 43.6 (2[redacted]-7[redacted]) years CAR: 51F; 205M; 43.6 (2[redacted]-7[redacted]) years	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E Population
201637 (SWORD-2)	60 centers: Spain: 15, US: 13, Canada: 7, Germany: 5, France: 6, Russia: 4, Taiwan: 4, Australia: 3,	21 April 2015 Ongoing LSLV for Week 48: 16 September 2016. Data cut-off for Week 48: [redacted]	Non-inferior antiviral activity of switching to DTG + RPV once daily compared to continuation of CAR over	148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-	HIV-1 infected adults with plasma HIV-1 RNA <50 c/mL. CAR for at least 6 months prior	DTG 50 mg + RPV 25 mg oral tablets once daily with a meal or CAR	ITT-E Population: DTG + RPV: 261 CAR: 255	DTG + RPV: 62F; 199M; 43.3 (2[redacted]-7[redacted]) years CAR: 57F; 198M; 43.2 (2[redacted]-6[redacted]) years	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)
	Argentina: 3, Italy: 2, UK: 1	[redacted]	48 weeks in HIV-1 infected ART-experienced subjects	inferiority study	to Screening with 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	(2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))			Population
202094 (DEXA)	32 centers: Argentina, Belgium, Canada, Spain, UK, US	11 June 2015 Ongoing LSLV for Week 48: 16 September 2016. Data cut-off for Week 48: [redacted]	Change in from Baseline in total hip BMD at 48 weeks following switch from ART regimen containing TDF to DTG + RPV compared to continued therapy with the TDF-containing regimen	Open-label, parallel group sub-study of the 2 identical pivotal, Phase III, randomized, multicentre, parallel-group, non-inferiority studies, 201636 and 201637	HIV-1 infected adults screened and eligible for either 201636 or 201637 and received a TDF-containing regimen	Same treatment 201636 or 201637: DTG 50 mg + RPV 25 mg oral tablets once daily with a meal or CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	DTG + RPV: 53 CAR: 49	DTG + RPV: 27F; 26M 42.6 (2[redacted], 6[redacted]) years CAR: 26F; 23M 44.8 (2[redacted], 7[redacted]) years	Percentage change from baseline at Week 48 in total hip BMD as assessed by areal density in g/cm^2

Appendix Table 2 Efficacy Results of Pivotal Efficacy Studies

Study	Treatment Arm	No. Enrolled/ Completed	Primary Efficacy Variable			Secondary Efficacy Endpoints	Other Comments
			Plasma HIV-1 RNA <50 c/mL at Week 48	Difference in Proportion[a]	Adjusted Difference in Proportion[b]		
			n/N (%)	% (95% CI)	% (95% CI)		
201636 (SWORD-1)							
	DTG 50 mg + RPV 25 mg once daily with a meal	252 Rand. 239 Ongoing	240 / 252 (95%)	−0.5% (−4.1%, 3.2%)	−0.6% (−4.3%, 3.0%)	At Week 48, virologic response rates were similar between the DTG + RPV and CAR treatment groups (95% and 96%, respectively). The rate of virologic failure was the same in the DTG + RPV and CAR groups (2 subjects each).	DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-4.3%) is greater than -8%.
	CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	256 Rand. 238 Ongoing	245 / 256 (96%)				
201637 (SWORD-2)							
	DTG 50 mg + RPV 25 mg once daily with a meal	261 Rand. 245 Ongoing	217 / 226 (96%)	0.1 (-3.9, 4.2)	0.2 (-3.9, 4.2)	At Week 48, virologic response rates were similar between the DTG + RPV and CAR treatment groups (94% and 95%, respectively). There was a lower rate of virologic failure in the DTG + RPV group (1 subject) compared to the CAR group (4 subjects).	DTG + RPV is non-inferior to CAR at Week 48 because the lower bound of the 95% CI for the adjusted treatment difference (-3.9%) is greater than -8%.
	CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	255 Rand. 239 Ongoing	218 / 226 (96%)				

a. Difference: Proportion on (DTG + RPV) – Proportion on CAR.

b. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: age (< vs. ≥ 50 years old) and Baseline third agent (PI, NNRTI, INSTI).

Appendix Table 3 Summary of Supportive SE Studies for Efficacy

Study	Study Title	SE Study Efficacy Conclusions
ING114467 (SINGLE) (DTG) GSK Document Number: 2014N198290_01 Status: Week 144 and End-of-Study CSRs Complete	A Phase 3, randomized, double-blind study of the safety and efficacy of GSK1349572 plus abacavir/lamivudine fixed-dose combination therapy administered once daily compared to Atripla over 96 weeks in HIV-1 infected antiretroviral therapy naive adult subjects	**At Week 48**, 88% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 81% of participants on the single tablet regimen Atripla [difference and 95% CI; 7.4% (+2.5% to +12.3%); difference in the primary endpoint was statistically significant, p=0.003]. **At Week 96**, 80% of study participants on the DTG + ABC/3TC regimen were virologically suppressed (<50 c/mL) vs. 72% of participants on the single tablet regimen Atripla [difference and 95% CI; 8.0% (+2.3% to +13.8%); difference in the primary endpoint was statistically significant, [p=0.006]. Response rates on DTG+ ABC/3TC and Atripla were generally consistent across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. **At Week 144**, 71% of study participants in the DTG + ABC/3TC treatment group were virologically suppressed (<50 c/mL) versus 63% of participants on the single tablet regimen of Atripla [adjusted difference and 95% CI; 8.3% (+2.0% to +14.6%); difference in the primary endpoint was statistically significant, [p=0.010]; therefore, statistical superiority at Week 144 was maintained. Differences in the Snapshot analysis were primarily driven by a lower rate of discontinuation due to AEs in the DTG + ABC/3TC treatment group. Response rates were similar between the DTG + ABC/3TC and the Atripla treatment groups across demographic subgroups, including race, gender, age, HIV risk factors, and Baseline CDC category. The longer term end-of-study data support the safety of DTG in combination with ABC/3TC once daily in an HIV-infected treatment-naive patient population. The majority of subjects receiving DTG + ABC/3TC FDC who entered the continuation phase past Week 144 maintained viral suppression, based on an observed analysis. In the DTG + ABC/3TC FDC arm, antiviral response was sustained with 93% (193/207) of subjects with HIV-1 RNA <50 c/mL at Week 156 based on the observed data. The data from this completed study continue to support the use of DTG 50 mg + ABC/3TC once daily for the management of HIV infection in INSTI-naive subjects.
ING113086 (SPRING-2) (DTG) GSK Document Number: 2013N158737_01 Status: Week 96 CSR	A Phase III, randomized, double blind study of the safety and efficacy of GSK1349572 50 mg once daily compared to raltegravir 400 mg twice daily both administered with fixed-dose dual nucleoside reverse transcriptase	**At Week 48**, Data through 96 weeks support DTG 50 mg once daily for INSTI-naive subjects, and provide evidence for durable efficacy and tolerability for DTG in combination therapy. In this study, DTG has shown non-inferior efficacy and a safety profile similar to RAL with no evidence of treatment emergent resistance in virologic failure. DTG administered once daily with 2 NRTIs demonstrated non-inferiority to RAL at Week 96 and was associated with good treatment response. DTG performed as well as RAL regardless of baseline viral load or background dual NRTI. DTG performed as well as RAL across demographic subgroups, including race, gender,

Study	Study Title	SE Study Efficacy Conclusions
Complete	inhibitor therapy over 96 weeks in HIV-1 infected antiretroviral naive adult subjects	age, HIV risk factors, Baseline CD4+ cell count and Baseline CDC category. **At Week 96**, DTG administered once daily with 2 NRTIs demonstrated non-inferiority to RAL at Week 96 and was associated with good treatment response. The proportion of subjects with HIV RNA <50 c/mL (81%) compared favorably with RAL (76%) through 96 weeks. DTG performed as well as RAL regardless of baseline viral load or background dual NRTI. DTG performed as well as RAL across demographic subgroups, including race, gender, age, HIV risk factors, Baseline CD4+ cell count and Baseline CDC category

Note: Supportive studies are briefly tabulated in this efficacy summary, but reports will be made available upon request for the convenience of the reviewer

Module 2.7.4

Summary of Clinical Safety

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8. APPENDIX 124

ABBREVIATIONS

3TC	Lamivudine
5-HT	5-hydroxytryptamine (serotonin)
ABC	Abacavir sulfate
AE	Adverse Event
AESI	Adverse event of special interest
AIDS	Acquired Immunodeficiency Syndrome
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
APR	Antiretroviral Pregnancy Registry
ART	Antiretroviral therapy
ARV	Antiretroviral
AST	Aspartate aminotransferase
AUC	Area under concentration-time curve
AUC(0-τ)	AUC from time zero (pre-dose) to last time of quantifiable concentration
AUC(0-∞)	AUC from time zero (pre-dose) extrapolated to infinite time
AUC24h	Area under the plasma concentration-time curve from time of administration up to 24 hours post dosing
BCRP	Breast cancer resistance protein
BCV	Boceprevir
BDI	Beck-Depressions-Inventar
BE	Bioequivalence
BMD	Bone Mineral Density
BMI	Body mass index
Cτ	Pre-dose (trough) concentration at the end of the dosing interval
c/mL	Copies per milliliter
C0	Pre-dose (trough) concentration
C24 or C24h	Plasma concentration after 24 hours
CAR	Current Antiretroviral Regimen
cART	Combination Antiretroviral Therapy
CCDS	Company Core DataSheet
CCR5	C-C chemokine receptor 5
CDC	Centers for Disease Control and Prevention
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
Cmax	Maximum observed concentration
Cmin	Minimum observed concentration
CPK	Creatine phosphokinase
CSF	Cerebrospinal fluid
CSR	Clinical Study Report
CT	Computed tomography
Ctrough	Trough concentration
CYP	Cytochrome P450
DAIDS	Division of Acquire Immunodeficiency Syndrome

DDI	Drug:drug interaction
DEXA	Dual-energy x-ray absorptiometry
DRV	Darunavir
DTG	Dolutegravir
DTG + RPV	Dolutegravir 50 mg single-entity tablet and rilpivirine 25 mg single-entity tablet
DTG/RPV FDC	Dolutegravir 50 mg and rilpivirine 25 mg fixed-dose combination tablet
EC50	Effective concentration at which virus replication is inhibited by 50%
EC90	Effective concentration at which virus replication is inhibited by 90%
ECG	Electrocardiogram
eC-SSRS	Electronic Columbia Suicidality Severity Rating Scale
EFV	Efavirenz
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDC	Fixed-dose combination
FSFV	First subject first visit
FTC	Emtricitabine
GABA	Gamma-aminobutyric acid
GDS	Global Data Sheet
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
GSK	GlaxoSmithKline
GSK1349572	Dolutegravir
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HIV	Human immunodeficiency virus
HIV-1	Human immunodeficiency virus type 1
HOMA-IR	Homeostatic model assessment-insulin resistance
HSR	Hypersensitivity reaction
IB	Investigator's Brochure
IC50	50% inhibitory concentration
IC90	90% inhibitory concentration
IDMC	Independent Data Monitoring Committee
IL-6	Interleukin-6
IMP	Investigational medicinal product
IMS	Intercontinental Medical Statistics
INSTI	Integrase strand transfer inhibitor
IQR	Interquartile range
IRIS	Immune reconstitution inflammatory syndrome
ISO	Integrated safety output
ITT-E	Intent-To-Treat Exposed
LDL	Low-density lipoprotein
MACDP	Metropolitan Atlanta Congenital Defects Program

MADRS	Montgomery-Asperg Depression Rating Scale
MAH	Marketing authorization holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
N(t)RTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NCEP	National Cholesterol Education Program
NMDA	N-methyl-D-aspartate
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NOAEL	No-observed-adverse-effect level
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
OCT	Organic cation transporter
P-gp	P-glycoprotein
PI	Protease inhibitor
PK	Pharmacokinetic
PSRAE	Possible Suicide Related Adverse Events (form)
q12h	Every 12 hours
q24h	Every 24 hours
QD	Once daily
QTc	Correct QT
QTcF	Fridericia's formula corrected QT
RAL	Raltegravir
RAP	Reporting and Analysis Plan
RBA	Relative bioavailability
RNA	Ribonucleic acid
RPV	Rilpivirine
RSI	Reference Safety Information
RTV	Ritonavir
SAE	Serious adverse event
SD	Standard deviation
SD	Standard deviation
SDAP	Summary Document Analysis Plan
SOC	System organ class
TAF	Tenofovir alafenamide
TBDR	Texas Birth Defects Registry
TDF	Tenofovir disoproxil fumarate
TMC278	Rilpivirine
TVR	Telaprevir
UGT	Uridine glucuronyl transferase
ULN	Upper Limit of Normal
US	United States of America
y	year

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1. EXPOSURE TO THE DRUG

ViiV Healthcare Company in partnership with Janssen Research and Development LLC are developing a FDC tablet containing dolutegravir and rilpivirine. ViiV is the Sponsor of the development program; various aspects of the program are also being conducted by GlaxoSmithKline on behalf of the Sponsor.

DTG (previously known as GSK1349572) is a 2-metal-binding INSTI. To date, the efficacy, PK, safety, and drug interaction potential of DTG has been evaluated in an extensive program of Phase I to III clinical trials as summarized in the DTG Investigator's Brochure [DTG IB, version 10, GlaxoSmithKline Document Number RM2007/00683/10]. On the basis of this development program, DTG was approved for the treatment of HIV-1 infection by the US FDA in August 2013, by the EMA in January 2014, and in over 85 other countries as of the writing of this document. DTG is marketed as TIVICAY™ [TIVICAY Product Information] and is also a component of an FDC product containing DTG/ABC/3TC, marketed as TRIUMEQ™ [TRIUMEQ Product Information].

DTG has been developed as an antiretroviral product for the treatment of HIV-1-infected adults and children over 12 years of age, as part of combination antiretroviral therapy. The recommended dosing for DTG is 50 mg once daily for ART-naïve and ART-experienced (INSTI-naïve) adult patients, and 50 mg twice daily for INSTI-experienced adults with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance. In the US, the indication for DTG has recently been extended to treatment of HIV infection in INSTI-naïve children less than 12 years of age and weighing at least 30 kg, as part of combination antiretroviral therapy; the US recommended dose in pediatric patients weighing 30 kg to less than 40 kg is 35 mg once daily. In the EU, the DTG indication has been extended to pediatric patients 6 to less than 12 years of age without resistance to the INSTI class, with weight band-based once daily dosing for patients weighing 15 kg up to 40 kg.

RPV (previously known as TMC278) is an NNRTI. To date, the efficacy, PK, safety, and drug interaction potential of RPV has been evaluated in an extensive program of Phase I to III clinical trials as summarized in the Investigator Brochure [RPV IB, 2017]. On the basis of this development program, RPV was approved for the treatment of HIV-1 infection by the US FDA in May 2011, by the EMA in November 2011, and in over 85 countries as of the writing of this document. RPV is marketed as EDURANT [EDURANT Product Information]. RPV is also a component of the FDC products containing FTC/RPV/TDF, marketed as Eviplera/Complera [Eviplera Product Information] or FTC/RPV/TAF, marketed as Odefsey [Odefsey Product Information].

RPV, as single-entity or as part of the FDC products Eviplera/Complera and Odefsey, has been developed as an antiretroviral product for the treatment of HIV−1−infected patients 12 years of age and older. The approved indications and registered formulations containing RPV vary per country. In most countries, including the US and Europe, approved indications are further restricted to patients with a viral load ≤100,000 c/mL.

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

1.1.1. Strategy for Establishing the Safety Profile for DTG/RPV FDC

The DTG/RPV FDC contains the active substances DTG and RPV at the same once daily doses as marketed for the individual components (i.e., 50 mg and 25 mg, respectively).

Establishing the risk/benefit profile of a FDC tablet includes an assessment of the safety of each individual component taken alone as well as the safety of the components when used in combination. The Applicant's strategy for providing a robust safety package to support the DTG and RPV single-entity components, as well as the DTG/RPV FDC, is outlined below.

To support the safety profile of the DTG/RPV FDC, the applicant has undertaken the following studies (further described in Section 1.1.1.1):

- **201636** (SWORD-1) and **201637** (SWORD-2) – two identical, ongoing, pivotal Phase III studies in HIV-1-infected adult subjects given DTG + RPV as 2 single tablets together; the data package includes individual study data and pooled data from the two studies;

- **201674** (RBA study) – a relative oral bioavailability study of different fixed-dose combinations of DTG and RPV in fasted and fed healthy subjects;

- **201676** (BE study) – a single-dose, crossover bioequivalence study in adults to confirm that the DTG/RPV FDC tablet is equivalent to the co-administration of DTG + RPV given together as two single tablets;

- **LAI116181** (DDI study) – a drug interaction study to evaluate the PK and safety of DTG and RPV in healthy adult subjects; and

- **202094** (DEXA substudy) – a safety study to assess bone mineral density in a subset of subjects from the 201636 and 201637 studies.

Furthermore, to support the safety information in the proposed company Reference Safety Information and Country Prescribing Information for the DTG/RPV FDC, relevant safety data from non-clinical studies and Phase I to III clinical trials conducted separately for the individual DTG and RPV single-entity components will be provided where data is not available for the DTG/RPV FDC. These studies are categorized as "key" studies or "supportive" studies, defined for the purposes of this submission as follows:

- Key single-entity studies: these studies provide data that may be included in labeling, and were conducted during the individual agent development programs. These studies are further described in Section 1.1.1.2.
- Supportive single-entity studies: these studies are not essential for the FDC benefit:risk assessment, but are considered helpful to the reviewer and supportive on the proposed indication. Supportive studies are briefly tabulated

in Appendix Table 1, and reports from these studies will be made available upon request for the convenience of the reviewer.

Single-entity data that are considered not to be relevant to this DTG/RPV FDC application, e.g. efficacy data not related to the indication, will not be provided in this FDC submission.

Finally, as both DTG and RPV are marketed products, safety data collected from post-marketing experience will also contribute to the FDC benefit:risk assessment (see Section 1.1.1.3).

1.1.1.1. Data from the DTG + RPV Development Program

Data from the Phase III clinical trials (201636 and 201637, including an integrated analysis of safety data) and the Phasse I RBA study (201674), Phase I BE study (201676), and Phase I DDI study (LAI116181) are considered pivotal to this application. Data from the DEXA substudy (202094) of the Phase III trials is also described herein to provide supportive safety information.

- Studies **201636** and **201637** are 2 identical pivotal Phase III studies, which provide data to demonstrate the safety of DTG + RPV. These studies are ongoing, randomized, parallel group, open-label, 148-week studies, designed to demonstrate non-inferior antiviral activity of switching to DTG 50 mg plus RPV 25 mg once daily compared to continuation of current INSTI-, NNRTI-, or PI-based ARV regimen in HIV-1-infected adults who are virologically suppressed (HIV-1 RNA <50 c/mL). The study is divided into an Early Switch Phase in which subjects are on their randomized study treatment (i.e., have switched at Baseline to DTG + RPV or have continued their Baseline antiretroviral regimen [CAR]) and a Late Switch Phase starting at Week 52 (i.e., the visit at which the CAR group has switched to DTG + RPV). Unless otherwise stated, the data analyses discussed herein represent treatment-emergent analyses of data collected up to the cut-off date ([redacted]) and during the Early Switch Phase. For the DTG + RPV group, this includes all available data up to 52 weeks after Day 1 and for the CAR group includes all available data up to the point of switch at the Week 52 visit. Additional key safety data (e.g., Grade 2-4 AEs, SAEs, withdrawals) for subjects who continued the study into the Late Switch Phase are also summarized. Additional details of study design for these 2 studies are provided in Section 1.1.5. A brief summary of these studies is also provided in Appendix Table 2.

- An **Integrated Safety Output (ISO)** comprising data on 513 total subjects receiving DTG + RPV as part of 201636 and 201637 (and compared with 511 subjects in the CAR group) will be included as a pooled analysis of safety data. The ISO, described in the SDAP, supplements the pooled data analyses described in the 201636/201637 RAP.
- Study **201674** is a Phase I, 2-part, single-dose, relative oral bioavailability study of different FDCs of DTG and RPV in fasted and fed healthy subjects to evaluate the relative bioavailability of several different FDC tablet formulation of DTG

50 mg and RPV 25 mg versus co-administration of the separate tablet formulations of DTG 50 mg plus RPV 25 mg, in the fed state. Data from this study are included in Section 5.2.1.1.

- Study **201676** is a Phase I, single-center, randomized, open-label, 2-period, single-dose, crossover study, which was designed to evaluate the bioequivalence between the DTG/RPV 50 mg/25 mg FDC tablet versus co-administration of the separate tablet formulations of DTG 50 mg and RPV 25 mg, in the fed state. Data from this study are included in Section 5.5.

- **LAI116181** is a Phase I, open-label, crossover study evaluating the pharmacokinetics and safety of DTG and RPV in healthy adult subjects. This study was previously submitted to support the DTG single-entity submissions as a DDI study between DTG and RPV. Data from this study are included in Section 5.3.1.

- Study **202094** (DEXA sub-study of 201636 and 201637) is an open-label, parallel-group study designed to evaluate BMD in HIV-1-infected adult subjects switching from a TDF-containing antiretroviral therapy regimen to a DTG + RPV regimen. Key inclusion criteria for this sub-study included HIV-1-infected subjects who were screened and eligible but not yet randomized to their treatment group in either parent study (201636 or 201637) and currently receiving a TDF-containing antiretroviral regimen. The primary endpoint was the percent change from Baseline at Week 48 in total hip BMD as assessed by areal density in g/cm^2. As this is a substudy of the Phase III studies, no additional subjects were exposed to DTG + RPV through their participation in this study, and adverse event and clinical data from this subset of subjects is a part of the 201636 and 201637 analyses presented in this safety summary. Bone mineral density data from this study is presented in Section 4.4.1. A brief summary of this study is also provided in Appendix Table 2.

1.1.1.2. Data from the Individual DTG and RPV Single-Entity Development Programs

Where data from the DTG + RPV combination are not available, e.g., to support safety information in the proposed company RSI and Country Prescribing Information for the DTG/RPV FDC, the Applicant will instead provide information on the DTG and RPV single-entity components, including information from non-clinical and pharmacology/drug-interaction studies performed with the individual components. Particular examples where this approach will be used include:

- Use in hepatic and renal impairment (Section 5.1.3 and Section 5.1.4);
- Drug Interactions (Section 5.3);
- Non-Clinical Reprotoxicity (Section 5.4.1);
- Human pregnancy data (Section 5.4.2);
- Experience in overdose (Section 5.7).

Detailed descriptions of non-clinical and clinical pharmacology data supporting the safety profile for DTG/RPV FDC are included in m2.7.1 and m2.7.2.

Table 1 below provides a listing of key single-entity studies (as defined in Section 1.1.1) for the DTG/RPV FDC.

Table 1 Summary of Completed Studies that were Previously Submitted as Part of the TIVICAY or EDURANT Registration and are Considered "Key" Single-Entity Studies for the Safety Assessment of the DTG/RPV FDC Submission

Study No. (Single Entity Component) Status	Study Design	Population	Treatment Details	Main Conclusion(s)
200901 (DTG) Status: Complete	Phase I, open-label, randomized, three period, fixed sequence crossover study to evaluate the effect of carbamazepine on DTG PK	Healthy adult subjects	Period 1: DTG 50 mg, tablet, oral, once daily (Days 1-5) Period 2: carbamazepine 100 mg, tablet, oral, BID (Days 1-3); carbamazepine 200 mg, tablet, oral, BID (Days 4-6); carbamazepine 300 mg, tablet, oral, BID (Days 7-16) Period 3: DTG 50 mg, tablet, oral, once daily + carbamazepine 300 mg, tablet, oral, BID (Days 1-5)	Co-administration of DTG with carbamazepine resulted in decreases in DTG Cmax, AUC and $C\tau$ by approximately 33%, 49%, and 73%, respectively, compared with DTG administered alone. DTG dose adjustment from 50 mg once daily to 50 mg twice daily is recommended when DTG is co-administered with carbamazepine.
201167 (DTG) Status: Complete	Phase I, open label, parallel group, three period, fixed sequence crossover study to evaluate the effect of DTG on metformin PK	Healthy adult subjects	Cohort 1: Period 1: Metformin IR 500 mg, tablet, oral, q12h (Days 1-5) Period 2: Metformin IR 500 mg, tablet, oral, q12h + DTG 50 mg, tablet, oral, q24h (Days 1-7) Period 3: Metformin IR 500 mg, tablet, oral, q12h (Days 1-10) Cohort 2: Period 1: Metformin IR 500 mg, tablet, oral, q12h (Days 1-5) Period 2: Metformin IR 500 mg, tablet, oral, q12h + DTG 50 mg, tablet, oral, q12h (Days 1-7) Period 3: Metformin IR 500 mg, tablet, oral, q12h (Days 1-10)	Co-administration of DTG 50 mg q24h with metformin 500 mg q12h resulted in increases in metformin AUC(0-τ) and Cmax by 79% and 66%, respectively, compared with metformin administered alone. Co-administration of DTG 50 mg q12h with metformin 500 mg q12h resulted in increases in metformin AUC(0-τ) and Cmax by 145% and 111%, respectively, compared with metformin administered alone. Effects were DTG dose dependent. Subjects should be monitored when starting and stopping co-administration of DTG with metformin and a dose adjustment of metformin should be considered to maintain glycemic control
ING111856 (TQT) (DTG) Status: Complete	Phase I, randomized, partial-blind, single-dose, three-period, crossover thorough QT study	Healthy adult subjects	DTG 250 mg; oral suspension; single dose Placebo; oral suspension; single dose Moxifloxacin 400 mg; tablet; oral; single dose	DTG had no effect on cardiac repolarization at a supratherapeutic dose of 250 mg suspension. The study was sensitive enough to detect the effect of moxifloxacin, the positive control, on QTcF, which confirmed that this study was valid for assessing the effects of DTG on cardiac repolarization.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
ING112941 (DTG) Status: Complete	Phase I, randomized, open-label, two-sequence, three-treatment crossover study to assess DTG-proton pump inhibitor drug interaction	Healthy adult subjects	Part 1: DTG 50 mg; tablet; oral; single dose; fasted DTG 50 mg; tablet; oral; single dose; within 30 minutes after the start of a high-fat meal DTG 50 mg; tablet; oral; single dose + omeprazole 40 mg; capsule; oral; once daily; fasted; 5 days	Co-administration with omeprazole had no significant effect on plasma DTG AUC(0-τ), AUC(0-∞), Cmax, and C24. DTG can be co-administered with OMP without dose adjustment.
ING113097 (DTG) Status: Complete	Phase I, single-dose, open-label, parallel-group, two-part, adaptive study to evaluate PK and safety of DTG	Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function	DTG 50 mg; tablet; oral; single dose	Total DTG exposure on plasma was similar between subjects with moderate hepatic impairment and matched healthy subjects. DTG can be taken without dose adjustment in subjects with mild to moderate hepatic impairment. DTG was generally well tolerated in both hepatic impaired and healthy subjects in this study.
ING113125 (DTG) Status: Complete	Phase I, single-dose, open-label, parallel-group, two-part study to evaluate PK and safety of DTG	Subjects with severe renal impairment and matched, healthy control subjects with normal renal function	DTG 50 mg; tablet; oral; single dose	DTG exposure was lower in subjects with severe renal impairment (creatinine clearance <30 mL/min) than in healthy, matched subjects: AUC(0-∞) and Cmax were 40% and 23% lower, respectively. The moderate reduction in DTG exposure in subjects with severe renal impairment was not considered clinically significant. No dose adjustment of DTG is needed in subjects with mild to severe renal impairment (not on renal replacement therapy). DTG was well tolerated in healthy and renally-impaired subjects in this study.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
ING116898 (DTG) Status: Complete	Phase I, open-label, randomized, two-cohort, four-period, crossover study to evaluate the effects of calcium carbonate and ferrous fumarate on PK of DTG	Healthy adult subjects	Cohort 1: DTG, 50 mg, tablet, oral, single dose, fasted DTG, 50 mg, tablet, oral single dose, + calcium carbonate, 1200 mg, tablet, oral, fasted DTG, 50 mg, tablet, oral, single dose, + calcium carbonate, 1200 mg, tablet, oral, fed DTG, 50 mg, tablet, oral, single dose, fasted, 2 hours prior to calcium carbonate, 1200 mg, tablet, oral Cohort 2: DTG, 50 mg, tablet, oral, single dose, fasted DTG, 50 mg, tablet, oral single dose, +324 mg ferrous fumarate, oral, fasted DTG, 50 mg, tablet, oral, single dose, + 324 mg ferrous fumarate, oral, fed DTG, 50 mg, tablet, oral, single dose, fasted, 2 hours prior to 324 mg ferrous fumarate, oral	Under fasted conditions, co-administration of calcium carbonate reduced DTG exposure by 37 to 39% and ferrous fumarate reduced DTG exposure by 54 to 57%. Co-administration of DTG with calcium carbonate or ferrous fumarate under fed conditions or dosing DTG 2 hours prior to these supplements showed DTG exposure similar to those when DTG was given alone under fasted conditions. DTG can be given concurrently with calcium or iron supplements with food; without food, DTG should be given 2 hours prior to or 6 hours after calcium or iron supplements.

Study No. (Single Entity Component) Status	Study Design	Population	Treatment Details	Main Conclusion(s)
TMC278-TiDP6-C130 (RPV) Status: Complete	Phase I, open-label, parallel, controlled, sequential study to evaluate PK and safety of RPV	Subjects with mild or moderate hepatic impairment and matched, healthy control subjects with normal hepatic function	RPV 25 mg once daily; oral; 11 days	After a single dose, RPV Cmax and AUC24h were 6% and 18% higher, respectively, in subjects with mild hepatic impairment, compared with healthy subjects. At steady-state (Day 11) Cmax, AUC24h, Cmin and C24h were 27%, 47%, 31% and 76% higher, respectively. After a single dose in subjects with moderate hepatic impairment, Cmax and AUC24h were 29% and 24% lower, respectively, compared with healthy subjects. At steady-state, Cmax was 5% lower and AUC24h was 5% higher. Mean Cmin and C24h were increased by 11% and 28%, respectively, in subjects with moderate hepatic impairment as compared with healthy subjects. The results of the trial also demonstrate that administration of RPV 25 mg once daily was generally safe and well tolerated and that no dose adjustment of RPV is needed in subjects with mild or moderate hepatic impairment.
TMC278-TiDP6-C131 (RPV) Status: Complete	Phase I, double-blind, double-dummy, randomized, 3-way crossover, placebo-controlled and positive-controlled thorough QT study	Healthy adult subjects	Treatment A: RPV 75 mg; Days 1-11 + RPV placebo; Days 1-11 + moxifloxacin placebo; Day 12; oral Treatment B: RPV 300 mg; Days 1-11 + moxifloxacin placebo; Day 12; oral Treatment C: RPV placebo; Days 1-11 + 400 mg moxifloxacin; Day 12; oral	A positive relationship between plasma concentrations of RPV (administered at doses of 75 and 300 mg once daily) and changes in QTcF interval was observed at Day 11, i.e., higher concentrations of RPV were associated with larger changes in the QTcF interval. This relationship was gender-dependent, with higher RPV plasma concentrations leading to a larger difference between females and males. RPV administered at doses of 75 and 300 mg once daily had a mild CYP3A4 inducing effect, which appeared to be dose-related.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
TMC278-TiDP6-C152 (RPV) Status: Complete	Phase I, randomized, double-blind, double-dummy, placebo- and active-controlled, crossover thorough QT study	Healthy adult subjects	RPV Panel: Treatment 1: RPV 25 mg once daily; Days 1-11 + 1 x moxifloxacin placebo; Day 11 Treatment 2: RPV placebo once daily; Days 1-11 + 1 x moxifloxacin placebo; Day 11 Treatment 3: RPV placebo once daily; Days 1-11 + 1 x moxifloxacin 400 mg; Day 11 EFV Panel: Treatment 4: EFV 600 mg once daily; 11 days Treatment 5: EFV placebo once daily; 11 days	At steady state (Day 11), RPV 25 mg once daily and EFV 600 mg once daily were not associated with clinically relevant effects on QTcF interval, as indicated by the 90% CIs of the observed time-matched differences vs. placebo in QTcF interval not exceeding the 10 ms threshold at any time point. At a dose of 25 mg once daily, no relationship was observed between RPV plasma concentrations and changes in QTcF interval from Baseline, i.e., higher plasma concentrations did not result in notable changes in QTcF interval. There was no clear gender-dependent relationship. There was also no relationship between EFV plasma concentrations and changes in QTcF interval from Baseline.
ING112276 (SPRING-1) (DTG) Status: Ongoing, Week 96 CSR Complete	Phase IIb randomized, multicenter, parallel group, dose-ranging study	HIV-1-infected, ART-naive adults	DTG 10 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; DTG 25 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; DTG 50 mg QD + ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; EFV 600 mg QD + ABC/3T;C 600 mg/300 mg or TDF/FTC 300 mg/200 mg At Week 96, subjects in the DTG arms were switched to open-label DTG 50 mg (dosed as two DTG 25 mg tablets); subjects in the EFV arm were discontinued.	Safety results of this study support selection of DTG 50 mg once daily for Phase III INSTI-naïve subjects. The tolerability profile for DTG was better than EFV and the safety profile for DTG was comparable to EFV, with some noted improvement to be further evaluated in Phase III.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
ING113086 (SPRING-2) (DTG) Status: Ongoing, Week 96 CSR Complete	Phase III, randomized, double blind safety and efficacy study	HIV-1-infected, ART-naive adults		DTG demonstrated a safety and tolerability profile that was similar to that of RAL over 96 weeks. Compared with RAL, there is no evidence of increased risk for DTG of renal or hepatic toxicity, psychiatric disorders, or serious hypersensitivity events. Mild to moderate general GI intolerance (mainly diarrhea and nausea) is associated with DTG treatment in a small proportion of subjects; however nonclinical findings for GI erosions did not translate into significant clinical findings. There is no evidence for increased risk of torsades de pointes with DTG. Other serious conditions that are labeled for RAL, such as serious rash (e.g., Stevens Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme) and rhabdomyolysis have not been observed in this study.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
ING114467 (SINGLE) (DTG) Status: Complete; Week 144 and End-of-Study CSRs Complete	Phase III, randomized, double blind safety and efficacy study	HIV-1-infected, ART-naive adults	DTG 50 mg + ABC/3TC 600 mg/300 mg EFV/TFD/FTC (Atripla)	DTG + ABC/3TC demonstrated a safety and tolerability profile that was generally favorable to that of Atripla over 144 weeks. Compared with Atripla, there appears to be no increased risk for DTG + ABC/3TC of hepatic toxicity, renal toxicity, or rash with or without systemic symptoms. Nervous system and psychiatric disorders were more frequent with Atripla, with the exception of insomnia, which was more frequent with DTG + ABC/3TC. Data from this study suggests that insomnia was a short term mild tolerability issue for the DTG + ABC/3TC combination, occurring early in treatment. Non-clinical evidence for GI toxicity (ulceration events) with DTG use did not translate into significant clinical findings for DTG. There is no evidence from this study for increased risk of torsades de pointes with DTG. There was no untoward effect on the overall lipid profile in either treatment group.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
ING114915 (FLAMINGO) (DTG) Status: Ongoing, Week 96 CSR Complete	Phase IIIb, randomized, open-label safety and efficacy study	HIV-1-infected, ART-naive adults	DTG 50 mg + either ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; once daily DRV 800 mg + RTV 100 mg + either ABC/3TC 600 mg/300 mg or TDF/FTC 300 mg/200 mg; once daily with food; once daily	DTG demonstrated a safety and tolerability profile that was generally comparable to that of DRV + RTV over 96 weeks. Compared to DRV + RTV based on Week 96 data, there is no increased risk for DTG of renal toxicity, hepatic toxicity rash with or without systemic symptoms. Serious rash (e.g., Stevens Johnson syndrome, toxic epidermal necrolysis or erythema multiforme) was not observed in this study. No cases suggestive of hypersensitivity reaction to DTG were reported. Non-clinical findings for GI erosions did not translate into significant clinical findings. The psychiatric AE profile for DTG was comparable to prior studies. There is no evidence from this study for increased risk of torsades de pointes with DTG. The changes in lipid profile through Week 96 were favorable for DTG compared with DRV + RTV.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
TMC278-TiDP6-C209 (RPV) Status: Complete	Phase III, randomized, double-blind study	HIV-1-infected, ART-naive adults	RPV 25 mg QD + TDF/FTC 300 mg/200 mg; once daily EFV 600 mg QD + TDF/FTC 300 mg/200 mg; once daily	There were no laboratory, cardiovascular, or endocrine signals to suggest safety issues with the use of RPV when combined with TDF/FTC. Treatment with RPV 25 mg QD was demonstrated to be generally safe and well-tolerated up to the Week 96 analysis cut-off ([redacted]). The most common AEs in the RPV group were upper respiratory tract infection (14.2% vs. 13.4% in the RPV and control group, respectively), diarrhea (13.9% vs. 17.2%, respectively), headache (13.9% vs. 12.5%, respectively), and nausea (12.4% vs. 10.2%, respectively). Compared with the Week 48 analysis, there were only small increases in the incidence of AEs in the Week 96 analysis. The Week 96 analysis confirms the favorable safety profile of RPV, as seen in the Week 48 analysis, with fewer discontinuations due to AEs compared with control and lower incidences of treatment-related AEs of at least Grade 2 in severity. There were no apparent relationships between the pharmacokinetics of RPV and safety parameters. RPV was shown to be generally safe and well tolerated up to Week 96.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
TMC278-TiDP6-C215 (RPV) Status: Complete	Phase III, randomized, double-blind study	HIV-1-infected, ART-naive adults	RPV 25 mg QD + background regimen of 2 NRTIs; once daily EFV 600 mg QD + background regimen of 2 NRTIs; once daily	There were no laboratory, cardiovascular, or endocrine signals to suggest safety issues with the use of RPV when combined with a background regimen of 2 N(t)RTIs. Treatment with RPV 25 mg QD was demonstrated to be generally safe and well-tolerated up to the Week 96 analysis cut-off ([redacted]). The most common AEs in the RPV group, irrespective of severity and causality were headache (17.1% vs. 15.7% in the RPV and control group, respectively), nausea (16.8% vs. 19.8%, respectively), nasopharyngitis (13.8% vs. 13.3%, respectively), diarrhea (13.5% vs. 15.4%, respectively) and dizziness (12.6% vs. 32.8%, respectively). Compared with the Week 48 analysis, there were only small increases in the incidence of AEs in the Week 96 analysis. The Week 96 analysis confirms the favorable safety profile of RPV, as seen in the Week 48 analysis, with lower incidences of treatment-related AEs of at least Grade 2 in severity. There were no apparent relationships between the pharmacokinetics of RPV and safety parameters. RPV was shown to be generally safe and well tolerated up to Week 96.
S-349572-TF-063-L (DTG) Status: Complete	Nonclinical oral fertility and early embryonic development to implantation study	Rats	DTG doses: 0 (control), 100, 300, and 1000 mg/kg/day via oral gavage from 28 days prior to mating, throughout the mating period, until 1 day prior to necropsy (63-66 days in total) for males and from 14 days prior to mating, throughout the mating period, until Day 7 of gestation for females (up to 42 total days of dosing).	There were no effects on fertility or early embryonic development in rats orally administered DTG at $\leq$1000 mg/kg/day in males or females. The NOAEL was 1000 mg/kg/day, which corresponds to ~44X above the expected human exposure for a 50 mg QD dose, based on gender averaged mean exposures achieved in the 4 week rat toxicity study.

Study No. (Single Entity Component) Status	**Study Design**	**Population**	**Treatment Details**	**Main Conclusion(s)**
NC124 (RPV) Status: Complete	Nonclinical oral male fertility study	Rats	RPV doses: 0 (control), 100, 400, and 1200 mg base eq./kg/day via oral gavage once daily for 10 weeks prior to pairing, during paring, and until necropsy, approximately 3-4 weeks after the pairing period.	No effects on fertility observed.
NC125 (RPV) Status: Complete	Nonclinical oral female fertility study	Rats	RPV doses: 0 (control), 40, 120, and 400 mg eq./kg/day via oral gavage once daily for 14 days prior to pairing, during pairing, and up to Day 7 of presumed pregnancy	No effects on fertility observed.
NC105 (RPV) Status: Complete	Nonclinical oral developmental toxicity study	Rats	RPV doses: 0 (control), 40, 120, and 400 mg/kg/day via oral gavage once daily from Day 6 to 17 inclusive of pregnancy	For 0 and 40 mg/kg/day: no effects For 120 and 400 mg/kg/day: Minimal to slight decrease in body weight gain, corrected maternal weight gain and food consumption. Slight increase in thyroid weight.
NC130 (RPV) Status: Complete	Nonclinical oral developmental toxicity study	Rabbits	RPV doses: 0 (control), 5, 10, and 20 mg/kg/day via oral gavage once daily from Day 6 through Day 19 of pregnancy (day of copulation = Day 0)	For 0, 5, and 10 40 mg/kg/day: no effects For 20 mg/kg/day: Fetal observations: slight increase in left subclavian artery branches arising from the aorta and the hypoplastic interparietal bone.

1.1.1.3. Data from Post-Marketing Experience for the DTG and RPV Single Entities

No post-marketing experience is available with the DTG/RPV FDC, as it is an investigational product and is not marketed or authorized for sale in any country at the time of this report. However, both DTG and RPV have been marketed for a number of years. An overview of any significant post-marketing information for DTG and RPV and any information, for example from the literature, describing the use of DTG and RPV together is provided in Section 6.

As limited data is available on pregnancies occurring in clinical trials with DTG, RPV, and DTG + RPV, data from the Antiretroviral Pregnancy Registry provides the best source of cumulative information regarding the use of DTG and RPV during pregnancy post-marketing. The APR data is summarized in Section 5.4.2.4.

1.1.2. Nonclinical Data Relevant to Human Safety

To support initial separate marketing, DTG and RPV have each been tested individually in comprehensive nonclinical development programs. There is no known overlapping toxicity for DTG and RPV. Thus, no nonclinical combination toxicity studies have been conducted on the combination of DTG and RPV as combination toxicity studies are not generally warranted for HIV products unless there is a specific cause for concern under clinically relevant conditions. This is supported by the lack of drug:drug interaction between the two components (LAI116181, see Section 5.3.1).

Refer to the Nonclinical Overview (m2.4) for information on nonclinical toxicology and pharmacology.

1.1.3. Clinical Development Program Overview

The overall clinical development and reporting strategy for the DTG/RPV FDC is summarized in m2.5 Section 1.2.

1.1.3.1. Compound and Formulation Nomenclature

The compound for registration is commonly referred to throughout this document as the DTG/RPV FDC. Across documents, the DTG/RPV FDC may also have been identified as GSK3365791 (GSK1349572 + GSK1329758). DTG has also been identified as GSK1349572 (S/GSK1349572, 572) and RPV as GSK1329758 (TMC278 or R278474).

1.1.4. Description Types of m2.7.4 Tabular Data Presentations

There are two types of data presentations referenced in this document: in-text presentations and SAS-generated statistical outputs (described in Table 2).

Table 2 Table, Figure, and Listing Types and Descriptions

Type	Tool Used to Generate	How Referenced
In-text tables or figures	Word	Consecutive integers (e.g., Table 1, Table 2, Figure 1, Appendix Table 1, etc.…)
Statistical outputs for the 201636 and 201637 CSR (tables, listings, and figures)	SAS	The CSR tables and figures use unique numbers that include a decimal, and listings are sequentially numbered. Safety tables and figures generated for the 201636 and 201637 studies are numbered as 3.X. The CSR listings are sequentially numbered. Tables, figures, and listings from the 201636 and 201637 CSR outputs will be identified as 201636/201637 Table 3.X, or 201636/201637 Listing X.
Statistical outputs for the 201636 and 201637 ISO (tables and listings)	SAS	The ISO tables and listings use unique numbers that include a decimal. Safety tables and listings generated for the 201636 and 201637 ISO are numbered as 3.X. Tables and listings from the 201636 and 201637 ISO will be identified as 201636/201637 Table 3.X, or 201636/201637 Listing X (note that some have a decimal, e.g., Listing 3.801).
Statistical outputs for other studies or programs (tables)	SAS	Source tables from other studies or programs (i.e., not from 201636 or 201637) will be identified using the associated study identifier followed by the table number (e.g., 202094 Table 2.X)

1.1.5. Description of 201636 and 201637 Study Design

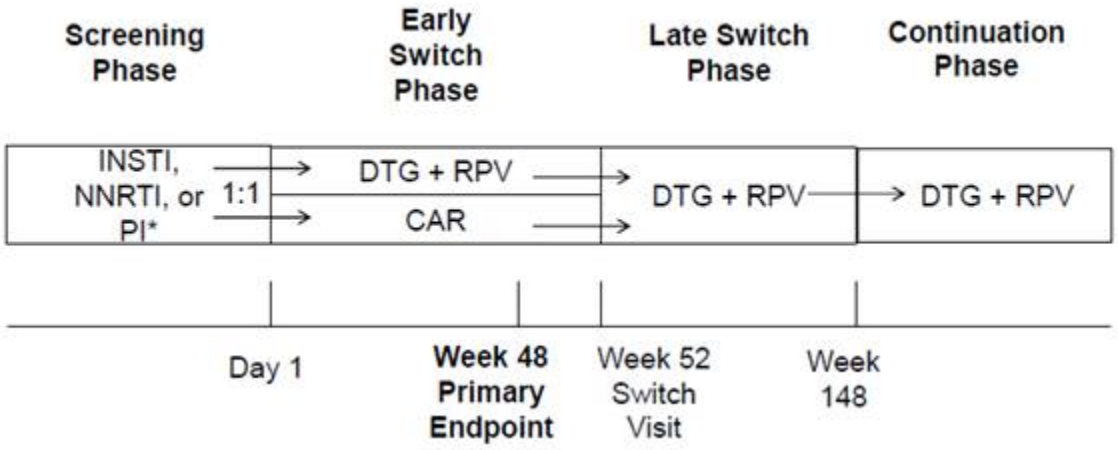
A tabular listing to describe the enrollment status, objectives, design, treatment details, number of subjects by treatment group, key demographics, and primary endpoints of the 2 Phase III studies contributing safety information in this submission is provided in Appendix Table 2.

These 2 ongoing studies are identical 148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority studies. They are being conducted in 510 (201636) and 518 (201637) adult HIV-1-infected patients who were on stable suppressive cART containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI. Eligible subjects were randomized 1:1 to continue their CAR or be switched to a 2-drug regimen consisting of DTG + RPV given as individual components administered once daily. Individuals who were originally assigned to continue their CAR and remained virologically suppressed at the Week 48 visit (primary endpoint of the studies), switched to DTG + RPV (at Week 52) and are to be followed to Week 148 (Figure 1).

The primary analysis took place after the last subject completed the Week 48 visit. Additional analyses may be conducted after the last subject completes the Week 100 visit, the Week 148 visit, and after the last subject withdraws from the study or transitions to commercial supplies (i.e., completes the Continuation Phase).

The studies include a Screening Phase (up to 28 days), an Early Switch Phase (Day 1 up to Week 52), a Late Switch Phase (Week 52 to Week 148), and a Continuation Phase. No non-protocol defined dose reductions, modifications in dosage, or changes in the frequency of dosing were allowed at any time in this study.

Figure 1 Study Schematic for 201636 (SWORD-1) and 201637 (SWORD-2)



*Plus 2 NRTIs
CAR = current antiretroviral regimen
N=510 (201636) and 518 (201637) randomized 1:1 to each arm and stratified by Baseline third agent class, age group (< or ≥50 years old) and planned participation in Study 202094 (DEXA substudy).
Must be on uninterrupted current regimen (either the initial or second cART regimen) for at least 6 months prior to Screening (See Protocol Section 5.1 and Protocol Section 5.2).
Documented evidence of at least 2 plasma HIV-1 RNA measurements <50 c/mL in the 12 months prior to Screening: one within the 6 to 12 month window, and one within 6 months prior to Screening.
No history of virologic failure.
No evidence of viral resistance based on the presence of any resistance-associated major PI, INSTI, NRTI, or NNRTI mutation and IN resistance-associated substitution R263K from prior resistance genotype assay results.
No current or prior history of ETV use.

1.1.6. Description of Populations for 201636 and 201637

Intent-to-Treat Exposed (ITT-E) Population and Safety Population analyses are included in this document for the individual studies and pooled analyses of 201636 and 201637.

The ITT-E consists of all randomized subjects who receive at least 1 dose of study medication, assessed according to their randomized treatment regardless of the treatment they received.

The Safety population consists of all subjects who received at least 1 dose of study medication. Subjects were assessed according to actual treatment received.

1.1.7. Statistical Methods for 201636 and 201637

1.1.7.1. Integrated Analysis

An integrated analysis of data from the 2 Phase III pivotal studies, 201636 and 201637, was performed to support the DTG/RPV FDC. For complete details of data handling and analysis for the individual studies, please refer to the respective Reporting and Analysis Plans in each CSR (201636 CSR RAP and 201637 CSR RAP); for the ISO, please refer to the Summary Document Analysis Plan (SDAP for DTG + RPV).

Data from these two identically-designed studies are reported side-by-side in the integrated safety analyses along with totals combining data from subjects across the 2 studies for both DTG + RPV and CAR, where applicable.

This submission contains safety data collected and analyzed through the Week 48 cut-off date for 201636 and 201637of [redacted]. Emphasis is placed on the complete early switch data. However, where relevant, available late switch data are also summarized with separate DTG + RPV summaries presented for those randomized to DTG + RPV at Baseline and those switching to DTG + RPV at Week 52.

All demography and study population tables are presented on the ITT-E Population and all safety analyses are performed on the Safety Population, as defined in the RAP and SDAP documents.

Safety analyses include summaries of extent of exposure, AEs and laboratory tests including special interest categories for AEs and laboratory tests.

This integrated output uses the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) and GSKDrug dictionaries for AEs and concomitant medications at the time of running the integrated analysis.

1.1.7.2. Treatment State Definitions

Definitions used within the integrated analyses to determine the treatment states of AEs and laboratory assessments are described, respectively in Table 3 and Table 4. All events and assessments considered to be either “on-treatment” or “post-treatment” are also considered “post-baseline”.

Table 3 Definitions for the Terms " Pre-Treatment", "On-Treatment", and "Post-Treatment" Used to Describe Adverse Event Timings

Adverse Events	
Treatment State	**Definition**
Pre-Treatment	AE Start Date < Study Treatment Start Date
On-Treatment	If AE onset date is on or after treatment start date & on or before treatment stop date. Study Treatment Start Date ≤ AE Start Date ≤ Study Treatment Stop Date
Post-Treatment	If AE onset date is after the treatment stop date. AE Start Date > Study Treatment Stop Date

Notes:
If the study treatment stop date was missing, then any event with a start date on or after study treatment Start Date is considered to be On-treatment.
If the start date of the AE was after study treatment Stop Date but was recorded as potentially related to study treatment, then it was classified as On-treatment.

Table 4 Definitions for the Terms " Pre-Treatment", "On-Treatment", and "Post-Treatment" Used to Describe Laboratory Assessment Timings

Laboratory Assessments	
Treatment State	**Definition**
Pre-Treatment	Date ≤ Study Treatment Start Date
On-Treatment	Study Treatment Start Date < Date ≤ Study Treatment Stop Date + 1
Post-Treatment	Date > Study Treatment Stop Date +1

Note: If the study treatment stop date was missing then the assessment was considered to be On-Treatment

1.1.8. Independent Data Monitoring Committee for the DTG + RPV Phase III Studies

An Independent Data Monitoring Committee (IDMC) for 201636 and 201637 was formed to ensure that subjects in the DTG + RPV group of the studies were not being sub-optimally treated, and to also ensure that the subjects who had switched from an NNRTI-based regimen to DTG + RPV were not being sub-optimally treated. Monitoring of the NNRTI subgroup was set up to address concerns that residual enzyme induction effects of NNRTIs could result in lower DTG and RPV concentrations upon immediately switching to a DTG + RPV regimen. The IDMC consisted of two independent physicians and an independent statistician. In addition, the IDMC also reviewed all adverse events and adverse events leading to withdrawal.

An interim futility analysis was performed by an independent statistical and data analysis center on the data from the individual studies as well as the pooled data from 201636 and 201637 approximately 9 months after first subject first visit (FSFV), when 50% of subjects were expected to have reached their Week 24 visit. This was to allow the IDMC to review data prior to subjects reaching the Week 48 visit, and to avoid progressing to the Late Switch Phase, at Week 52, if there was sub-optimal efficacy in the Early Switch Phase. The sponsor remained blinded to this analysis. Based on their review, the IDMC recommended to continue the studies as planned.

1.2. Overall Extent of Exposure

The median time of exposure to DTG + RPV and CAR was 364 days (52 weeks) for both studies and for the pooled data (Table 5).

For those subjects randomized to DTG + RPV in the Early Switch Phase, there was no schedule to switch treatment (and no Week 52 assessment visit). As a result, their exposure within the Early Switch Phase was considered to be 52 weeks (364 days) unless they withdrew earlier in the study.

Extent of exposure for CAR is calculated using medication start and stop dates. The late switch from CAR to DTG + RPV takes place at the Week 52 visit, but there is variability in the actual day that subjects attend the clinic. As a result, in contrast with the DTG + RPV group, there were some subjects with less than 52 weeks of treatment and others with at least 52 weeks of treatment.

In the Early Switch Phase, the exposure was comparable between DTG + RPV and CAR.

Table 5 Summary of Extent of Exposure during the Early Switch Phase in Studies 201636, 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV (N=252)	CAR (N=256)	DTG + RPV (N=261)	CAR (N=255)	DTG + RPV (N=513)	CAR (N=511)
Exposure (Weeks) n (%)						
<2 weeks	0	1 (<1)	3 (<1)	0	3 (<1)	1 (<1)
2 to <4 weeks	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
4 to <8 weeks	2 (<1)	2 (<1)	0	1 (<1)	2 (<1)	3 (<1)
8 to <12 weeks	1 (<1)	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)
12 to <16 weeks	1 (<1)	0	2 (<1)	1 (<1)	3 (<1)	1 (<1)
16 to <20 weeks	1 (<1)	0	1 (<1)	0	2 (<1)	0
20 to <24 weeks	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
24 to <28 weeks	1 (<1)	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)
28 to <32 weeks	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)	3 (<1)
32 to <36 weeks	0	2 (<1)	3 (<1)	0	3 (<1)	2 (<1)
36 to <40 weeks	2 (<1)	0	1 (<1)	3 (1)	3 (<1)	3 (<1)
40 to <44 weeks	2 (<1)	0	0	1 (<1)	2 (<1)	1 (<1)
44 to <48 weeks	1 (<1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)
48 to <52 weeks	0	93 (36)	1 (<1)	103 (40)	1 (<1)	196 (38)
≥52 weeks[b]	239 (95)	152 (59)	244 (93)	141 (55)	483 (94)	293 (57)
Exposure (Days)						
Mean (SD)	354.3 (47.01)	354.8 (50.08)	350.6 (57.96)	356.3 (40.58)	352.4 (52.85)	355.5 (45.55)
Median (IQR)	364.0 (364.0 - 364.0)	364.0 (362.0 - 365.0)	364.0 (364.0 - 364.0)	364.0 (361.0 - 364.0)	364.0 (364.0 - 364.0)	364.0 (362.0 - 365.0)
Duration of dosing in cumulative subject years[a]	244.4	248.6	250.5	248.8	495.0	497.4

Data Source: 201636/201637 Table 3.010
Note: Dose interruptions are not excluded.
a. Cumulative sum across subjects of (treatment stop date - treatment start date + 1) divided by 365.25
b. For CAR subjects, exposure in the Early Switch Phase is calculated to the day prior to switching to DTG + RPV or to withdrawal where withdrawal took place sooner. For DTG + RPV subjects, exposure in the Early Switch Phase is calculated as 52 weeks (364 days) or to withdrawal if withdrawal took place sooner.

1.3. Demographic and Other Characteristics of Study Population

1.3.1. Demographic Characteristics

Demographic characteristics were well balanced across treatment groups (Table 6).

Of note, >20% of subjects were women for both studies pooled (DTG + RPV 23%, CAR 21%) and 29% of subjects in the DTG + RPV group and 28% of subjects in the CAR group were 50 years of age or older. Thus, the study met enrollment goals, which targeted enrolling approximately 15% women and approximately 15% subjects aged 50 years or older.

Table 6 Summary of Demographic Characteristics for Study 201636, Study 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV N=252	CAR N=256	DTG + RPV N=261	CAR N=255	DTG + RPV N=513	CAR N=511
Age (y), median (range)	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-6[redacted])	43.0 (2[redacted]-7[redacted])	43.0 (2[redacted]-7[redacted])
Age group (y), n (%)						
<35	53 (21)	60 (23)	64 (25)	55 (22)	117 (23)	115 (23)
35 - <50	130 (52)	125 (49)	119 (46)	129 (51)	249 (49)	254 (50)
≥50	69 (27)	71 (28)	78 (30)	71 (28)	147 (29)	142 (28)
Sex, n (%)						
Female	58 (23)	51 (20)	62 (24)	57 (22)	120 (23)	108 (21)
Male	194 (77)	205 (80)	199 (76)	198 (78)	393 (77)	403 (79)
Ethnicity, n (%)						
Hispanic/Latino	30 (12)	34 (13)	37 (14)	48 (19)	67 (13)	82 (16)
Not Hispanic/Latino	222 (88)	222 (87)	224 (86)	207 (81)	446 (87)	429 (84)
Race, n (%)						
American Indian or Alaska Native	3 (1)	6 (2)	11 (4)	8 (3)	14 (3)	14 (3)
Asian	25 (10)	34 (13)	13 (5)	16 (6)	38 (7)	50 (10)
Central/South Asian Heritage	0	0	0	1 (<1)	0	1 (<1)
Japanese/East Asian Heritage/South East Asian Heritage	25 (10)	34 (13)	13 (5)	15 (6)	38 (7)	49 (10)
Black/African American	24 (10)	27 (11)	13 (5)	20 (8)	37 (7)	47 (9)
Native Hawaiian or other Pacific Islander	1 (<1)	0	1 (<1)	0	2 (<1)	0
White	198 (79)	188 (73)	223 (85)	210 (82)	421 (82)	398 (78)
White & African American/African Heritage	0	0	0	1 (<1)	0	1 (<1)
White and American Indian or Alaska Native	0	1 (<1)	0	0	0	1 (<1)
Asian and African American/African Heritage	1 (<1)	0	0	0	1 (<1)	0

Data Source: 201636/201637 Table 1.150, Table 1.171, Table 1.172, and Table 1.173.

1.3.2. Baseline Characteristics

Baseline characteristics were also well balanced across the treatment groups (Table 7). Overall, most subjects had negative test results at screening for HCV infection (DTG + RPV 94%, CAR 92%) and were in CDC Class A (DTG + RPV 78%, CAR 75%).

Table 7 Summary of Baseline Characteristics for Study 201636, Study 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV N=252	CAR N=256	DTG + RPV N=261	CAR N=255	DTG + RPV N=513	CAR N=511
Baseline HIV-1 RNA (c/mL)						
<50 c/mL	247(98)	253 (99)	259 (99)	251 (98)	506 (99)	504 (99)
≥50 c/mL	5 (2)	3 (1)	2 (1)	4 (2)	7 (1)	7 (1)
Baseline CD4+ (log_{10} c/mm^3)						
Median	2.786	2.805	2.785	2.798	2.786	2.805
Min., Max.	1.57, 3.18	1.98, 3.18	2.06, 3.25	2.03, 3.22	1.57, 3.25	1.98, 3.22
Hepatitis B & C Test Results						
B only	0	1 (<1)	0	1 (<1)	0	2 (<1)
C only	15 (6)	19 (7)	13 (5)	21 (8)	28 (5)	40 (8)
B and C	0	0	0	0	0	0
Borderline C only	0	0	1 (<1)	0	1 (<1)	0
Neither	237 (94)	236 (92)	247 (95)	233 (91)	484 (94)	469 (92)
CDC Category						
A: Asymptomatic or Lymphadenopathy or Acute HIV	203 (81)	198 (77)	197 (75)	187 (73)	400 (78)	385 (75)
B: Symptomatic, not AIDS	20 (8)	35 (14)	35 (13)	33 (13)	55 (11)	68 (13)
C: AIDS	29 (12)	23 (9)	29 (11)	34 (13)	58 (11)	57 (11)
Missing	0	0	0	1 (<1)	0	1 (<1)

Data Source: 201636/201637 Table 1.200, Table 1.210, Table 1.230, Table 2.101, Table 2.102, Table 2.103, Table 2.111, Table 2.112, and Table 2.113

1.3.3. Antiretroviral Therapy at Screening by Individual Component

Data on individual antiretroviral agents received by study participants at Screening are shown in Table 8. Data on antiretroviral therapies by full regimen received by study participants at Screening are described in m2.7.3 Section 3.1.2.4.

As per the protocol for these studies, all subjects (100%) were receiving NRTIs as part of their ART regimen at screening. In the pooled grouped, the most commonly reported individual NRTIs were TDF (DTG + RPV 73%, CAR 70%) and FTC (DTG + RPV 69%, CAR 67%).

In addition, 54% of subjects in both groups were receiving NNRTIs, 26% of subjects in the DTG + RPV group and 27% of subjects in the CAR group were receiving PIs, and 20% in the DTG + RPV group and 19% of subjects in the CAR group were receiving INSTIs at screening. Of the subjects in DTG + RPV group, 6% were taking RPV and 6% were taking DTG at Screening, and thus at least 88% of subjects were switching to an entirely new regimen compared with their Screening regimen.

Table 8 Summary of Antiretroviral Therapy at Screening for Study 201636, Study 201637, and Pooled Data (ITT-E Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any medication	**252 (100)**	**256 (100)**	**261 (100)**	**255 (100)**	**513 (100)**	**511 (100)**
NRTI						
Any medication	252 (100)	256 (100)	261 (100)	255 (100)	513 (100)	511 (100)
Tenofovir	184 (73)	172 (67)	190 (73)	187 (73)	374 (73)	359 (70)
Emtricitabine	166 (66)	156 (61)	186 (71)	185 (73)	352 (69)	341 (67)
Lamivudine	85 (34)	100 (39)	75 (29)	70 (27)	160 (31)	170 (33)
Abacavir	56 (22)	66 (26)	48 (18)	55 (22)	104 (20)	121 (24)
Zidovudine	11 (4)	17 (7)	21 (8)	10 (4)	32 (6)	27 (5)
Didanosine	1 (<1)	1 (<1)	1 (<1)	2 (<1)	2 (<1)	3 (<1)
Phosphazide	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Stavudine	1 (<1)	0	0	0	1 (<1)	0
NNRTI						
Any medication	131 (52)	134 (52)	144 (55)	144 (56)	275 (54)	278 (54)
Efavirenz	83 (33)	86 (34)	102 (39)	103 (40)	185 (36)	189 (37)
Nevirapine	29 (12)	31 (12)	27 (10)	18 (7)	56 (11)	49 (10)
Rilpivirine	18 (7)	17 (7)	15 (6)	22 (9)	33 (6)	39 (8)
Etravirine	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
PI						
Any medication	75 (30)	74 (29)	58 (22)	62 (24)	133 (26)	136 (27)
Darunavir-Ritonavir	31 (12)	19 (7)	27 (10)	21 (8)	58 (11)	40 (8)
Atazanavir-Ritonavir	24 (10)	23 (9)	15 (6)	18 (7)	39 (8)	41 (8)
Lopinavir	7 (3)	7 (3)	10 (4)	18 (7)	17 (3)	25 (5)
Ritonavir	7 (3)	7 (3)	10 (4)	20 (8)	17 (3)	27 (5)
Atazanavir	10 (4)	22 (9)	4 (2)	4 (2)	14 (3)	26 (5)
Lopinavir-Ritonavir	10 (4)	10 (4)	10 (4)	18 (7)	20 (4)	28 (5)
Darunavir	0	0	1 (<1)	0	1 (<1)	0
Fosamprenavir-Ritonavir	0	0	1 (<1)	0	1 (<1)	0
Nelfinavir	0	0	0	1 (<1)	0	1 (<1)
INSTI						
Any medication	46 (18)	48 (19)	59 (23)	49 (19)	105 (20)	97 (19)
Raltegravir	13 (5)	22 (9)	30 (11)	22 (9)	43 (8)	44 (9)
Dolutegravir	16 (6)	17 (7)	17 (7)	16 (6)	33 (6)	33 (6)
Elvitegravir-Cobicistat	17 (7)	9 (4)	12 (5)	11 (4)	29 (6)	20 (4)
Other ART						
Any medication	15 (6)	9 (4)	12 (5)	11 (4)	27 (5)	20 (4)
Cobicistat	15 (6)	9 (4)	12 (5)	11 (4)	27 (5)	20 (4)

Data Source: 201636/201637 Table 1.400

2. ADVERSE EVENTS

2.1. Analysis of Adverse Events

2.1.1. Common Adverse Events

During the Early Switch Phase, AEs were reported in 77% of subjects in the pooled DTG + RPV group and 71% of subjects in the pooled CAR group (Table 9). There were

also greater proportions of subjects reporting drug-related events, Grade 2-4 AEs, and AEs leading to withdrawal in the DTG + RPV group compared with the CAR group. However, in the case of Grade 2-4 AEs, the 6% difference observed between the treatment groups for the pooled data was largely driven by study 201637 results, as the proportions of subjects with Grade 2-4 AEs was similar between the two treatment groups in study 201636.

Table 9 Overall Summary of Adverse Events during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any AE	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Drug-related AEs	47 (19)	5 (2)	50 (19)	4 (2)	97 (19)	9 (2)
Grade 2 to 4 AEs	72 (29)	68 (27)	76 (29)	52 (20)	148 (29)	120 (23)
Drug-related Grade 2 to 4 AEs	12 (5)	0	17 (7)	3 (1)	29 (6)	3 (<1)
AEs Leading to Withdrawal	9 (4)	2 (<1)	12 (5)	1 (<1)	21 (4)	3 (<1)
Drug-related AEs Leading to Withdrawal	5 (2)	0	9 (3)	1 (<1)	14 (3)	1 (<1)
Any SAE	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
Drug-related SAEs	2 (<1)	0	2 (<1)	1 (<1)	4 (<1)	1 (<1)
Fatal SAEs	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Drug-related Fatal SAEs	0	0	0	0	0	0

Data Source: 201636/201637 Table 3.040, Table 3.121, Table 3.122, Table 3.123, Table 3.100, Table 3.150, Listing 23, Table 3.230, and Table 3.291
Note: Only on-treatment events are considered.

2.1.1.1. Frequently Reported Adverse Events

The most commonly reported AEs for the DTG + RPV and CAR groups reported in subjects during the Early Switch Phase are shown in Table 10.

Table 10 Most Common Adverse Events (Reported in >=5% of Subjects in Any Treatment Group) by Preferred Term during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Nasopharyngitis	28 (11)	28 (11)	21 (8)	22 (9)	49 (10)	50 (10)
Headache	23 (9)	17 (7)	18 (7)	6 (2)	41 (8)	23 (5)
Upper respiratory tract infection	7 (3)	10 (4)	17 (7)	27 (11)	24 (5)	37 (7)
Diarrhoea	21 (8)	16 (6)	11 (4)	11 (4)	32 (6)	27 (5)
Back pain	9 (4)	19 (7)	6 (2)	12 (5)	15 (3)	31 (6)
Bronchitis	7 (3)	5 (2)	16 (6)	10 (4)	23 (4)	15 (3)
Influenza	4 (2)	13 (5)	10 (4)	4 (2)	14 (3)	17 (3)
Arthralgia	8 (3)	4 (2)	13 (5)	5 (2)	21 (4)	9 (2)

Data Source: 201636/201637 Table 3.080
Note: Only on-treatment events are considered.

There were also 2 post-treatment AEs (i.e., AEs that occurred after the subject had discontinued study treatment) reported during the Early Switch Phase: Grade 1 syphilis (Day 97) and Grade 2 delirium (Day 84), both in the DTG + RPV group (Data Source: 201636/201637 Table 3.683).

2.1.1.2. Adverse Events by System Organ Class

Adverse events most commonly reported in both treatment groups were from the system organ classes of infections and infestations and GI disorders. Events in the infections and infestations SOC occurred at similar frequencies across both treatment groups, while events in the GI disorders SOC occurred at a higher frequency in the DTG + RPV treatment group (Table 11).

In the pooled analysis, there were imbalances between the groups in the incidence of AEs reported for several of the SOCs, most notably GI disorders, nervous system disorders, skin and subcutaneous tissue disorders, psychiatric disorders, and respiratory, thoracic and mediastinal disorders. Several differences in individual AE preferred terms reported within these SOCs contributed to the imbalances (Data Source: 201636/201637 Table 3.040).

- For GI disorders, the largest differences in numbers of subjects reporting events occurred for AEs of flatulence (DTG + RPV 13 [3%], CAR 0), abdominal distention (DTG + RPV 12 [2%], CAR 0), and constipation (DTG + RPV 13 [3%], CAR 2 [<1%]).

- For nervous system disorders, 41 (8%) subjects from the DTG + RPV group compared with 23 (5%) subjects from the CAR group reported headache, and dizziness was reported for 15 (3%) DTG + RPV subjects compared with 1 (<1%) CAR subjects.

- For skin and subcutaneous tissue disorders, 12 (2%) subjects in the DTG + RPV group versus 3 (<1%) subjects in the CAR group reported rash.

- For psychiatric disorders, insomnia, depression, and abnormal dreams were reported at higher rates for the DTG + RPV group; for the DTG + RPV versus CAR groups, rates were, respectively: insomnia, 17 (3%) versus 10 (2%); depression, 17 (3%) versus 6 (1%); and abnormal dreams, 6 (1%) versus 0.

- For respiratory, thoracic and mediastinal disorders, reporting of specific AEs was similar, with the largest difference occurring for the preferred term of rhinitis allergic (DTG + RPV 5 [<1%], CAR 0).

The number of subjects reporting events in other SOCs that differed between the treatment groups (e.g., blood and lymphatic system disorders and immune system disorders) are too small to draw any conclusions.

Table 11 Summary of Adverse Events by System Organ Class during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Infections and infestations	108 (43)	115 (45)	115 (44)	119 (47)	223 (43)	234 (46)
Gastrointestinal disorders	71 (28)	56 (22)	58 (22)	26 (10)	129 (25)	82 (16)
Musculoskeletal and connective tissue disorders	35 (14)	50 (20)	43 (16)	32 (13)	78 (15)	82 (16)
Nervous system disorders	37 (15)	28 (11)	40 (15)	14 (5)	77 (15)	42 (8)
Skin and subcutaneous tissue disorders	30 (12)	22 (9)	38 (15)	23 (9)	68 (13)	45 (9)
Psychiatric disorders	34 (13)	18 (7)	27 (10)	14 (5)	61 (12)	32 (6)
General disorders and administration site conditions	28 (11)	29 (11)	21 (8)	22 (9)	49 (10)	51 (10)
Respiratory, thoracic and mediastinal disorders	23 (9)	16 (6)	22 (8)	8 (3)	45 (9)	24 (5)
Injury, poisoning and procedural complications	23 (9)	23 (9)	18 (7)	26 (10)	41 (8)	49 (10)
Reproductive system and breast disorders	12 (5)	16 (6)	9 (3)	10 (4)	21 (4)	26 (5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (3)	10 (4)	11 (4)	7 (3)	18 (4)	17 (3)
Renal and urinary disorders	5 (2)	5 (2)	10 (4)	4 (2)	15 (3)	9 (2)
Ear and labyrinth disorders	6 (2)	8 (3)	6 (2)	3 (1)	12 (2)	11 (2)
Vascular disorders	6 (2)	8 (3)	5 (2)	4 (2)	11 (2)	12 (2)
Investigations	7 (3)	8 (3)	5 (2)	2 (<1)	12 (2)	10 (2)
Eye disorders	3 (1)	1 (<1)	6 (2)	7 (3)	9 (2)	8 (2)
Metabolism and nutrition disorders	2 (<1)	2 (<1)	7 (3)	6 (2)	9 (2)	8 (2)
Blood and lymphatic system disorders	3 (1)	3 (1)	5 (2)	2 (<1)	8 (2)	5 (<1)
Immune system disorders	5 (2)	1 (<1)	3 (1)	3 (1)	8 (2)	4 (<1)
Hepatobiliary disorders	3 (1)	1 (<1)	2 (<1)	1 (<1)	5 (<1)	2 (<1)
Cardiac disorders	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)	2 (<1)
Endocrine disorders	0	0	1 (<1)	2 (<1)	1 (<1)	2 (<1)
Congenital, familial and genetic disorders	1 (<1)	0	0	0	1 (<1)	0
Social circumstances	1 (<1)	0	0	0	1 (<1)	0

Data Source: 201636/201637 Table 3.040.
Note: Only on-treatment events are considered.

2.1.1.3. Adverse Events by Grade

The majority of events reported had an intensity of Grade 1 or Grade 2 for both treatment groups (Table 12). Overall, a higher proportion of subjects who switched to DTG + RPV reported Grade 2 to 4 AEs compared with subjects who continued their antiretroviral regimen (29% compared with 23%) (Table 13).

During the Early Switch Phase, 7 Grade 4 events were reported in 5 (<1%) subjects in the DTG + RPV group (Data Source: 201636/201637 Listing 18):

- Subject [redacted] – anxiety and depression, both non-serious with only anxiety considered related to study treatment;
- Subject [redacted] – hepatitis A, non-serious and considered not related to study treatment;
- Subject [redacted] – pancreatitis acute, serious and considered related to study treatment (narrative provided in Section 2.1.4);
- Subject [redacted] – suicidal ideation, serious and considered not related to study treatment (this was later determined by the site to be a suicide attempt) (narrative provided in Section 2.1.6.3);
- Subject [redacted] – Kaposi's sarcoma (this was a fatal event and is described in Section 2.1.2) and respiratory symptom; only Kaposi's sarcoma was considered serious and both were considered not related to study treatment.

During the Early Switch Phase, 3 Grade 4 events were reported in 3 (<1%) subjects in the CAR group:

- Subject [redacted] – blood creatine phosphokinase increased, non-serious and considered not related to study treatment;
- Subject [redacted] – hepatitis C, serious and considered not related to study treatment;
- Subject [redacted] – suicide attempt (see Section 2.1.4), serious and considered related to study treatment.

There were 27 subjects reporting Grade 3 events in the DTG + RPV group and 17 in the CAR group: In the DTG + RPV group, 2 events of drug-induced liver injury were reported in 2 subjects and 2 events of depression were reported in 2 subjects; all other Grade 3 AEs for both treatment groups were reported in 1 subject only (Data Source: 201636/201637 Table 3.053). Grade 3 events that were considered drug-related were: tremor, acute eosinophilic pneumonia, suicidal ideation, two events of depression, and one of the events of drug-induced liver injury (all in the DTG + RPV group) (Data Source: 201636/201637 Listing 18).

Table 12 Summary of Adverse Events by Maximum Toxicity during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	200 (79)	190 (74)	195 (75)	174 (68)	395 (77)	364 (71)
Grade 1	128 (51)	122 (48)	119 (46)	122 (48)	247 (48)	244 (48)
Grade 2	57 (23)	53 (21)	59 (23)	47 (18)	116 (23)	100 (20)
Grade 3	11 (4)	13 (5)	16 (6)	4 (2)	27 (5)	17 (3)
Grade 4	4 (2)	2 (<1)	1 (<1)	1 (<1)	5 (<1)	3 (<1)

Data Source: 201636/201637 Table 3.051, Table 3.052, and Table 3.053
Note: Only on-treatment events are considered.

Table 13 Most Common (Reported in >=1% of Subjects in Any Treatment Group) Grade 2-4 Adverse Events by Overall Frequency during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
Preferred Term	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any Grade 2-4 event	72 (29)	68 (27)	76 (29)	52 (20)	148 (29)	120 (23)
Bronchitis	3 (1)	1 (<1)	7 (3)	2 (<1)	10 (2)	3 (<1)
Diarrhoea	5 (2)	2 (<1)	4 (2)	2 (<1)	9 (2)	4 (<1)
Headache	1 (<1)	6 (2)	5 (2)	2 (<1)	6 (1)	8 (2)
Depression	4 (2)	1 (<1)	2 (<1)	3 (1)	6 (1)	4 (<1)
Gastroenteritis	4 (2)	1 (<1)			6 (1)	2 (<1)
Insomnia	3 (1)	1 (<1)	3 (1)	1 (<1)	6 (1)	2 (<1)
Back pain	2 (<1)	6 (2)	1 (<1)	4 (2)	3 (<1)	10 (2)
Upper respiratory tract infection	1 (<1)	2 (<1)	2 (<1)	7 (3)	3 (<1)	9 (2)
Nasopharyngitis	1 (<1)	4 (2)	0	2 (<1)	1 (<1)	6 (1)

Data Source: 201636/201637 Table 3.100.
Note: Only on-treatment events are considered.

2.1.1.4. Drug-Related Adverse Events

Drug-related AEs reported in ≥1% of subjects in any individual study or pooled treatment group are shown in Table 14. Drug-related AEs (as assessed by the reporting investigator in these open-label studies) were more commonly reported for the DTG + RPV group compared with the CAR group.

Table 14 Most Common Drug-Related Adverse Events (Reported in >=1% of Subjects in Any Treatment Group) by Preferred Term during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	47 (19)	5 (2)	50 (19)	4 (2)	97 (19)	9 (2)
Headache	5 (2)	0	6 (2)	0	11 (2)	0
Diarrhoea	4 (2)	1 (<1)	4 (2)	0	8 (2)	1 (<1)
Abdominal distention	5 (2)	0 (0)	2 (<1)	0	7 (1)	0
Nausea	4 (2)	0 (0)	3 (1)	0	7 (1)	0
Insomnia	3 (1)	1 (<1)	3 (1)	0	6 (1)	1 (<1)
Dizziness	2 (<1)	1 (<1)	4 (2)	0	6 (1)	1 (<1)
Flatulence	1 (<1)	0	5 (2)	0	6 (1)	0
Abnormal dreams	3 (1)	0	3 (1)	0	6 (1)	0
Anxiety	3 (1)	1 (<1)	2 (<1)	0	5 (<1)	1 (<1)
Fatigue	5 (2)	0	0	0	5 (<1)	0
Depression	3 (1)	0	2 (<1)	0	5 (<1)	0
Abdominal pain upper	2 (<1)	0	3 (1)	0	5 (<1)	0

Data Source: 201636/201637 Table 3.121, Table 3.122, Table 3.123
Note: Only On-treatment events are considered.

In the pooled analysis, for the DTG + RPV group, the majority of subjects reported drug-related AEs that were Grade 1; 68 (13%) subjects reported Grade 1 events, compared with 21 (4%) reporting Grade 2, 6 (1%) reporting Grade 3, and 2 (<1%) reporting Grade 4 events. For the CAR group, 6 (1%) subjects reported Grade 1, 2 (<1%) subjects reported Grade 2, 0 subjects reported Grade 3, and 1 (<1%) subject reported Grade 4 events (Data Source: 201636/201637 Table 3.123).

For both treatment groups, the highest proportion of subjects reported a drug-related AE from the GI disorders SOC compared with any other SOC; 36 (7%) subjects in the DTG + RPV group and 5 (<1%) subjects in the CAR group experienced drug-related AEs from this SOC. In the DTG + RPV group, there was 1 Grade 4 drug-related AE of acute pancreatitis from this SOC (narrative provided in Section 2.1.4), and all other drug-related events for both treatment groups were Grade 1 or 2 (Data Source: 201636/201637 Table 3.123).

As shown in Table 15, a higher proportion of subjects in the DTG + RPV group compared with the CAR group reported Grade 2 to 4 drug-related AEs. The most common Grade 2-4 drug related AEs were depression (4 events) and a sampling of gastrointestinal events. However, all were reported by only a few subjects. There was no pattern of drug related Grade 2-4 AEs highlighting any specific SOC.

Table 15 Summary of All Drug-Related Grade 2-4 Adverse Events by Overall Frequency during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	12 (5)	0	17 (7)	3 (1)	29 (6)	3 (<1)
Depression	2 (<1)	0	2 (<1)	0	4 (<1)[a]	0
Asthenia	1 (<1)	0	2 (<1)	0	3 (<1)	0
Diarrhoea	2 (<1)	0	1 (<1)	0	3 (<1)	0
Dyspepsia	0	0	2 (<1)	1 (<1)	2 (<1)	1 (<1)
Abdominal distension	1 (<1)	0	1 (<1)	0	2 (<1)	0
Anxiety	1 (<1)[b]	0	1 (<1)	0	2 (<1)	0
Headache	0	0	2 (<1)	0	2 (<1)	0
Insomnia	1 (<1)	0	1 (<1)	0	2 (<1)	0
Abnormal dreams	0	0	1 (<1)	0	1 (<1)	0
Alopecia	0	0	1 (<1)	0	1 (<1)	0
Anhedonia	0	0	1 (<1)	0	1 (<1)	0
Constipation	0	0	1 (<1)	0	1 (<1)	0
Depressed mood	0	0	1 (<1)	0	1 (<1)	0
Dizziness	0	0	1 (<1)	0	1 (<1)	0
Drug-induced liver injury	1 (<1)[c]	0	0	0	1 (<1)	0
Eosinophilic pneumonia acute	0	0	1 (<1)[d]	0	1 (<1)	0
Erectile dysfunction	1 (<1)	0	0	0	1 (<1)	0
Pancreatitis acute	1 (<1)[e]	0	0	0	1 (<1)	0
Photosensitivity reaction	0	0	1 (<1)	0	1 (<1)	0
Rash	0	0	1 (<1)	0	1 (<1)	0
Rash pruritic	1 (<1)	0	0	0	1 (<1)	0
Renal failure	0	0	1 (<1)	0	1 (<1)	0
Suicidal ideation	0	0	1 (<1)[f]	0	1 (<1)	0
Tremor	0	0	1 (<1)[g]	0	1 (<1)	0
Vision blurred	1 (<1)	0	0	0	1 (<1)	0
Vitamin D deficiency	0	0	1 (<1)	0	1 (<1)	0
Hyperglycaemia	0	0	0	1 (<1)	0	1 (<1)
Suicide attempt	0	0	0	1 (<1)[h]	0	1 (<1)

Data Source: 201636/201637 Table 3.150 and Listing 18

Note: Only On-treatment events are considered.

Note: All drug-related events reported as Grade 3 or 4 are footnoted below; all other events listed are Grade 2.

a. Grade 3 depression was reported in 2 subjects (Subject [redacted] [see Section 2.1.6.3] and Subject [redacted] [see Section 2.1.4])
b. Grade 4 anxiety (Subject [redacted] [see Section 2.1.6.3])
c. Grade 3 drug-induced liver injury (Subject [redacted] [see Section 2.1.4])
d. Grade 3 eosinophilic pneumonia acute (Subject [redacted] [see Section 2.1.4])
e. Grade 4 pancreatitis acute (Subject [redacted] [see Section 2.1.4])
f. Grade 3 suicidal ideation (Subject [redacted] [see Section 2.1.6.3])
g. Grade 3 tremor (Subject [redacted])
h. Grade 4 suicide attempt (Subject [redacted] [see Section 2.1.4])

2.1.2. Deaths

Two deaths were reported at the time of the cut-off date for this Week 48 analysis (Data Source: 201636/201637 Listing 21); both occurred in the Early Switch Phase. One subject in the DTG + RPV group died due to an AE of Kaposi's sarcoma (Subject [redacted]; see Study 201637 CSR Section 15 for a case narrative) and 1 subject in the CAR group (Subject [redacted]; see Study 201636 CSR Section 15 for a case narrative) died due to an AE of lung neoplasm malignant. Neither event was considered related to study treatment by the investigator. Brief narratives for each of the cases are as follows:

- **Subject** [redacted] was a 3[redacted]-year old White male, who was fully suppressed at Baseline on a regimen of DRV, RTV, TDF/FTC (all started a* , with breaks from a* to b* , and c* to d*). The subject had a CD4+ count of 196 cells/mm^3 at Screening and 308 mm^3 at Baseline (Day 1)(Data Source: 201636/201637 Listing 53). He was randomly assigned to switch to DTG + RPV at Baseline (started on [redacted]). The subject's CDC classification at Baseline was Category C (AIDS) (Data Source: 201636/201637 Listing 40). Past relevant medical history included immune systems disorder (excluding HIV-1 infection) and skin and subcutaneous tissue disorder (Data Source: 201636/201637 Listing 43). The subject's viral load was <40 c/mL at all visits through his last visit at Week 24. His CD4 count was 289 cells/mm^3 at Week 24 (i.e., around the time the event of Kaposi's sarcoma was reported). AEs reported during the study included respiratory tract infection (day 179, Grade 2, not related to study treatment), oral candidiasis (day 195, Grade 1, not related to study treatment). The subject experienced a fatal AE of Kaposi's sarcoma on Day 207, which was considered not related to study treatment by the Investigator (Data Source: 201636/201637 Listing 18).
- **Subject** [redacted] was a 5[redacted]-year old White male, with a Baseline regimen of DRV, RTV, TDF/FTC; he was randomized to CAR and continued this regimen. The subject had a past history that included lung cancer. e* , the subject presented with pain in the back. Magnetic resonance tomography of the lungs was performed and neoplasms were found in the lungs. The subject died f* ; an autopsy was performed, and the reported cause of death was lung cancer.

2.1.3. Other Serious Adverse Events

The incidences of subjects reporting at least one SAE and those assessed by the investigator as drug-related SAEs during the Early Switch Phase are summarized in Table 16. The incidence of subjects developing any SAE and the incidence of drug-related SAEs was similar between treatment groups. Refer to Section 2.1.4 for information on each of the 5 drug-related SAEs reported.

a*: 14 months ago
b*: 13 months ago
c*: 12 months ago
d*: 11 months ago
e*: The Day 149
f*: after 2 months

* 新薬承認情報提供時に置き換え

Table 16 Incidence of Subjects Reporting at Least One Serious Adverse Event (All and Drug-Related) during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
Drug-related	2 (<1)	0	2 (<1)	1 (<1)	4 (<1)	1 (<1)

Data Source: 201636/201637 Table 3.160 and Table 3.200

During the Early Switch Phase, the most frequently reported SAEs were pneumonia (reported in 3 subjects in the DTG + RPV group) and suicide attempt (reported in 1 subject each for the DTG + RPV and CAR groups) (Table 17). All other SAEs were reported in 1 subject each. Full narratives for SAEs are presented in Study 201636 CSR Section 15 and Study 201637 CSR Section 15 (Case Narratives).

Table 17 Summary of All Serious Adverse Events by Preferred Term during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	210636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Any event	9 (4)	12 (5)	18 (7)	9 (4)	27 (5)	21 (4)
Pneumonia	1 (<1)	0	2 (<1)	0	3 (<1)	0
Suicide attempt[a]	0	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)
Abscess limb	0	0	1 (<1)	0	1 (<1)	0
Acute kidney injury	0	0	1 (<1)	0	1 (<1)	0
Alcohol poisoning	0	0	1 (<1)	0	1 (<1)	0
Cholecystitis chronic	0	0	1 (<1)	0	1 (<1)	0
Depression	0	0	1 (<1)	0	1 (<1)	0
Drug-induced liver injury	1 (<1)	0	0	0	1 (<1)	0
Eosinophilic pneumonia acute	0	0	1 (<1)	0	1 (<1)	0
Facial bones fracture	0	0	1 (<1)	0	1 (<1)	0
Gastroenteritis	1 (<1)	0			1 (<1)	0
Gastrointestinal haemorrhage	0	0	1 (<1)	0	1 (<1)	0
Gastrooesophageal reflux disease	0	0	1 (<1)	0	1 (<1)	0
Haemarthrosis	0	0	1 (<1)	0	1 (<1)	0
Headache	0	0	1 (<1)	0	1 (<1)	0
Hodgkin's disease mixed cellularity stage unspecified	1 (<1)	0	0	0	1 (<1)	0
Kaposi's sarcoma	0	0	1 (<1)	0	1 (<1)	0
Lymphogranuloma venereum	0	0	1 (<1)	0	1 (<1)	0
Orchitis	0	0	1 (<1)	0	1 (<1)	0
Pancreatitis acute	1 (<1)	0	0	0	1 (<1)	0
Panic attack	1 (<1)	0	0	0	1 (<1)	0

	210636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Periorbital cellulitis			1 (<1)	0	1 (<1)	0
Plasmablastic lymphoma	1 (<1)	0	0	0	1 (<1)	0
Pulmonary sepsis	0	0	1 (<1)	0	1 (<1)	0
Renal colic	0	0	1 (<1)	0	1 (<1)	0
Rotavirus infection	0	0	1 (<1)	0	1 (<1)	0
Tibia fracture	0	0	1 (<1)	0	1 (<1)	0
Vertigo	1 (<1)	0	0	0	1 (<1)	0
Wrist fracture	1 (<1)	0	0	0	1 (<1)	0
Anal fistula	0	1 (<1)	0	0	0	1 (<1)
Breast cancer	0	1 (<1)	0	0	0	1 (<1)
Bronchitis	0	1 (<1)	0	0	0	1 (<1)
Drug hypersensitivity	0	0	0	1 (<1)[b]	0	1 (<1)[b]
Fibula fracture	0	0	0	1 (<1)	0	1 (<1)
Foreign body	0	0	0	1 (<1)	0	1 (<1)
Hepatitis C	0	1 (<1)	0	0	0	1 (<1)
Influenza	0	1 (<1)	0	0	0	1 (<1)
Intervertebral disc protrusion	0	1 (<1)	0	0	0	1 (<1)
Jarisch-Herxheimer reaction	0	0	0	1 (<1)[b]	0	1 (<1)[b]
Joint injury	0	0	0	1 (<1)	0	1 (<1)
Keratitis	0	0	0	1 (<1)	0	1 (<1)
Lung neoplasm malignant	0	1 (<1)	0	0	0	1 (<1)
Non-cardiac chest pain	0	1 (<1)	0	0	0	1 (<1)
Peritonsillar abscess	0	1 (<1)	0	0	0	1 (<1)
Proctitis	0	1 (<1)	0	0	0	1 (<1)
Pulmonary embolism	0	0	0	1 (<1)	0	1 (<1)
Rectal abscess	0	1 (<1)			0	1 (<1)
Retinal detachment	0	0	0	1 (<1)	0	1 (<1)
Thyroglossal cyst infection	0	1 (<1)	0	0	0	1 (<1)
Toxic encephalopathy	0	1 (<1)	0	0	0	1 (<1)
Tympanic membrane perforation	0	0	0	1 (<1)	0	1 (<1)

Data Source: 201636/201637 Table 3.160.

a. There was 1 subject (Subject [redacted]) with a Grade 4 event of suicidal ideation that was classified by the site as non-serious and not related to drug; this event is not included in the above table, however, the event was later determined by the site to be a suicide attempt.

b. The events of drug hypersensitivity and Jarisch-Herxheimer reaction occurred in the same subject and were reported for the same reaction in this subject.

Fourteen subjects (DTG + RPV 8, CAR 6) reported a total of 18 SAEs with an onset during the Late Switch Phase, none of which were considered related to study treatment (Data Source: 201636/201637 Listing 22). These are listed below.

Early Switch DTG + RPV subjects (i.e., randomized to DTG + RPV at Baseline) who reported an SAE onset during the Late Switch Phase:

- Subject [redacted] experienced Grade 4 non-small cell lung cancer and a Grade 2 SAE of procedural pneumothorax (Day 428 for both events)

- Subject [redacted] experienced Grade 2 hemorrhoidal hemorrhage (Day 411)
- Subject [redacted] experienced Grade 3 ovarian cyst (Day 385)
- Subject [redacted] experienced Grade 3 abscess (Day 485), a Grade 3 anal squamous cell carcinoma (Day 457 onset), and a Grade 3 metastases to lymph nodes (Day 457 onset)
- Subject [redacted] experienced Grade 3 periorbital cellulitis (Day 391)
- Subject [redacted] experienced Grade 2 ligament rupture (Day 372)
- Subject [redacted] experienced Grade 1 basal cell carcinoma (Day 379)
- Subject [redacted] experienced Grade 2 abdominal pain and Grade 2 vomiting (Day 369 for both events)

Late Switch DTG + RPV subjects (i.e., randomized to CAR at Baseline) who reported an SAE onset during the Late Switch Phase:

- Subject [redacted] experienced Grade 4 pulmonary embolism (20 days after switching to DTG + RPV)
- Subject [redacted] experienced Grade 3 arthritis bacterial (122 days after switching to DTG + RPV)
- Subject [redacted] experienced Grade 3 thyroid cancer (35 days after switching to DTG + RPV)
- Subject [redacted] experienced Grade 3 pericarditis (46 days after switching to DTG + RPV)
- Subject [redacted] experienced Grade 2 Hodgkin's disease (87 days after switching to DTG + RPV)
- Subject [redacted] experienced Grade 3 groin abscess (103 days after switching to DTG + RPV)

2.1.4. Drug-Related Serious Adverse Events

Five subjects experienced SAEs considered by the Investigator to be drug-related (DTG + RPV 4, CAR 1) (Data Source: 201636/201637 Table 3.200), all during the Early Switch Phase. Brief descriptions are provided below and additional details are provided in study 201636 CSR Section 15.2 and study 201637 CSR Section 15.2. There were no drug-related SAEs reported with an onset during the Late Switch Phase (Data Source: 201636/201637 CSR Listing 22).

SAEs considered by the investigator to be related to study treatment (DTG + RPV) (n=4):

- **Subject [redacted] (SAE - Pancreatitis acute)** is a 3[redacted] year old male with a past medical history of fatty food and alcohol intake, including a significantly higher alcohol and fatty food intake than usual reported for the week prior to the SAE. The subject had a Baseline lipase value of 173 U/L (normal range of 7-60). At the Week 24 visit (Day 174), the subject was symptomless, but had a Grade 4 increase in lipase (to 1153 U/L per the site [or 228 U/L converted data for normal range of 7 - 60]). The subject's lipase was 2200 U/L per the site the following day upon re-test, he described a slight abdominal pain, and was hospitalized (serious criteria included this hospitalization as well as "GSK medically significant"). The subject was treated with glucose + dextrose. DTG and RPV were discontinued. The day following discontinuation of DTG + RPV, the subject did not have any sign or symptoms, there were no findings from an abdomen CT examination, and lipase values normalized; lipase remained in the normal range and the SAE of pancreatitis acute was considered recovered/resolved 3 days after hospitalization (lipase 218 U/L). There was no evidence of clinical pancreatitis.
- **Subject [redacted] (SAE - Drug-induced liver injury)** is a 5[redacted] year old male. The subject had a Baseline current history of drug related liver disease (Data Source: 201636/201637 Listing 43). On Day 34 after the first dose of DTG + RPV, the subject developed severe Grade 3 drug-induced liver injury (ALT 466 IU/L [Grade 3], AST 696 IU/L [Grade 4], bilirubin 38 μmol/L [Grade 2]) (Data Source: 201636/201637 Listing 28). The subject reported right hypochondrium pain (persistent, not colic), associated with choluria, and no other symptoms of hepatitis. DTG and RPV were discontinued 3 days later when laboratory results became available. ALT, AST, and bilirubin had returned to within the normal range at a subsequent Follow-up on study Day 45. This case does not meet criteria for serious hepatotoxicity as bilirubin increased <2 x ULN and direct bilirubin was also <35%.
- **Subject [redacted] (SAE – Depression)** is a 3[redacted] year old male with an onset at Day 214 of Grade 3 depression (verbatim text: worsening of depressive disorder) that was considered serious, related to study drug, and led to withdrawal. At Baseline, the subject had a past history of depression (Data Source: 201636/201637 Listing 43) and had been taking a regimen of RAL + TDF/FTC (Data Source: 201636/201637 Listing 48). The subject was hospitalized 27 days later due to depressive disorder with suicidal tendencies, and DTG and RPV were discontinued. The subject was treated with lorazepam and venlafaxine (Data Source: 201636/201637 Listing 44). The subject reported a "nervous breakdown" 10 years early, which recovered without any medical/psychiatric intervention; for the current episode, the subject reported no psycho-social stressors. Relevant tests included: Montgomery-Asperg-Depression- Rating-Scale (MADRS; initial, 26 points; at discharge, 3 Points [mild = 12-21, moderate = 21-28, severe = >28]); Beck-Depressions-Inventar (BDI-II; initial, not done; at discharge, 0 points [mild depression = 14-19, moderate depression = 20-28, severe depression = >28]). The outcome of the depression was not recovered/not resolved at the time of the Week 48 analysis cut-off date although there was improvement as evidenced by the result of the MADRS.

- **Subject [redacted] (SAE – Eosinophilic pneumonia acute)** is a 5[redacted] year old non-smoking female with an onset on 5th January a* (Day 195) of Grade 3 eosinophilic pneumonia acute. The subject received her first dose of study treatment in June [redacted], but had been taking DTG since April b* . Concomitant products included azithromycin, fluticasone propionate, salmeterol xinafoate, prednisone, cefuroxime, ranitidine, and flurazepam. The subject was hospitalized and treated with methylprednisolone, meropenem, moxifloxacin, paracetamol, codeine, insulin nos, levofloxacin, acetylcysteine, and paracetamol. Thoracic TC on 20 January a* showed interstitial subpleural, patch, moderate affectation suggestive of infectious involvement. A bronchoalveolar lavage (29 January a*) showed inflammatory smear with polymorphonuclear neutrophils predominance (65%) and macrophages (35%); not eosinophils; negative for malignant cells. On 03 February a*, C-reactive protein result was 20.37 mg/dL (normal low: 0.00, normal high: 0.5) and eosinophil count result was '1400 ul' (normal low: 0.00, normal high: 0.4). Once the different infectious diseases differential diagnoses (bacterial, fungal and parasitic) were discarded, treatment began on 06/feb/ a* with corticosteroids at doses of 1 mg / kg of methylprednisolone. After 3 days there was a clinical and radiological improvement of the process. The outcome of eosinophilic pneumonia acute was not recovered/not resolved on 08 February a* , but the subject was discharged from the hospital on 08 February a* and continued on corticoids treatment. DTG and RPV were discontinued on 23-Feb- a* . Follow up visit performed on 23-Mar- a* .

SAEs considered by the investigator to be related to study treatment (CAR) (n=1):

- **Subject [redacted] (SAE – Suicide attempt)** is a 3[redacted] year old female who was receiving EFV/FTC/TDF fixed-dose combination. The subject's past medical history included anxiety; concomitant products included lorazepam. On Day 80, the subject developed a Grade 4 suicide attempt, presented as an emergency department visit with "a lot of anxiety and suicidal thoughts". The event was considered resolved within 5 days. The subject was withdrawn from study the day following onset of this SAE.

2.1.5. Other Significant Adverse Events

Adverse events leading to withdrawal/permanent discontinuation of study treatment are presented below in Section 2.1.5.1. There were no other significant AEs.

2.1.5.1. Adverse Events Leading to Withdrawal

During the Early Switch Phase, 21 (4%) subjects in the DTG + RPV group and 3 (<1%) subjects in the CAR group experienced AEs leading to withdrawal/permanent discontinuation of study treatment (Table 18 and Data Source: 201636/201637 Table 3.230). AEs leading to withdrawal were most frequently reported from the psychiatric disorders (DTG + RPV, 9; CAR, 1) and GI disorders (DTG + RPV, 7) SOCs. All AEs leading to withdrawal had an incidence of <1%.

During the Late Switch Phase, an additional 6 subjects discontinued due to AEs (1 randomized to DTG + RPV at Baseline and 5 who switched to DTG + RPV at Week 52) (Table 18).

a*: Following year
b*: 4 years ago

Baseline ART third-agent class (PI, INSTI, or NNRTI) did not seem to influence withdrawals in the DTG + RPV treatment group. Of subjects switching to DTG + RPV at Baseline, 7 of 133 (5%) subjects switching from a PI-containing regimen, 8 of 275 (3%) subjects switching from an NNRTI-containing regimen, and 6 of 105 (6%) subjects switching from an INSTI-containing regimen had an AE leading to withdrawal/ permanent discontinuation of study treatment during the Early Switch Phase (Data Source: 201636/201637 Table 3.780).

Table 18 Listing of Subjects Who Experienced AEs Leading to Withdrawal/Permanent Discontinuation of Study Drug in Study 201636 and Study 201637 (Safety Population)

Subject ID	AE Preferred Term(s)	Phase[a]	Study Day (Days Since Switch[b])	Maximum Intensity	Serious AE	Drug Related	Baseline Third-Agent (Class)
Subjects Randomized to DTG + RPV at Baseline							
[redacted]	Pancreatitis acute	Early Switch	174	Grade 4	Yes	Yes	ATV/RTV (PI)
[redacted]	Drug-induced liver injury	Early Switch	35	Grade 3	Yes	Yes	EFV (NNRTI)
	Eosinophilic pneumonia acute	Early Switch	195	Grade 3	Yes	Yes	DTG (INSTI)
	Depression	Early Switch	214	Grade 3	Yes	Yes	RAL (INSTI)
	Panic attack	Early Switch	313	Grade 3	Yes	No	EVG/COBI (INSTI)
	Anxiety	Early and Late Switch	313	Grade 4	No	Yes	
[redacted]	Plasmablastic lymphoma	Early Switch	29	Grade 3	Yes	No	DRV/RTV (PI)
[redacted]	Hodgkin's disease mixed cellularity stage unspecified	Early and Late Switch	345	Grade 3	Yes	No	EVG/COBI (INSTI)
[redacted]	Kaposi's sarcoma[c]	Early Switch	207	Grade 4	Yes	No	DRV/RTV (PI)
	Gastrointestinal haemorrhage	Early Switch	12	Grade 3	Yes	No	EFV (NNRTI)
	Abscess	Late Switch	485	Grade 3	Yes	No	RAL (INSTI)
	Anal squamous cell carcinoma	Late Switch	457	Grade 3	Yes	No	
	Metastases to lymph nodes	Late Switch	457	Grade 3	Yes	No	
[redacted]	Depression	Early Switch	238	Grade 3	No	Yes	NVP (NNRTI)
	Peptic ulcer	Early Switch	128	Grade 3	No	No	DRV/RTV (PI)
	Abdominal distension	Early Switch	2	Grade 1	No	Yes	DRV/RTV (PI)
	Anxiety	Early Switch	119	Grade 1	No	Yes	
[redacted]	Tremor	Early Switch	31	Grade 3	No	Yes	EFV (NNRTI)
	Suicidal ideation	Early Switch	57	Grade 3	No	Yes	DRV/RTV (PI)
	Dyspepsia	Early Switch	12	Grade 2	No	Yes	RAL (INSTI)
	Headache	Early Switch	90	Grade 2	No	Yes	
[redacted]	Abdominal distension	Early Switch	1	Grade 2	No	Yes	EFV (NNRTI)
	Dyspepsia	Early Switch	59	Grade 2	No	Yes	RAL (INSTI)
	Anxiety (verbatim text: anguish)	Early Switch	6	Grade 2	No	Yes	LPV/RTV (PI)
	Anxiety (verbatim text: anxiety)	Early Switch	6	Grade 2	No	Yes	
	Depression	Early Switch	6	Grade 2	No	Yes	
[redacted]	Depressed mood	Early Switch	2	Grade 2	No	Yes	EFV (NNRTI)
	Insomnia	Early Switch	2	Grade 1	No	No	

Subject ID	AE Preferred Term(s)	Phase[a]	Study Day (Days Since Switch[b])	Maximum Intensity	Serious AE	Drug Related	Baseline Third-Agent (Class)
[redacted]	Insomnia	Early and Late Switch	331	Grade 1	No	No	EFV (NNRTI)
[redacted]	Anxiety	Early Switch	192	Grade 2	No	No	EFV (NNRTI)
Subjects Randomized to CAR at Baseline							
[redacted]	Suicide attempt	Early Switch	80	Grade 4	Yes	Yes	EFV (NNRTI)
[redacted]	Hodgkin's disease	Late Switch	447 (87)	Grade 2	Yes	No	EFV (NNRTI)
[redacted]	Lung neoplasm malignant[c]	Early Switch	164	Grade 3	Yes	No	ATV (unboosted PI)
[redacted]	Breast cancer	Early Switch	185	Grade 3	Yes	No	ATV (unboosted PI)
[redacted]	Blood glucose increased	Late Switch	391 (29)	Grade 2	No	Yes	NVP (NNRTI)
	Transaminases increased	Late Switch	391 (29)	Grade 2	No	Yes	
[redacted]	Pain in extremity (verbatim text: pain in finger left hand)	Late Switch	395 (31)	Grade 2	No	Yes	EFV (NNRTI)
	Eczema	Late Switch	399 (35)	Grade 1	No	Yes	
	Pain in extremity (verbatim text: foot plant pain)	Late Switch	419 (55)	Grade 2	No	Yes	
	Pain in extremity (verbatim text: pain in right hand)	Late Switch	419 (55)	Grade 2	No	Yes	
	Diarrhoea	Late Switch	420 (56)	Grade 1	No	Yes	
	Abdominal distension	Late Switch	420 (56)	Grade 2	No	Yes	
	Constipation	Late Switch	424 (60)	Grade 2	No	Yes	
[redacted]	Abulia	Late Switch	370 (6)	Grade 2	No	Yes	DTG (INSTI)
	Aphasia	Late Switch	370 (6)	Grade 2	No	Yes	
	Chest discomfort	Late Switch	423 (59)	Grade 2	No	Yes	
	Confusional state	Late Switch	370 (6)	Grade 2	No	Yes	
	Disturbance in attention	Late Switch	370 (6)	Grade 2	No	Yes	
[redacted]	Abortion induced	Late Switch	406 (42)	Grade 1	No	No	NVP (NNRTI)

Data Source: 201636/201637 Listing 16, Listing 18, Listing 23, and Listing 48

a. Early Switch indicates the event occurred prior to the Week 52 visit; Late Switch indicates the event occurred at or after the Week 52 visit

b. Days Since Switch = number of days from the switch to DTG + RPV at Week 52 to the onset of the event; calculated for CAR group subjects who had an event leading to withdrawal with an onset in the Late Switch Phase (i.e., after subject switched to DTG + RPV)

c. Outcome was fatal (see Section 2.1.2)

2.1.6. Analysis of Adverse Events by Organ System or Syndrome

For DTG + RPV, adverse events of special interest (AESIs) are based on the identified and potential ongoing risks recognized for DTG and RPV. Data on these risks arose during the original non-clinical and clinical development programs for DTG and RPV (i.e., hypersensitivity for DTG, severe skin reactions for RPV) or through post marketing surveillance activities (e.g., depression and suicidal behavior for DTG) and are discussed in this section. Based on this information, the AESIs for the DTG + RPV were identified and are described in Table 19.

Some of the AESIs included in this section are best addressed in conjunction with laboratory data or vital signs. Where this applies, readers are cross-referred to the appropriate subsection on Clinical Laboratory Evaluations or Vital Signs (Section 3 or Section 4, respectively) where all of the applicable data (e.g., laboratory and clinical events) are discussed together.

Event terms were pre-determined for the DTG + RPV AESI groupings at the time of planning the analyses and were defined in the SDAP. At the time of final integrated database compilation of the Phase III studies, the project safety development leader reviewed all the verbatim terms and MedDRA terms by SOC in a blinded manner to identify any other terms that should be included in the AESI analyses.

AESI summary tables were produced for rash, drug hypersensitivity, insomnia, nightmare/abnormal dreams, anxiety, depression and suicidality, which summarized the following event characteristics data separately: serious, drug related, severe or Grade 3/4, fatal, number of events per subject, outcome, maximum grade/intensity, action taken, time to onset, and duration of all events. For outcome and action taken, if a subject had multiple events, that subject was counted once for each unique outcome or action taken. Time to onset and duration of first event were also summarized separately. For depression and suicidality, relevant events by maximum DAIDS grade were produced separately for subjects with and without a previous history of depression or anxiety.

Table 19 Adverse Events of Special Interest for DTG/RPV FDC

AESI	Description
Hypersensitivity Reaction DTG Section 2.1.6.1	DTG: HSR has been reported with integrase inhibitors, and has been observed uncommonly with DTG. HSR is characterized by rash, constitutional findings, and sometimes, organ dysfunction, including liver injury.
Hepatobiliary disorders DTG, RPV Section 2.1.6.2	DTG: Non-clinical data suggested a possible, albeit low, risk for hepatobiliary toxicity with DTG. From analysis of integrated Phase IIb and III clinical trial data, drug-related hepatitis is considered an uncommon risk for ART containing DTG regardless of dose or treatment population. For subjects with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, improvements in immunosuppression as a result of HIV virologic and immunologic responses to DTG-containing ART, along with inadequate therapy for HBV co-infected subjects, likely contributed to significant elevations in liver chemistries. RPV: Hepatic events have been reported in patients receiving a RPV containing regimen. Patients with underlying HBV or HCV, or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations with use of RPV.
Psychiatric disorders including depression and suicidality DTG, RPV Section 2.1.6.3	DTG: Psychiatric disorders including suicidal ideation and behaviors are common in HIV-infected patients. Psychiatric disorders including suicide ideation and behaviors are listed events in the Local Country Prescribing Information for RAL. From analysis of integrated Phase IIb and III clinical study data, the psychiatric profile for DTG (including suicidality, depression, bipolar and hypomania, anxiety, and abnormal dreams) was favorable compared with EFV and similar to RAL. Following a review of post-marketing and clinical trial data, depression, suicidal ideation and behaviors were added to the DTG label and informed consent documents, prior to FSFV. While the reporting rate for insomnia was statically higher for blinded DTG+ABC/3TC compared with EFV in Study ING114467, this was not duplicated by any other Phase IIb/III study conducted with DTG. RPV: In Phase III clinical trials the incidence and grading of depressive disorders (regardless of causality), and the incidence of episodes resulting in subject withdrawal, were comparable between the RPV and EFV treatment groups. Most depressive disorder events in either treatment group were of Grade 1 or 2 intensity. Suicidal ideation was reported in 4 subjects in each arm while suicide attempt was reported in 2 subjects in the RPV arm.

AESI	Description
Drug resistance DTG, RPV Section 2.1.6.4	Resistance may develop to any antiretroviral regimen particularly in the setting of incomplete adherence to therapy.
Skin and subcutaneous tissues disorders DTG, RPV Section 2.1.6.5	DTG: Rash was commonly reported in DTG Phase IIb/III clinical trials; episodes were generally mild to moderate in intensity; no episodes of severe rash, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, and erythema multiforme were reported. Severe, potentially life-threatening, and fatal skin reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis) are listed events in the Local Country Prescribing Information for RAL. RPV: Rash is a recognized risk for the NNRTI class; however, the severe rashes defined above that are labeled for EFV and NVP were not seen with RPV in clinical trials. In Phase III clinical trials, skin events of interest were reported at a lower incidence and grades, and resulted in fewer subject withdrawals in the RPV group than in the EFV group and were mostly driven by the individual preferred term “rash”.
Gastrointestinal disorders DTG Section 2.1.6.6	DTG: Non- clinical toxicology studies showed upper and lower GI toxicity, including vomiting, diarrhea and gastric erosions observed in monkey toxicology studies (thought to be related to local toxicity).
Renal and urinary disorders DTG, RPV Section 2.1.6.7 and Section 3.1.2	DTG: Mild elevations of creatinine have been observed with DTG, which are related to a likely benign effect on creatinine secretion with blockade of OCT-2. DTG has been shown to have no significant effect on glomerular filtration rate or effective renal plasma flow. RPV: Small increases in creatinine were observed in RPV clinical program. RPV has been shown to inhibit OCT-2. The pattern observed does not indicate RPV-induced nephrotoxicity.
Musculoskeletal and connective tissue disorders DTG Section 2.1.6.8 and Section 3.1.3	DTG: Rhabdomyolysis and myositis are listed events in the Local Country Prescribing Information for RAL. During the studies, arthralgia and myalgia were added to the DTG label but no changes were considered necessary to the ICF documents, as these events are already included in the ICF in the context of Warning and Precaution on the risk of HSR. Rhabdomyolysis and myositis are not considered signals for DTG. Asymptomatic CPK elevations mainly in association with exercise have been reported with DTG therapy.

AESI	Description
Grade 3 to 4 lipase elevations and pancreatitis DTG Section 2.1.6.9 and Section 3.1.4	DTG: No nonclinical findings for lipase elevations were observed with DTG. Although transient and asymptomatic lipase elevations are common in subjects with HIV infection [Argiris, 1999] and pancreatitis has been associated with some ART drugs.

2.1.6.1. Hypersensitivity

METHOD

Data for the DTG + RPV are presented to address this risk.

RESULTS

At the data cut-off for this Week 48 analysis, 2 subjects in the Early Switch Phase (1 in the DTG + RPV treatment group and 1 in the CAR treatment group) (Data Source: 201636/201637 Table 3.804) and 2 subjects in the Late Switch Phase (taking DTG + RPV) reported events coded to the preferred terms of either "hypersensitivity" or "drug hypersensitivity". The 3 events reported in subjects taking DTG + RPV were Grade 1; the event reported in the CAR group was Grade 2. None of the events were considered related to study treatment and none of the events resulted in withdrawal of study treatment or withdrawal from the study. Two of these events were reported as allergy to a drug other than study treatment (Data Source: 201636/201637 Listing 18).

2.1.6.2. Hepatobiliary Disorders

Adverse events and liver chemistries are discussed in Section 3.1.1.

2.1.6.3. Psychiatric Disorders Including Depression and Suicidality

METHOD

Data for DTG + RPV are presented to address this risk.

Psychiatric terms were split into five separate groups of special interest:

1. Insomnia: Preferred terms containing 'insomnia';
2. Nightmare/abnormal dreams: Preferred terms of nightmare or abnormal dreams;
3. Anxiety: Preferred terms of anxiety or nervousness;
4. Depression: Preferred terms of depressed mood, depression, depressive, hypomania or bipolar;
5. Suicidality: Preferred terms containing 'suicide', 'suicidal' or intentional self-injury.

These were identified from the DTG + RPV ISO data, and were included in the SAS AESI summary tables in the ISO.

RESULTS

Adverse events in the psychiatric disorders SOC were reported more frequently in the DTG + RPV treatment group (DTG + RPV 12%, CAR 6%) (Data Source: 201636/201637 Table 3.040). Insomnia (3%), depression (3%), anxiety (2%), and abnormal dreams (1%) were the most commonly reported individual AE preferred terms from this SOC in the DTG + RPV treatment group, and all other AE preferred terms from this SOC were reported in <1% of subjects. In the CAR treatment group, insomnia (2%),

anxiety (2%), and depression (1%) were the most commonly reported AE preferred terms, and all other AE preferred terms from this SOC were reported in <1% of subjects.

The majority of the events in both treatment groups were considered Grade 1 or 2 (Data Source: 201636/201637 Table 3.053). Of 61 subjects in the DTG + RPV group reporting any event from the psychiatric disorders SOC, 3 reported Grade 3 events and 2 reported Grade 4 events; of 32 subjects in the CAR group reporting any event from this SOC, 1 reported a Grade 3 event and 1 reported a Grade 4 event.

The incidence of insomnia was low and comparable in both treatment groups (DTG + RPV 3%, CAR 2%). Nightmare and abnormal dreams were reported in 7 subjects (1%) in the DTG + RPV treatment group, with none in the CAR group. This is a listed event for both DTG and RPV. The incidence of anxiety was low (2% in both treatment groups).

Although the incidence of depression and suicidal behaviors was higher in those with a previous history of anxiety or depression (12%) compared with those without a history (3%) in the DTG + RPV treatment group, the majority of patients with this history (100/114) did not report recurrences during the study. In the CAR group 5% of subjects with a history of anxiety or depression reported depression or suicidal behavior compared with 1% who did not have a history (Data Source: 201636/201637 Table 3.825).

The reporting rate for AEs relating to depression (preferred terms containing "depression", "depressed mood", "depressive", "hypomania", or "bipolar") was higher in the DTG + RPV treatment group (22, 4%) compared with the CAR treatment group (8, 2%). All events were single occurrences in both treatment groups. Median time to onset was 196 days (range 2 to 334 days) in the DTG + RPV treatment group and 136.5 days (range 6 to 338 days) in the CAR treatment group. There were 6 events considered drug-related in the DTG + RPV treatment group and none in the CAR group.

Nine subjects in the DTG + RPV group withdrew due to an event from the psychiatric disorders SOC (Data Source: 201636/201637 Table 3.230, Listing 23, and Listing 43):

- Subject [redacted] due to an AE of depression, who had a current history at Baseline of depression, anxiety, and sleep disorder;
- Subject [redacted] due to an AE of anxiety;
- Subject [redacted] due to AEs of anxiety and panic attack, who had a past history of panic attacks and depression;
- Subject [redacted] due to an AE of insomnia, who had a current history at Baseline of sleep disorder;
- Subject [redacted] due to suicidal ideation, who had a past history of depression;
- Subject [redacted] due to an AE of depression, who had a past history of depression;
- Subject [redacted] due to AEs of depression and anxiety;
- [redacted] due to AEs of depressed mood and insomnia, who had a past history of sleep disorder and current history of anxiety at Baseline;
- Subject [redacted] due to an AE of anxiety.

One subject in the CAR group ([redacted]) withdrew during the Early Switch Phase after a suicide attempt (see Section 2.1.4).

Drug-related AEs in the psychiatric disorders SOC were also reported more frequently in the DTG + RPV treatment group (DTG + RPV 5%, CAR <1%) (Data Source: 201636/201637 Table 3.123). The majority of these drug-related events were Grade 1 with ≤1% of subjects reporting events from this SOC for any category of Grade 2, Grade 3, or Grade 4 drug-related events. In the DTG + RPV treatment group, 1 drug-related AE of anxiety was considered Grade 4 and 2 drug-related AEs of depression and 1 drug-related AE of suicidal ideation were considered Grade 3. One Grade 4 drug-related suicide attempt was reported in the CAR treatment group.

Suicidality:

The reporting rate for AEs relating to suicidal behaviors (preferred terms containing "suicide", "suicidal", or "intentional self-injury") was low and comparable across the treatment groups (DTG + RPV 4 [<1%], CAR 3 [<1%]). One of the CAR group subjects reported a suicidal behavior with 2 occurrences; all other events in both treatment groups were single occurrences. Two subjects (1 in each treatment group) reported an event that was considered drug-related and led to withdrawal (Grade 3 suicidal ideation in DTG + RPV Subject [redacted] who had a past history of depression; Grade 4 suicide attempt in CAR Subject [redacted]); all events reported in the remaining 5 subjects were considered not related to study treatment and did not lead to withdrawal. Of these 5 remaining subjects, 1 subject reported a Grade 4 event (suicidal ideation in DTG + RPV Subject [redacted] who had a current history of depression; this event was later confirmed to be a suicide attempt and not just ideation), and all other events

were Grade 1 or 2. Three of the 4 subjects in the DTG + RPV group had a history of depression (2 current, 1 past) and 1 of 3 subjects in the CAR group had a history of current depression. Time to onset was 26, 57, 151 and 172 days for the DTG + RPV group subjects and 28, 80 and 338 days for the CAR group subjects (Data Source: 201636/201637 Table 3.817). All events were reported as recovered or recovered with sequelae. None of the events resulted in completed suicide (Data Source: 201636/201637 Table 3.810, Table 3.817, and Listing 43).

In addition to events reported on AE or SAE forms, events of suicidal ideation and behavior were also identified via the Possible Suicide Related Adverse Events (PSRAE) forms. Suicidality assessments were also administered via the electronic Columbia Suicidality Severity Rating Scale (eC-SSRS). Findings from both are further detailed below.

By review of the PSRAE forms, 3 additional cases were identified post database freeze of subjects with suicidal behaviors (all in the DTG + RPV group). The Investigator sites did not complete AE forms for these events; hence, these are not accounted for in the AE data listing or tables.

- **Subject** [redacted] (see Section 7.3.5.1 of the 201636 Week 48 CSR for a narrative) reported an AE of worsening depression, which led to withdrawal. However, this subject also had suicidal ideation, described on the PSRAE form, but this was not reported in the eCRF and therefore did not appear in the statistical outputs.

- **Subject** [redacted] (see Section 7.3.5.1 of the 201636 Week 48 CSR for a narrative) reported a PSRAE of passive suicidality. There was not a corresponding AE entered in the eCRF and therefore this subject did not appear in the statistical outputs.

- **Subject** [redacted] did report an SAE of worsening depression, which led to withdrawal (see Section 2.1.4 for a narrative for this SAE). Suicidal ideation was also indicated on the PSRAE form for this subject (described as worsening of depressive disorders with "suicidal tendencies"). However, an AE of suicidal ideation was not reported in the eCRF and therefore did not appear in the statistical outputs.

These 3 subjects identified by review of the PSRAE forms did not have positive alerts on the eC-SSRS.

As described above, based on the AEs entered by the site/Investigator, the incidence of subjects who reported suicidal ideation or behavior post Baseline was low in both treatment groups. Most of these AEs of suicidal ideas or behaviors were identified through the eC-SSRS alerts.

The definitions of behavioral suicidal events used in eC-SSRS are based on those used in the Columbia Suicide History Form [Posner, 2007; Posner, 2011]. The eC-SSRS was self-administered by subjects via telephone or using a computer/tablet connected to the internet. Assessments administered via the eC-SSRS include levels 1-9, with positive

alerts sent to the Sponsor and site for level 4 or 5 ideation or any suicidal behavior (levels 6-9). Levels 1-3 of ideation are distinct from levels 4 and 5 because they do not include any intent to act. If a subject has only level 1-3 ideation or non-suicidal self injurious behavior, a positive alert is not sent to the Sponsor or the site, but all reports are still expected to be reviewed by the site.

There are no source notes for this subject reported data. Therefore, on receipt of a positive alert of suicide ideation or behavior (levels 4-9) from the vendor (ERT), the Sponsor's study team and the vendor prompted the site in real time to follow up with the subject for validation of the alert and for clinical management, if appropriate. In some cases, the alert was not confirmed as positive due to subject error or not confirmed following subject interview at site. Due to the potential for subject error, which could result in false alerts, the study team maintained a real time log of known incorrect entries.

Based on the eC-SSRS source table and the real-time log of known incorrect subject entries (based on information provided by the site in response to the ERT alert), there were 16 subjects with positive ERT alerts post Baseline (11 subjects in the DTG + RPV group; 5 subjects in the CAR group). Of these 16 subjects, 7 subjects had validated true positive alerts (4 subjects in DTG +RPV group; 3 subjects in the CAR group) and the other 9 subjects were confirmed to have either entered responses into the eC-SSRS in error (4 subjects in the DTG + RPV group; 0 subjects in the CAR group) or were confirmed by the Investigator on interview not to have any suicidal risk (3 subjects in the DTG + RPV group; 2 subjects in the CAR group). The clinical events leading to the validated true positive post Baseline alerts are documented in the PSRAE (and AE or SAE forms).

Brief narratives for subjects having validated post Baseline positive eC-SSRS alerts are provided below.

DTG +RPV treatment group:

- **Subject** [redacted] had a current history of depression recorded in the eCRF and a positive eC-SSRS assessment at Baseline and evidence of prior self harm listed on the PSRAE form. He reported a positive eC-SSRS assessment at Week 4 after experiencing an AE of intention to suicide (verbatim text) on 21-Aug- [redacted]. The verbatim text was incorrectly coded to suicide ideation but was actually a suicide attempt. The AE resolved with sequelae the same day and was deemed by the investigator to be unrelated to study treatment. The subject interrupted study treatment due to the AE from 27-Jul- a* through 20-Aug- a* and then continued to receive study treatment starting on 21-Aug- a*. The subject underwent medical/psychiatric evaluations and treatment with hyperbaric oxygen therapy. The subject reported an additional positive eC-SSRS assessment at Week 12 but was considered by the investigator to be in stable condition and he remains in the study.

a*: The year

* 新薬承認情報提供時に置き換え

- **Subject** [redacted] was negative in eCRF for past or current history of depression at Baseline and did not have an ERT alert at Baseline. An ERT alert was reported at Week 12 due to suicidal ideation, but the PSRAE and SAE forms describe a suicide attempt of low lethality considered by the investigator to be unrelated to study treatment. The subject recovered from the suicide attempt on the day of the attempt and remains on study.

- **Subject** [redacted] had a past history of depression and adjustment disorder recorded in eCRF. The subject did not have an ERT alert at Baseline, however, an ERT alert was reported at Week 24 due to marked suicidal ideation. The PSRAE form describes massive suicidal thoughts experienced by the subject in association with amphetamine, crystal, and speed use and regular alcohol consumption. This AE recorded in the eCRF was considered by the investigator to be attributable to study treatment, with resolution 40 days following onset. The subject was withdrawn from study due to this AE of suicidal ideation.

- **Subject** [redacted] had a current medical history recorded in the eCRF at Day 1 that included generalized anxiety disorder, obsessive-compulsive disorder, mood disorder due to general medical condition, and depression. The subject had a positive ERT alert at Baseline, however, the Investigator, on review, considered the subject eligible for the study. Grade 2 suicidal thoughts and Grade 2 intermittent panic attacks, both not related to study treatment, were recorded during the study period in the eCRF. The positive ERT alert at Week 24 was due to the subject's report of suicidal ideation and one attempted suicide. The PSRAE form completed at Week 24 reports suicidal ideation with no specific plans, past history of agoraphobia, and past suicidal ideation, and reports the subject is a crystal meth user. This AE of suicidal ideation recorded in the eCRF resolved 81 days following onset, and was considered by the Investigator not to be attributable to study treatment. The subject remains on study.

CAR treatment group:

- **Subject** [redacted] had a current history of depression and sleep disorder recorded in the eCRF and a positive eC-SSRS assessment at Baseline. The subject reported positive eC-SSRS assessments at Weeks 4 and 8 that were consistent with past medical history and did not meet the definition of AE. At Week 48, the subject reported a positive eC-SSRS assessment after experiencing an AE of suicidal ideation on14-Jun-[redacted]. The AE resolved on 9-Aug- a* and was deemed by the investigator to be unrelated to study treatment. The subject continued to receive study treatment.

a*: The year

* 新薬承認情報提供時に置き換え

- **Subject** [redacted] had no past or current history of depression recorded in the eCRF but had a positive eC-SSRS assessment at Baseline and evidence of past history of suicide attempt listed on PSRAE form. The subject reported a positive eC-SSRS assessment at Week 4 after experiencing an AE of suicide ideation on 24-Aug-[redacted]. The AE resolved on 21-Sept- a* and was deemed by the investigator to be unrelated to study treatment. The subject reported a positive eC-SSRS assessment at Week 48 after experiencing an AE of suicide ideation on 13-Jun- b* . The AE resolved on 22-Aug- b* and was deemed by the investigator to be unrelated to study treatment. The subject continued to receive study treatment. The subject remains under the care of a psychologist.

- **Subject** [redacted] was negative in the eCRF for a past or current history of depression at Baseline. The subject had positive ERT alerts at Baseline due to a subject-reported past history of suicidal ideation and at Week 12 due to suicidal ideation and a suicide attempt. The PSRAE form describes a suicide attempt. The SAE form describes the suicide attempt as being resolved 4 days following the attempt, and as attributable to study medication and leading to the withdrawal of the subject from study.

2.1.6.4. Drug Resistance

Drug resistance is discussed in m2.7.2.4.

Resistance may develop to any antiretroviral regimen particularly in the setting of incomplete adherence to therapy.

Overall, a single occurrence of genotypic substitution without increase in phenotype was observed, yet this was in a non-adherent subject. Further, given the lack of plasma Baseline resistance testing, and that the subject responded to <50 c/mL HIV-1 RNA on resumption of DTG + RPV therapy, it is not possible to quantify the risk of developing clinical resistance to DTG + RPV based on this single subject's data.

2.1.6.5. Skin and Subcutaneous Tissues Disorders

METHOD

Data for DTG + RPV combination are presented to address this risk.

For rash AESIs, any events related to a rash were identified for the DTG + RPV ISO by searching for preferred terms containing the words "rash", "eruption", "photosensitivity", or "urticaria", such as rash erythematous, rash generalized, rash papular, rash pruritic, toxic skin eruption, photosensitivity, and urticaria. There were no reports in the database for severe rash with terms that included Stevens-Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme.

RESULTS

Rash AESIs identified in the ISO (i.e., identified using key words as described above) were reported in 22 (4%) subjects in the DTG + RPV group and 7 (1%) subjects in the

a*: The year
b*: Following year

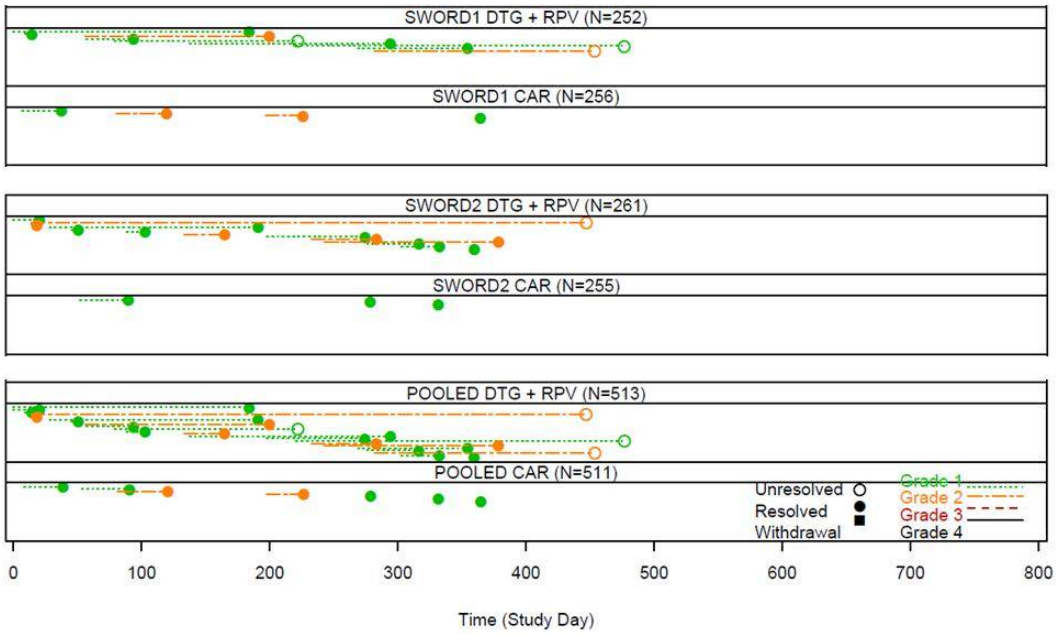
CAR group (ISO Table 3.803). There were no rash AESIs that were serious, Grade 3-4 or severe, lead to withdrawal, or fatal. Six of the rash AESIs (all in the DTG + RPV group) were considered drug related.

For events reported from the skin and subcutaneous tissue disorders SOC, a higher proportion of subjects reported events in the DTG + RPV treatment group (DTG + RPV 13%, CAR 9%) (Data Source: 201636/201637 Table 3.040). Except for the preferred term of "rash", which was reported at 2% in the DTG + RPV group, all other event preferred terms in both treatment groups were reported at ≤1%. (Note the preferred term of "rash" here is distinct from rash AESIs, which comprises "rash" plus other preferred terms). All events in the DTG + RPV treatment group were Grade 1 or 2; in the CAR group, 1 Grade 3 event was reported and all other events were considered Grade 1 or 2 (Data Source: 201636/201637 Table 3.053).

Drug-related AEs in the Skin and subcutaneous disorders SOC were reported in 2% of subjects in the DTG + RPV group and no (0%) subjects in the CAR group (Data Source: 201636/201637 Table 3.123). The only drug-related events reported in more than 1 subject were rash (4, <1%) and alopecia (2, <1%). All other drug-related skin events occurred in single subjects and included the following: eczema (Grade 1), hyperhidrosis (Grade 1), lipodystrophy acquired (Grade 1), nail disorder (Grade 1), photosensitivity reaction (Grade 2), pruritus (Grade 1), and rash pruritic (Grade 2). There were no Grade 3 or 4 drug-related skin events.

The onset, duration, and severity of the first occurrence of rash AESIs (excluding hypersensitivity) are shown in Figure 2. This plot demonstrates that first onset was spread over the study period for both treatment groups. Duration tended to be longer for events occurring in the DTG + RPV treatment group compared with the CAR treatment group.

Figure 2 Onset, Duration, and Severity of the First Occurrence of Post Baseline Rash AESIs (Excluding Hypersensitivity) during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)



Data Source: 201636/201637 Figure 3.801
Note: Events shown are those for which the preferred terms containing "rash", "eruption", "photosensitivity", or "urticaria".
Note: SWORD1 = 201636; SWORD2 = 201637

2.1.6.6. Gastrointestinal Disorders

METHOD

Data for the DTG + RPV combination are presented to further characterize this risk.

DTG + RPV: Events in 201636/201637 Table 3.053 from the gastrointestinal disorders SOC were identified.

RESULTS

GI disorders events were reported more frequently in the DTG + RPV treatment group (DTG + RPV, 25%; CAR, 16%). The most commonly reported events in both treatment groups were diarrhea and dyspepsia. In the DTG + RPV group, there were 5 Grade 3 events reported by 4 subjects (peptic ulcer, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, and gastrointestinal hemorrhage) and 1 Grade 4 event of acute pancreatitis (narrative provided in Section 2.1.4). All other events in the DTG + RPV group and all events in the CAR group were Grade 1 or 2 (Data Source: 201636/201637 Table 3.053).

Drug-related GI disorders were also reported more frequently in the DTG + RPV group (DTG + RPV 7%, CAR <1%) (Data Source: 201636/201637 Table 3.123).

The most commonly reported drug-related AE in the DTG + RPV group was diarrhea (2% of subjects) and for the CAR treatment group was dyspepsia (<1% of subjects). The majority of drug-related GI events in both treatment groups were Grade 1. Of drug-related events reported in the DTG + RPV group, 8 events were Grade 2 (3 events of diarrhea, 2 events each of dyspepsia and abdominal distension, and 1 event of constipation). There was 1 Grade 4 drug-related event reported in the DTG + RPV group of acute pancreatitis (narrative provided in Section 2.1.4). All other drug-related events in the DTG + RPV were considered Grade 1. All drug-related events reported in the CAR group were Grade 1 or 2.

There were 5 SAEs reported: acute pancreatitis, gastrointestinal hemorrhage, and gastroesophageal reflux disease in the DTG + RPV group; and anal fistula and proctitis in the CAR group (Data Source: 201636/201637 Table 3.160).

2.1.6.7. Renal Disorders

Adverse events, clinical chemistry, and urinalysis data are discussed in Section 3.1.2.

2.1.6.8. Musculoskeletal and Connective Tissue Disorders

The incidence of subjects reporting events in the musculoskeletal and connective tissue disorders SOC was comparable between the two treatment groups (DTG + RPV 15%, CAR 16%) (Data Source: 201636/201637 Table 3.040). No events of rhabdomyolysis were reported. The majority of events from this SOC were Grade 1 for both treatment groups (Data Source: 201636/201637 Table 3.053). Two subjects reported Grade 3 events (hemarthrosis in the DTG + RPV group and back pain in the CAR group); no Grade 4 events were reported in either group from the musculoskeletal and connective tissue disorders SOC. Three subjects in the DTG + RPV group reported drug-related events (arthralgia, muscle spasms, and musculoskeletal pain, all Grade 1), and no drug-related AEs were reported from the CAR group (Data Source: 201636/201637 Table 3.123).

Refer to Section 3.1.3 for information on changes in CPK and AEs of CPK elevations.

2.1.6.9. Grade 3 to 4 Lipase Elevations

Adverse events and laboratory data related to lipase elevations and pancreatitis are discussed in Section 3.1.4.

2.2. Narratives

Case narratives for all fatal SAEs and other SAEs reported through to the data cut-off date for the most recent analyses for each of the concerned studies are included in the corresponding CSRs as follow:

- 201636 Week 48 CSR Section 15.1 (Deaths) and Section 15.2 (SAEs)

- 201637 Week 48 CSR Section 15.1 (Deaths) and Section 15.2 (SAEs)

2.3. Labeling and Adverse Drug Reactions

Adverse reactions are listed by MedDRA body system organ class and by frequency category. Frequency categories are defined according to MedDRA convention, as follows:

Very common: ≥1/10

Common: ≥1/100 to <1/10

Uncommon: ≥1/1000 to <1/100

Rare: ≥1/10,000, <1/1000

Very Rare: <1/10,000

ADRs from Clinical Trials

All ADRs from Clinical Trials currently in the Reference Safety Information for DTG and RPV will be presented in the RSI for the DTG/RPV FDC (Table 20).

Adverse events judged by the investigator to be reasonably attributable to IMP with a frequency of at least 1% in the pooled DTG + RPV treatment group (see Table 14) were reviewed against those already listed in the labeling for the individual active moieties DTG and RPV (Table 20). Similarly, Grade 3 to 4 laboratory abnormalities of at least 1% in the pooled DTG + RPV treatment group were reviewed in the same way (Data Source: 201636/201637 Table 3.560).

The adverse reactions observed for the combination of DTG + RPV in analysis of pooled data were consistent with the adverse reaction profiles and severities for the individual components. No additional ADRs or increased frequency or severity of ADRs were observed with the combination of DTG + RPV.

This is followed by a description of clinically significant changes from Baseline in clinical chemistries, which were not considered ADRs for DTG or RPV per se by the Sponsor, but were considered worthy of mention in the Company Core Safety Information to assist prescribers with patient management. Where information was available for the DTG + RPV combination, this was added.

Table 20 Summary of ADRs Listed for the Individual Components of the DTG/RPV FDC Tablet Based on Clinical Trial Data

System	Frequency	DTG	RPV
Immune system disorders	Uncommon	Hypersensitivity Immune Reconstitution Syndrome	
Metabolism and nutrition disorders	Common		Decreased appetite

System	Frequency	DTG	RPV
Psychiatric disorders	Common	Insomnia Abnormal dreams Depression	Depression Insomnia Abnormal dreams Sleep disorders
	Uncommon	Suicidal ideation or suicide attempt (particularly in patients with a pre-existing history of depression or psychiatric illness)	Depressed mood
Nervous system disorders	Very common	Headache	
	Common	Dizziness	Headache Dizziness
	Uncommon		Somnolence
Gastrointestinal disorders	Very common	Nausea Diarrhoea	
	Common	Abdominal pain Vomiting Flatulence Upper abdominal pain Abdominal discomfort	Abdominal pain Nausea Vomiting
	Uncommon		Abdominal discomfort
Hepatobiliary disorders	Uncommon	Hepatitis	
Skin and subcutaneous tissue disorders	Common	Rash Pruritus	Rash
General disorders and administration site conditions	Common	Fatigue	Fatigue
Investigations	Common		Transaminases increased

Changes in Laboratory Chemistries

Increases in serum creatinine occurred within the first 4 weeks of treatment with DTG + RPV and remained stable through 48 weeks. A mean change from Baseline of 8.22 μmol/L (range: -26 μmol/L to 51.2 μmol/L) was observed after 48 weeks of treatment. These changes are not considered to be clinically relevant since they do not reflect a change in glomerular filtration rate (see Section 3.1.2).

Small increases in total bilirubin (without clinical jaundice) were observed. These changes are not considered clinically relevant as they likely reflect competition between DTG and unconjugated bilirubin for a common clearance pathway (UGT1A1) (see Section 5.3.1.

Asymptomatic CPK elevations mainly in association with exercise have also been reported (see Section 3.1.3).

ADRs from Post-Marketing Experience

In addition to the ADRs included from clinical trial data, below are the events identified during post-approval use of DTG in combination with other antiretroviral agents (i.e., from spontaneous ADR report data, epidemiological data, review of the medical literature and/or aggregate review of subsequent clinical trial data). These events have been chosen for inclusion due to a potential causal connection to DTG.

- **Musculoskeletal and connective disorders**: *Uncommon*: arthralgia, myalgia

3. CLINICAL LABORATORY EVALUATIONS

3.1. Clinical Chemistry

Graded treatment-emergent clinical toxicities in selected laboratory parameters of interest are summarized in Table 21. The majority of the post-baseline emergent clinical chemistry toxicities were Grade 1 or Grade 2 in intensity. Among the lipase elevations, there was a single asymptomatic event of pancreatitis (Subject [redacted]; Grade 4 pancreatitis acute) that occurred in a subject in the DTG + RPV treatment group (narrative provided in Section 2.1.4). Treatment-emergent lipid toxicities are discussed in Section 3.1.5.

Table 21 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Toxicities for Selected Laboratory Parameters during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Alanine Aminotransferase						
Grade 1	17 (7)	11 (4)	18 (7)	11 (4)	35 (7)	22 (4)
Grade 2	1 (<1)	4 (2)	7 (3)	0	8 (2)	4 (<1)
Grade 3	3 (1)	0	0	2 (<1)	3 (<1)	2 (<1)
Grade 4	0	1 (<1)	0	0	0	1 (<1)
Aspartate Aminotransferase						
Grade 1	11 (4)	8 (3)	14 (5)	8 (3)	25 (5)	16 (3)
Grade 2	1 (<1)	5 (2)	4 (2)	3 (1)	5 (<1)	8 (2)
Grade 3	2 (<1)	1 (<1)	0	2 (<1)	2 (<1)	3 (<1)
Grade 4	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Bilirubin						
Grade 1	9 (4)	5 (2)	8 (3)	5 (2)	17 (3)	10 (2)
Grade 2	6 (2)	10 (4)	5 (2)	8 (3)	11 (2)	18 (4)
Grade 3	0	7 (3)	0	4 (2)	0	11 (2)
Grade 4	0	2 (<1)	0	0	0	2 (<1)
Creatine Kinase						
Grade 1	7 (3)	9 (4)	12 (5)	10 (4)	19 (4)	19 (4)
Grade 2	1 (<1)	3 (1)	3 (1)	2 (<1)	4 (<1)	5 (<1)
Grade 3	2 (<1)	2 (<1)	1 (<1)	0	3 (<1)	2 (<1)
Grade 4	3 (1)	4 (2)	0	5 (2)	3 (<1)	9 (2)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Creatinine						
Grade 1	7 (3)	2 (<1)	3 (1)	1 (<1)	10 (2)	3 (<1)
Grade 2	0	1 (<1)	0	0	0	1 (<1)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Hyperglycemia						
Grade 1	25 (10)	25 (10)	28 (11)	25 (10)	53 (10)	50 (10)
Grade 2	9 (4)	16 (6)	12 (5)	10 (4)	21 (4)	26 (5)
Grade 3	3 (1)	0	2 (<1)	1 (<1)	5 (<1)	1 (<1)
Grade 4	0	0	0	0	0	0
Hypoglycemia						
Grade 1	4 (2)	4 (2)	6 (2)	2 (<1)	10 (2)	6 (1)
Grade 2	1 (<1)	3 (1)	0	0	1 (<1)	3 (<1)
Grade 3	0	0	1 (<1)	0	1 (<1)	0
Grade 4	0	1 (<1)	0	0	0	1 (<1)
Lipase						
Grade 1	9 (4)	19 (7)	6 (2)	19 (7)	15 (3)	38 (7)
Grade 2	10 (4)	13 (5)	15 (6)	11 (4)	25 (5)	24 (5)
Grade 3	6 (2)	3 (1)	3 (1)	2 (<1)	9 (2)	5 (<1)
Grade 4	1 (<1)	2 (<1)	1 (<1)	4 (2)	2 (<1)	6 (1)
Hypophosphataemia (Phosphate)						
Grade 1	0	0	0	0	0	0
Grade 2	21 (8)	39 (15)	23 (9)	40 (16)	44 (9)	79 (15)
Grade 3	2 (<1)	7 (3)	1 (<1)	4 (2)	3 (<1)	11 (2)
Grade 4	0	0	0	0	0	0

Data Source: 201636/201637 Table 3.560.
Note: Fasting data is shown for lipids and glucose.
Note: Subjects with missing Baseline are assumed to be normal.

3.1.1. Liver Chemistries

Seven subjects reported hepatobiliary AEs in the Early Switch Phase (DTG + RPV 5 [<1%], CAR 2 [<1%]) (Data Source: 201636/201637 Table 3.040). One event of drug-induced liver injury was considered serious and related to study treatment (Subject [redacted] in the DTG +RPV group, [see Section 2.1.4]), and one event of cholecystitis chronic was considered serious in a patient who also had non-serious biliary colic (Subject [redacted]). All other events were not serious and were not considered related to study treatment. There were no Grade 4 events. The remaining events reported from the hepatobiliary disorders SOC were as follows: acetaminophen Grade 3 drug-induced liver injury was reported in 1 subject in the DTG + RPV group (Subject [redacted]). Grade 1 jaundice was reported in 1 subject in the DTG + RPV group, although his serum bilirubin was normal throughout the study, including the day on which jaundice was reported (Subject [redacted]). Grade 1 hypertransaminasaemia (Subject [redacted]) was reported in 1 subject in the CAR group, but this was associated with an elevated CPK (8206/UL) due to exercise, confirming muscle as the source of the elevated transaminase. Two subjects, 1 from each

treatment group, developed Grade 1 cholelithiasis (Subject [redacted] in the DTG + RPV group and Subject [redacted] in the CAR group) (Data Source: 201636/201637 Listing 18).

There were no hepatobiliary AEs reported with an onset during the Late Switch Phase.

There were 9 subjects with elevations of ALT >3 x ULN in the DTG + RPV group during the Early Switch Phase (Table 22). Six of the elevations were due to other causes: viral hepatitis (1), alcohol (3) and other drugs (2). Two of the remaining 3 subjects had mild elevations, which returned to normal despite continuing treatment with DTG + RPV. One subject was diagnosed with drug-induced liver injury and this was the only subject who withdrew in the DTG + RPV group. There was 1 subject in the Late Switch group with an elevation of ALT >3 x ULN due to acute HCV (Table 23). There were 5 subjects with elevations of ALT >3 x ULN in the CAR group. Four of the elevations were attributed to concurrent viral hepatitis and 1 to co-trimoxazole. Two subjects in the CAR group withdrew; one due to the need for HCV treatment and the other due to reaching protocol defined stopping criteria.

Table 22 Summary of Subjects with ALT >=3 x ULN during the Early Switch Phase for Study 201636, Study 201637, and Pooled Data (Safety Population)

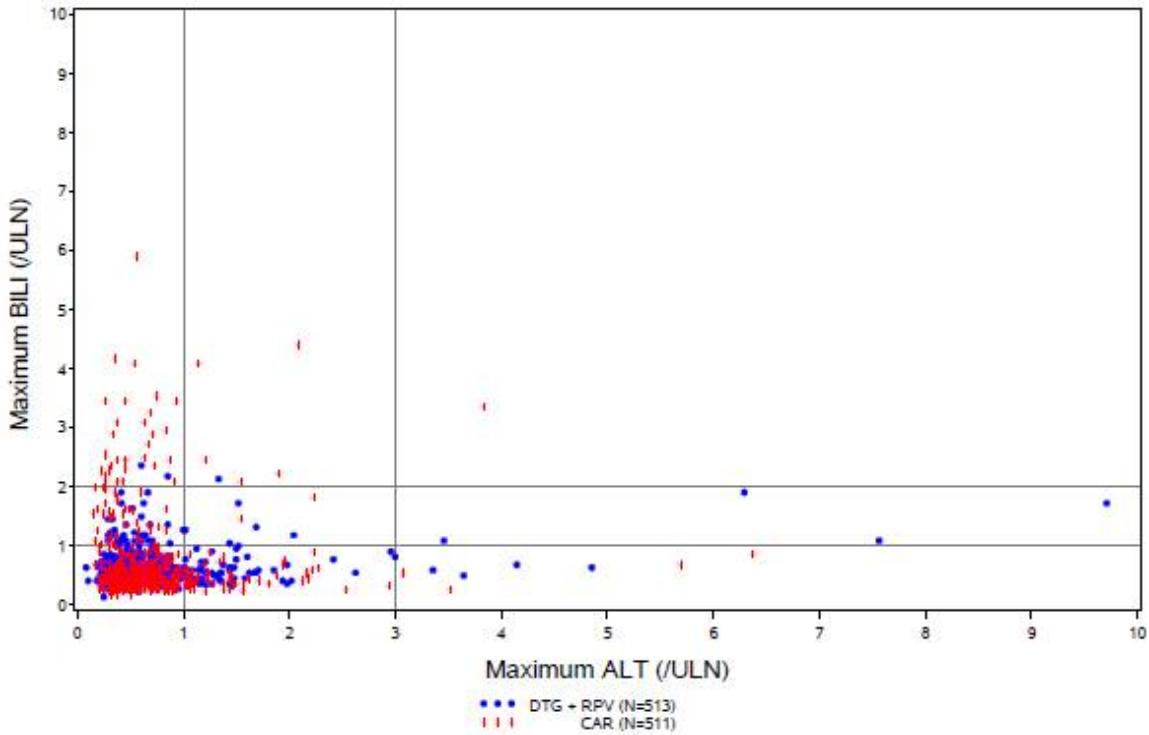
	201636		201637		POOLED	
Hepatobiliary Criteria	**DTG + RPV N=252 n (%)**	**CAR N=256 n (%)**	**DTG + RPV N=261 n (%)**	**CAR N=255 n (%)**	**DTG + RPV N=513 n (%)**	**CAR N=511 n (%)**
ALT ≥3 x ULN	4 (2)	3 (1)	5 (2)	2 (<1)	9 (2)	5 (<1)
ALT ≥3 x ULN - <5 x ULN	1 (<1)	2 (<1)	5 (2)	0	6 (1)	2 (<1)
ALT ≥5 x ULN - <10 x ULN	3 (1)	0	0	2 (<1)	3 (<1)	2 (<1)
ALT ≥10 x ULN - <20 x ULN	0	0	0	0	0	0
ALT ≥20 x ULN	0	1 (<1)	0	0	0	1 (<1)

Data Source: 201636/201637 Table 3.613

Note: For ALT ≥3 x ULN - <5 x ULN, ≥5xULN - <10 x ULN, ≥10 x ULN - <20 x ULN, ≥20 x ULN, subjects are summarized based on the maximum value post Baseline.

The eDISH plot of maximum bilirubin versus maximum ALT is provided as Figure 3. There were several subjects with bilirubin ≥2 x ULN, the majority of which were related to concurrent treatment with ATV in the CAR group.

Figure 3 Maximum Total Bilirubin versus Maximum ALT (eDISH Plot) during the Early Switch Phase for Pooled Data (Safety Population)



Data Source: 201636/201637 Figure 3.033

At the time of the data cut-off for this analysis, 2 further subjects were withdrawn from the studies after switching to DTG + RPV in the Late Switch Phase (Subjects [redacted] and [redacted]) due to elevations in transaminases with no alternative diagnoses established (Data Source: 201636/201637 Table 3.633).

Post-Baseline Emergent ALT >3 x ULN with Total Bilirubin >=2 x ULN and ALP <2 x ULN

No subjects treated with DTG + RPV had a combination of ALT >3 x ULN with total bilirubin ≥2 x ULN and alkaline phosphatase (ALP) <2 x ULN during either the Early Switch Phase or the Late Switch Phase (Data Source: 201636/201637 Table 3.613 and Table 3.623).

For the CAR treatment group, there was 1 subject (Subject [redacted]) that had a combination of ALT >3 x ULN with ALP <2 x ULN and total bilirubin ≥2 x ULN, which occurred during the Early Switch Phase and was due to acute HCV infection (Data Source: 201636/201637 Table 3.613, Table 3.633, and Table 3.643).

Maximum Post-Baseline Emergent ALT >=10 x ULN

No subjects treated with DTG + RPV had post-baseline emergent ALT values ≥10 x ULN during either the Early Switch Phase or the Late Switch Phase (Data Source: 201636/201637 Table 3.613 and Table 3.623).

For the CAR treatment group, 1 subject (Subject [redacted]) had post-baseline emergent ALT values ≥10 x ULN during the Early Switch Phase and 1 subject (Subject [redacted]) had post-baseline emergent ALT values ≥10 x ULN during the Late Switch Phase (Data Source: 201636/201637 Table 3.613 and Table 3.633). Neither was considered to be related to treatment, and both were new acute HCV infections.

Table 23 Subjects with Maximum Post-Baseline Emergent ALT>=10 x ULN for Pooled Data (Safety Population)

Subject ID	Treatment Group	Phase	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No, Reason
Subjects in 201636						
[redacted]	CAR	Early Switch	25	8.1	Acute HCV	Yes discontinued to start prohibited drug for HCV treatment
[redacted]	CAR[a]	Late Switch	16[b]	0.82[b]	Acute HCV	No
Subjects in 201637 (none met criteria)						

Data Source: 201636/201637 Table 3.641, Table 3.671, Listing 4, Listing 28, Listing 75, Listing 3.801

a. CAR is the subject's Baseline randomization group; the ALT ≥10 x ULN occurred after the subject's Week 52 switch to DTG + RPV

b. Calculated from: maximum (IU/L) ALT / ULN = 767 / 48; maximum (μmol/L) bilirubin / ULN = 18 / 22

Post-Baseline Emergent Increases in ALT >=5 x ULN but <10 x ULN

A summary of subjects with post-baseline emergent ALT ≥5 x ULN but <10 x ULN is provided in Table 24.

Table 24 Subjects with Maximum Post-Baseline Emergent ALT >=5 x ULN but <10 x ULN for Pooled Data (Safety Population)

Subject ID	Treatment Group	Phase	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No (Y/N), Reason
Subjects in 201636						
[redacted]	DTG + RPV	Early Switch	7.6	1.1	Alcohol related	No
[redacted]	DTG + RPV	Early Switch	6.3	1.9	Acetaminophen-associated hepatotoxicity	No
[redacted]	DTG + RPV	Early Switch	9.7	1.7	Drug-induced liver injury considered related to study drug	Yes, AE
Subjects in 201637						
[redacted]	CAR	Early Switch	5.7	0.68	Acute HCV	No
[redacted]	CAR	Early Switch	6.4	0.86	Baseline current history of chronic HCV	Yes Subject reached protocol-defined stopping criteria

Data Source: 201636/201637 Table 3.641, Listing 4, Listing 75, Listing 3.801

Post-Baseline Emergent Increases in ALT >=3 x ULN but <5 x ULN

A summary of subjects with post-baseline emergent ALT ≥3 x ULN but <5 x ULN is provided in Table 25. All of these subjects were non-reactive at Baseline for hepatitis B and hepatitis C (Data Source: 201636/201637 Listing 39). Relevant AEs or other findings are noted in the "Comment" column.

Table 25 Subjects with Maximum Post-Baseline Emergent ALT >=3 x ULN but <5 x ULN for Pooled Data (Safety Population)

Subject ID	Treatment Group	Phase	Max ALT /ULN	Max Bilirubin /ULN	Comment	Study Withdrawal? Yes/No (Y/N), Reason
Subjects in 201636						
[redacted]	DTG + RPV	Early Switch	4.9	0.64	Grade 2 ALT at Week 24 and Grade 1 on re-test; within normal range at Week 36 and thereafter	No
[redacted]	CAR	Early Switch	3.5	0.27	Acute Hepatitis E virus	No
[redacted]	CAR	Early Switch	3.8	3.4	Bronchitis treated with co-trimoxazole. Bilirubin due to atazanavir	No
Subjects in 201637						
[redacted]	DTG + RPV	Early Switch	3.5	1.1	Acute HCV	No
[redacted]	DTG + RPV	Early Switch	4.1	0.68	No cause identified. Grade 2 ALT at Week 8 and subsequently fluctuated between Grade 1 and normal range	No
[redacted]	DTG + RPV	Early Switch	3.6	0.50	Co-trimoxazole related	No
[redacted]	DTG + RPV	Early Switch	3.4	0.59	Alcohol related	No
[redacted]	DTG + RPV	Early Switch	3.0	0.82	Alcohol related	No

Data Source: 201636/201637 Table 3.643, Listing 4, Listing 18, Listing 28, Listing 43, Listing 3.801

3.1.2. Renal Function

Prior studies with DTG and with RPV have shown that subjects receiving DTG or RPV had mean increases in serum creatinine evident by Week 2 that remained stable while subjects remained on drug.

In the present studies, subjects in the DTG + RPV group had mean increases in serum creatinine evident at Week 4 (the earliest time point assessed) that remained stable through Week 48. Consistent with this, the mean change from Baseline in estimated GFR from CKD-EPI equation showed a small decrease in the DTG + RPV group compared with little change in the CAR group (Table 26).

Table 26 Mean (SD) Change from Baseline in Creatinine and Estimated Glomerular Filtration Rate during the Early Switch Phase for Pooled Data (Safety Population)

	POOLED	
	DTG + RPV N=513 Mean (SD)	CAR N=511 Mean (SD)
Creatinine (μmol/L)		
Baseline (DTG + RPV n=513, CAR n=511)	77.38 (15.024)	78.01 (14.694)
Week 4 (DTG + RPV n=499, CAR n=496)	7.88 (8.547)	0.95 (7.206)
Week 8 (DTG + RPV n=496, CAR n=491)	8.62 (9.024)	1.25 (6.849)
Week 12 (DTG + RPV n=498, CAR n=498)	8.07 (8.887)	1.00 (7.306)
Week 24 (DTG + RPV n=499, CAR n=500)	8.25 (10.268)	0.27 (7.607)
Week 48 (DTG + RPV n=483, CAR n=484)	8.22 (9.412)	0.32 (7.652)
Estimated GFR from CKD-EPI equation (mL/min per 1.73 m^2)		
Baseline (DTG + RPV n=513, CAR n=511)	100.7135 (17.29776)	100.3933 (15.89845)
Week 4 (DTG + RPV n=499, CAR n=496)	-8.5030 (8.86792)	-1.1472 (7.40492)
Week 8 (DTG + RPV n=496, CAR n=490)	-9.3407 (9.61831)	-1.4939 (7.07692)
Week 12 (DTG + RPV n=497, CAR n=497)	-8.6660 (9.42870)	-1.2777 (7.47303)
Week 24 (DTG + RPV n=497, CAR n=499)	-8.7706 (10.15285)	-0.4489 (7.78133)
Week 48 (DTG + RPV n=483, CAR n=484)	-9.1843 (10.13811)	-0.7955 (7.91188)

Data Source: 201636/201637 Table 3.403
Note: Only on-treatment records are being considered.
Note: Baseline values are actual values.

In contrast to the results using creatinine, the change from Baseline in CKD-EPI GFR using cystatin C showed no difference between the DTG + RPV group and CAR group and little change from Baseline in either treatment group (Table 27).

Table 27 Mean (SD) Change from Baseline in CKD-EPI Cystatin C during the Early Switch Phase for Pooled Data (Safety Population)

	POOLED	
	DTG + RPV N=513 Mean (SD)	CAR N=511 Mean (SD)
CKD –EPI Cystatin C (mL/min per 1.73 m^2)		
Baseline (DTG + RPV n=511, CAR n=505)	114.31 (18.797)	113.67 (16.578)
Week 48 (DTG + RPV n=483, CAR = 482)	0.94 (12.533)	0.73 (11.166)

Data Source: 201636/201637 Table 3.403
Note: Only on-treatment records are being considered.
Note: Baseline values are actual values.

Additionally, change from Baseline in CKD-EPI estimated GFR was assessed using cystatin C during the Early Switch Phase for subgroups of subjects who were or were not receiving TDF at Baseline. For subjects in both treatment groups, regardless of whether they were receiving TDF at Baseline, there was no change from Baseline to Week 48 in median cystatin C (Data Source: 201636/201637 Table 3.693). This confirms that DTG + RPV had no effect on glomerular filtration rate, but only reduced creatinine clearance.

Ten (2%) subjects in the DTG + RPV group had Grade 1 maximum post-baseline emergent elevations in creatinine and there were no Grade 2-4 elevations. Three (<1%) and 1 (<1%) subjects in the CAR group had Grade 1 and Grade 2, respectively, maximum post-baseline emergent elevations in creatinine and there were no Grade 3-4 elevations (Data Source: 201636/201637 Table 3.560).

There was 1 subject who reported renal failure. This was a case of creatinine elevation reported as renal failure with no other signs of renal failure, which was considered by the Investigator to be non-serious and related to study treatment. Subject [redacted] in the DTG + RPV group had a Grade 2 AE of renal failure on Day 171. The subject had pre-existing nephropathy due to HIV and HCV. The subject's creatinine increased from 111 µmol/L and varied to maximum of 137 µmol/L (Grade 1) and this was reported as renal failure. The AE did not lead to withdrawal, and the subject's creatinine has remained stable with no graded elevation since the Week 64 visit.

There was 1 report of acute renal impairment in the DTG + RPV group, which was considered non-serious and not related to study treatment. Subject [redacted] was a 5[redacted] year old male with a medical history of Type 1 diabetes, nephropathyand hypertension who had Grade 3 acute renal impairment (non-serious and considered not related to study treatment) reported on Day 163 with a Grade 1 creatinine elevation to 158.2 µmol/L (101.7 µmol/L at Screening and 71.6 µmol/L at Day 1). His creatinine subsequently varied but was less than Grade 1 (123.8 µmol/L to 96.4 µmol/L at Week 64). His urine albumin/creatinine ratio improved from 27.6 mg/mmol at Baseline to 13.3 mg/mmol at Week 48 (Data Source: 201636/201637 Listing 18, Listing 43, Listing 28, and Listing 30).

There were 2 AEs of nephropathy (1 in each treatment group), which were both Grade 1, non-serious, considered not related to study treatment, and did not result in withdrawal) (Data Source: 201636/201637 Listing 18 and Listing 28):

- Subject [redacted] in the DTG + RPV group was a 2[redacted] year old female with no relevant medical history who had nephropathy (Grade 1, non-serious, considered not related to study treatment) reported on Day 339 due to a finding of a trace of protein on dipstick testing of her urine. Her urine albumin/creatinine ratio had fallen from 3.8 mg/mmol to 1.1 mg/mmol at this time. Her creatinine was 69.8 µmol/L compared with 66.8 µmol/L at screening and 54.8 µmol/L on Day 1. Her maximum serum creatinine was 73.4 µmol/L at Week 64.

- Subject [redacted] in the CAR group was a 3[redacted] year old female with no relevant medical history who had nephropathy reported on Day 169 due to a finding of 2+ protein on dipstick testing of her urine. There was no resolution date but her serum creatinine was 72.8 µmol/L compared with 77.8 µmol/L at screening, 67.9 µmol/L on Day 1, and <70 µmol/L for the rest of the study. She did have a mild elevation of her urine albumin/creatinine ratio to 5.4 mg/mmol from 0.5 mg/mmol at Baseline and later to 8.8 mg/mmol, but this had decreased to 0.8 mg/mmol at Week 48.

There were 2 renal SAEs, which were both considered not related to study treatment (Data Source: 201636/201637 Listing 18):

- Subject [redacted] in the DTG + RPV group had a Grade 3 SAE of acute kidney injury on Day 53, which was due to dehydration from acute gastroenteritis. Study treatment was temporarily interrupted, but the subject subsequently continued in study.

- Subject [redacted] in the DTG + RPV group had a Grade 3 SAE of renal colic on Day 350. The subject continued in the study and at the time of the data cut-off the outcome was reported as not recovered.

Urine Albumin/Creatinine and Protein/Creatinine Ratio Assessments

Urine albumin/creatinine ratio and protein/creatinine ratio were also evaluated to further assess for any impact of study treatment on renal function (particularly glomerular function).

The median urine albumin/creatinine ratios and protein/creatinine ratios showed little change in either treatment group up to Week 48 confirming there was no adverse effect on renal tubular function (Table 28 and Table 29, respectively).

Table 28 Summary of Change from Baseline in Urine Albumin/Creatinine Ratio (g/mol) during the Early Switch Phase for Pooled Data (Safety Population)

	POOLED			
	DTG + RPV N=513		CAR N=511	
	n	Median (Range)	n	Median (Range)
Baseline	445	0.60 (0.1, 83.3)	449	0.60 (0.2, 484.8)
Week 48	344	-0.10 (-57.1, 13.3)	352	-0.05 (-366.7, 13.0)

Data Source: 201636/201637 Table 3.453
Notes:
Only on-treatment values are considered.
Baseline values are actual values.
Refer to the 201636 CSR and 201637 CSR for individual study data.

Table 29 Summary of Change from Baseline in Urine Protein/Creatinine Ratio (g/mol) during the Early Switch Phase for Pooled Data (Safety Population)

	POOLED			
	DTG + RPV N=513		CAR N=511	
	n	Median (Range)	n	Median (Range)
Baseline	453	8.60 (2.0, 185.8)	443	8.60 (2.6, 701.5)
Week 48	368	-1.60 (-175.6, 23.4)	375	0.40 (-554.6, 117.2)

Data Source: 201636/201637 Table 3.453
Notes:
Only on-treatment values are considered.
Baseline values are actual values.
Refer to the 201636 CSR and 201637 CSR for individual study data.

One subject (CAR treatment group) developed Grade 2 AEs of urine albumin/creatinine ratio increased and urine protein/creatinine ratio increased, neither considered related to study treatment (Data Source: 201636/201637 Listing 18).

Renal Biomarker Assessments

Additionally, renal biomarkers were also evaluated to further assess for any impact of study treatment on renal function, particularly given a majority of subjects were switching from a TDF-containing regimen (Section 1.3.3). Creatinine is discussed earlier in this section (Section 3.1.2).

Although there was a decrease in the median urine retinol binding protein in both groups, this was greater in the DTG + RPV group. Similarly, there was a decrease in the median urine beta-2-microglobulin concentration in the DTG + RPV group. This suggests a possible favorable effect of the switch to DTG + RPV on renal tubular function. There were no clinically significant changes in the other renal biomarkers (Table 30).

Table 30 Summary of Chemistry Changes from Baseline in Renal Biomarkers during the Early Switch Phase for Pooled Data (Safety Population)

	POOLED			
	DTG + RPV N=513		CAR N=511	
Cystatin C (mg/L)	**n**	**Median (Min, Max)**	**n**	**Median (Min, Max)**
Baseline	511	0.70 (0.3, 1.3)	505	0.70 (0.4, 1.3)
Week 48	483	0.00 (-0.4, 0.5)	482	0.00 (-0.4, 0.4)
Retinol Binding Protein (nmol/L) (urine)				
Baseline	487	5.6111 (0.371, 190.500)	484	5.1318 (0.371, 190.500)
Week 48	453	-1.8654 (-189.978, 17.917)	455	-0.7564 (-169.056, 186.729)
Beta-2-Microglobulin (nmol/L) (urine)				
Baseline	319	14.4068 (6.780, 11271.218)	325	14.4068 (6.780, 4830.522)
Week 48	161	-3.3898 (-11129.692, 125.424)	174	0.0000 (-333.052, 3411.027)
Urine Phosphate (mmol/L)				
Baseline	486	19.700 (3.22, 81.40)	480	19.540 (3.22, 64.60)
Week 48	453	-0.650 (-66.86, 66.21)	453	-0.970 (-43.93, 59.76)

Data Source: 201636/201637 Table 3.403 and Table 3.453
Note: Only on-treatment records were considered.
Note: Baseline values are actual values.

3.1.3. Creatine Phosphokinase

During the Early Switch Phase, 29 subjects in the DTG + RPV group and 35 subjects in the CAR group experienced post-baseline-emergent elevated CPK levels (Table 21). All reported elevations were considered to be exercise related.

In the DTG + RPV treatment group, one Grade 1 AE of blood CPK increased was reported (Subject [redacted]) during the Early Switch Phase that resolved during the Late Switch phase, although the CPK elevation did not reach DAIDS Grade 1 at any time. In the CAR treatment group, 1 Grade 4 AE of blood CPK increased was reported (Subject [redacted]) during the Early Switch Phase, which was considered exercise-related. Neither event was considered serious or related to study treatment.

3.1.4. Lipase

Although there were increases in lipase up to Grade 4, none of these were symptomatic. One subject in the DTG + RPV group was reported as having Grade 4 acute pancreatitis (Subject [redacted]). However, this was an asymptomatic Grade 4 increase in lipase with normal abdominal CT findings, which returned to normal within 3 days. This was considered serious and led to treatment withdrawal. There was no evidence of clinical pancreatitis. A brief narrative is provided in Section 2.1.4.

Post-baseline emergent lipase elevations were observed more frequently in the CAR group (DTG + RPV 10%, CAR 14%) (Table 31). The majority of these changes were considered Grade 1 or 2 and were asymptomatic.

Table 31 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Toxicities for Lipase during the Early Switch Phase (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Lipase (U/L)						
Grade 1	9 (4)	19 (7)	6 (2)	19 (7)	15 (3)	38 (7)
Grade 2	10 (4)	13 (5)	15 (6)	11 (4)	25 (5)	24 (5)
Grade 3	6 (2)	3 (1)	3 (1)	2 (<1)	9 (2)	5 (<1)
Grade 4	1 (<1)	2 (<1)	1 (<1)	4 (2)	2 (<1)	6 (1)

Data Source: 201636/201637 Table 3.560
Note: Subjects with missing Baseline are assumed to be normal.

3.1.5. Lipid Parameters

A small proportion of subjects in both treatment groups had treatment-emergent cholesterol and triglycerides toxicity of Grade 2 or higher at Week 48 (Table 32).

Table 32 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Toxicities for Lipid Parameters during the Early Switch Phase (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N=252 n (%)	CAR N=256 n (%)	DTG + RPV N=261 n (%)	CAR N=255 n (%)	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Cholesterol						
Grade 1	44 (17)	47 (18)	33 (13)	28 (11)	77 (15)	75 (15)
Grade 2	19 (8)	15 (6)	15 (6)	18 (7)	34 (7)	33 (6)
Grade 3	2 (<1)	3 (1)	2 (<1)	2 (<1)	4 (<1)	5 (<1)
Grade 4	0	0	0	0	0	0
Calculated LDL Cholesterol						
Grade 1	33 (13)	34 (13)	27 (10)	27 (11)	60 (12)	61 (12)
Grade 2	19 (8)	11 (4)	13 (5)	10 (4)	32 (6)	21 (4)
Grade 3	6 (2)	6 (2)	3 (1)	2 (<1)	9 (2)	8 (2)
Grade 4	0	0	0	0	0	0
Triglycerides						
Grade 1	0	0	0	0	0	0
Grade 2	1 (<1)	3 (1)	2 (<1)	5 (2)	3 (<1)	8 (2)
Grade 3	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)
Grade 4	0	1 (<1)	0	1 (<1)	0	2 (<1)

Data Source: 201636/201637 Table 3.560
Note: Fasting data is shown for lipids.
Note: Subjects with missing Baseline are assumed to be normal.

The differences between Baseline and Week 48 in the various lipid parameters were mild, and varied little between the DTG + RPV group and the CAR group, regardless of Baseline third agent and despite TDF/FTC being stopped in approximately 73% of subjects who switched to DTG + RPV in the Early Switch Phase.

NCEP Categories

The overall effects of study treatment on changes in NCEP lipid category from Baseline to maximum post-Baseline category are shown for triglycerides (Data Source: 201636/201637 Table 3.473), total cholesterol (Data Source: 201636/201637 Table 3.483), HDL cholesterol (Data Source: 201636/201637 Table 3.493), and LDL cholesterol (Data Source: 201636/201637 Table 3.503). Although there were small changes from Baseline in the proportion of subjects in each lipid category, the changes were similar between the 2 treatment groups.

Total Cholesterol/HDL Cholesterol Ratio

Table 33 shows the proportions of subjects at Baseline and at maximum for categories of total cholesterol/HDL cholesterol ratio. Although there were some changes in the proportions of subjects in the different risk categories, this was similar between the 2 treatment groups, and the changes to the overall risk profiles were not substantially different from Baseline.

Table 33 Summary of TC/HDL Ratio Maximum Changes from Baseline during the Early Switch Phase for Pooled Data (Safety Population)

	Maximum Post-Baseline Category					
Baseline Category	**<3.5**	**3.5 to <4.4**	**4.4 to <5**	**≥5**	**Missing**	**Total**
DTG + RPV, N=513						
Missing	7 (8%)	3 (3%)	1 (1%)	7 (8%)	68 (79%)	86 (17%)
<3.5	148 (71%)	43 (21%)	7 (3%)	4 (2%)	6 (3%)	208 (41%)
3.5 to <4.4	18 (16%)	56 (48%)	24 (21%)	16 (14%)	2 (2%)	116 (23%)
4.4 to <5	2 (5%)	10 (24%)	12 (29%)	17 (40%)	1 (2%)	42 (8%)
≥5	2 (3%)	4 (7%)	9 (15%)	42 (69%)	4 (7%)	61 (12%)
Total	177 (35%)	116 (23%)	53 (10%)	86 (17%)	81 (16%)	513 (100%)
CAR, N=511						
Missing	13 (14%)	9 (10%)	1 (1%)	10 (11%)	58 (64%)	91 (18%)
<3.5	137 (67%)	54 (26%)	3 (1%)	7 (3%)	5 (2%)	206 (40%)
3.5 to <4.4	13 (11%)	69 (58%)	26 (22%)	10 (8%)	2 (2%)	120 (23%)
4.4 to <5	2 (5%)	10 (26%)	14 (36%)	11 (28%)	2 (5%)	39 (8%)
≥5	0	5 (9%)	4 (7%)	42 (76%)	4 (7%)	55 (11%)
Total	165 (32%)	147 (29%)	48 (9%)	80 (16%)	71 (14%)	511 (100%)

Data Source: 201636/201637 Table 3.513

3.2. Hematology

Overall, there were few post-baseline toxicities. The maximum intensity of post-baseline emergent hematology toxicities was comparable across treatment groups (Table 34).

Table 34 Summary of Maximum Post-Baseline Emergent Hematology Toxicities during the Early Switch Phase (Safety Population)

	201636		201637		POOLED	
	DTG + RPV N = 252 n (%)	CAR N = 256 n (%)	DTG + RPV N = 261 n (%)	CAR N = 255 n (%)	DTG + RPV N = 513 n (%)	CAR N = 511 n (%)
Hemoglobin						
Grade 1	1 (<1)	4 (2)	1 (<1)	3 (1)	2 (<1)	7 (1)
Grade 2	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)
Grade 3	1 (<1)	0	1 (<1)	0	2 (<1)	0
Grade 4	0	1 (<1)	0	0	0	1 (<1)
Leukocytes						
Grade 1	0	0	1 (<1)	0	1 (<1)	0
Grade 2	1 (<1)	0	0	0	1 (<1)	0
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Neutrophils						
Grade 1	4 (2)	6 (2)	2 (<1)	6 (2)	6 (1)	12 (2)
Grade 2	0	0	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Grade 3	1 (<1)	1 (<1)	2 (<1)	0	3 (<1)	1 (<1)
Grade 4	0	0	1 (<1)	0	1 (<1)	0
Platelets						
Grade 1	7 (3)	1 (<1)	8 (3)	2 (<1)	15 (3)	3 (<1)
Grade 2	1 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)
Grade 3	1 (<1)	0	0	0	1 (<1)	0
Grade 4	0	0	0	0	0	0

Data Source: 201636/201637 Table 3.590
Note: Subjects with missing Baseline are assumed to be normal.

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

4.1. Vital Signs

Vital signs measurements were recorded at Baseline only. There are no findings to report with regard to vital signs.

4.2. Cardiac Evaluations

A 12-lead ECG was performed at Screening visit to assure subjects met QTc safety criteria. No additional ECG was performed.

There was 1 ECG finding reported of atrial fibrillation at Day 393 (Late Switch Phase) for Subject [redacted] who was randomized at Baseline to the CAR group and had switched to DTG + RPV at the time of the event (Data Source: 201636/201637 Listing 57). This was later updated by Investigator site to "premature ventricular contractions".

4.3. Cardiovascular Biomarkers

Cardiovascular biomarkers (blood) assessed included C-reactive protein, d-dimer, fatty acid binding protein-2, glucose, HOMA-IR (insulin resistance), IL-6, oxidized LDL cholesterol, soluble CD14, soluble CD163, soluble vascular cell adhesion molecule-1, and insulin.

There was no obvious pattern in changes from Baseline to Week 48 for these biomarkers (Table 35). At the time of reporting, data for insulin were not available.

Table 35 Summary of Chemistry Changes from Baseline for Cardiovascular Biomarkers in the Early Switch Phase for Pooled Data (Safety Population)

	DTG + RPV N=513		CAR N=511	
	n	Median [IQR]	n	Median [IQR]
C-Reactive Protein (mg/L)				
Baseline	512	1.30 [0.60, 2.75]	505	1.30 [0.60, 2.70]
Week 48	480	0.00 [-0.60, 0.70]	482	0.00 [-0.50, 0.90]
D-Dimer (nmol/L FEU)				
Baseline	504	1.15 [1.04, 1.72]	496	1.10 [1.04, 1.64]
Week 48	463	0.00 [-0.05, 0.38]	466	0.00 [-0.11, 0.27]
Fatty Acid Binding Protein-2 (ng/mL)				
Baseline	512	2.25 [1.41, 3.75]	501	2.37 [1.38, 3.91]
Week 48	478	-1.46 [-2.61, -0.67]	478	-1.03 [-2.02, -0.34]
Glucose (mmol/L)				
Baseline	500	5.00 [4.70, 5.40]	489	5.00 [4.60, 5.30]
Week 48	469	0.00 [-0.30, 0.40]	462	0.20 [-0.10, 0.50]
Insulin Resistance				
Baseline	504	2.53 [1.74, 3.70]	491	2.56 [1.76, 3.80]
Week 48	466	0.48 [-0.47, 1.48]	461	0.37 [-0.54, 1.51]
Interleukin-6 (ng/L)				
Baseline	512	1.61 [1.13, 2.58]	503	1.57 [1.07, 2.64]
Week 48	478	-0.04 [-0.76, 0.61]	480	-0.05 [-0.65, 0.59]
Oxidized LDL Cholesterol (μg/L)				
Baseline	512	65.85 [35.00, 195.00]	503	76.10 [35.00, 243.10]
Week 48	479	0.00 [-13.40, 86.90]	479	0.00 [-37.60, 62.00]
Soluble CD14 (ng/mL)				
Baseline	510	1677.46 [1369.23, 1999.04]	502	1696.34 [1384.00, 1977.52]
Week 48	479	363.72 [-41.43, 849.12]	479	773.83 [336.09, 1185.67]
Soluble CD163 (μg/L)				
Baseline	509	537.70 [435.60, 697.70]	501	555.40 [446.40, 701.10]
Week 48	477	52.80 [-31.50, 139.20]	477	26.00 [-43.70, 133.80]
Soluble Vascular Cell Adhesion Molecule-1 (μg/L)				
Baseline	512	1894.63 [1557.74, 2265.11]	503	1871.05 [1579.91, 2242.29]
Week 48	479	-21.45 [-412.14, 341.55]	480	16.12 [-383.28, 429.40]

Data Source: 201636/201637 Table 3.703
Note: Lipid parameters only summarized on fasting data.
Note: Only on-treatment records are considered.
Note: Baseline values are actual values.

4.4. Bone Evaluations

4.4.1. Bone Mineral Density Assessments

Findings from the DEXA substudy are described in full in the 202094 CSR.

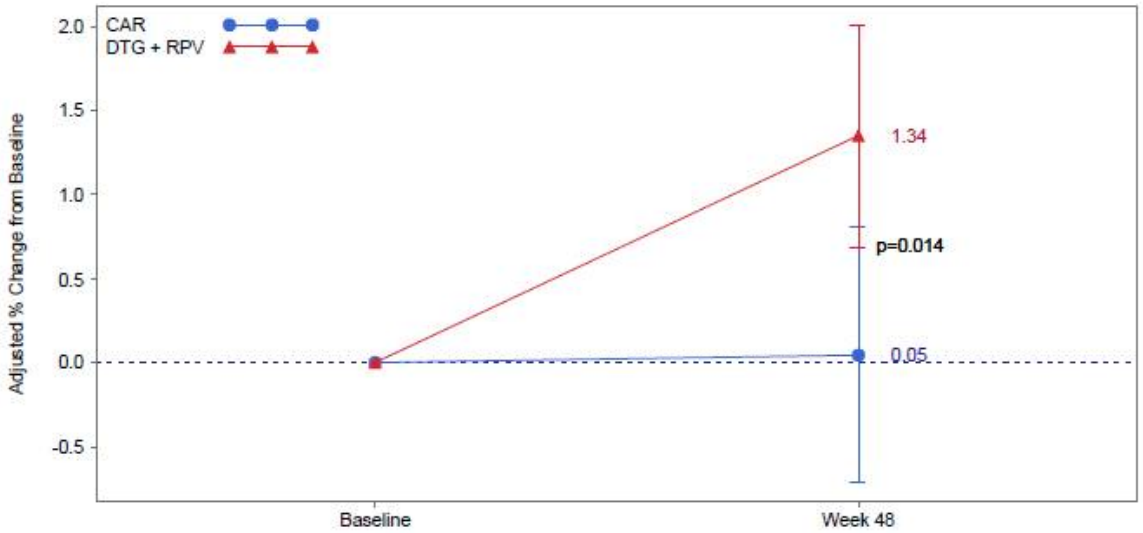
The primary endpoint of 202094 was the percent change from Baseline at Week 48 in total hip BMD as assessed by areal density. The mean (SD) change from Baseline to Week 48 in total hip BMD was greater for subjects in the DTG + RPV group compared with the CAR group (Table 36). Notably, there was almost no change in the mean BMD in the total hip in the CAR group. An analysis of the difference between the 2 treatment groups in the percent change from Baseline at Week 48 in total hip BMD, using an ANCOVA model adjusted for age at study entry, BMI at Baseline, and BMD at Baseline, demonstrated a statistically significant improvement in total hip BMD for the DTG + RPV group (Figure 4).

Table 36 Change from Baseline in Total Hip BMD (Assessed as Areal Density) at Week 48 (ITT-Exposed DEXA Population)

Treatment group	Baseline BMD Mean (SD) (g/cm^2)	Change from Baseline at Week 48 Mean (SD) (g/cm^2)	Mean adjusted % change from Baseline to Week 48 (95% CI)[a]	Difference in adjusted % change from Baseline to Week 48 between treatment groups (DTG – CAR) (95% CI)[a]	p-value[a]
DTG + RPV N=53	n=50 0.964 (0.1457)	n=46 0.012 (0.0229)	n=46 1.34 (0.68, 2.01)	1.29 (0.27, 2.31)	0.014
CAR N=49	n=40 0.974 (0.1146)	n=35 0.000 (0.0167)	n=35 0.05 (-0.71, 0.82)		

Data Source: 202094 Table 2.200 and Table 2.240
Note: Actual values shown at Baseline visit
a. Estimates and associated p-value are from an ANCOVA model adjusted for Baseline BMD value, age at study entry, and Baseline BMI.

Figure 4 Adjusted Percent Change from Baseline in Total Hip BMD (g/cm^2) at Week 48 – Early Switch Phase (ITT-Exposed DEXA Population)



Data Source: 202094 Figure 2.050
Note: Estimates are from an ANCOVA model adjusted for Baseline BMD value, age at study entry, and Baseline BMI. N = 46 for DTG + RPV; N = 35 for CAR.

4.4.2. Bone Biomarker Assessments

HIV infection alone has been associated with BMD loss. Further, ART has been associated with somewhat increased risk of BMD loss, with some drugs thought to have increased risk of bone loss. Changes in certain specific biomarkers have been associated with increased rate of bone turnover, which has been associated with increased risk of loss of BMD. Lower rates of biomarkers suggest less bone turnover.

Vitamin D is not a biomarker for bone turnover. However, adequate levels are required for maintenance of BMD. As some ARVs have been possibly associated with changes in Vitamin D levels, changes in Vitamin D were measured in this study, along with bone biomarkers.

In the DTG + RPV group, all bone turn over biomarkers (bone-specific alkaline phosphatase, osteocalcin, and procollagen 1 N-terminal propeptide) decreased from Baseline to Week 48. The decrease in bone biomarkers observed for the DTG + RPV group was statistically significantly greater than the changes observed in the CAR group (Table 37). For bone-specific alkaline phosphatase and osteocalcin there was a significant interaction between treatment group and Baseline third agent class, therefore the results for these biomarkers are presented by this strata. However, the overall conclusion of a significant reduction in the DTG + RPV group compared with CAR is maintained within each Baseline third agent class. Change from Baseline to Week 48 in bone biomarkers is presented in 201636/201637 Table 3.523 and Table 3.403. Type 1 collagen cross-linked C-telopeptide was also collected for this study; however, these data are not complete at the time of the Week 48 analysis.

Table 37 Statistical Analysis of Bone Biomarkers (Ratio of Week 48 over Baseline) by Third Agent Treatment Class – Observed Case – for the Pooled Data (Safety Population)

Third Agent	Covariate	N	n	Week 48/ Baseline Ratio	95% CI for Ratio	Treatment Ratio	95% CI for Treatment Ratio	P-Value
Bone marker: Bone Specific Alkaline Phosphate (µg/L)								
INSTI	DTG + RPV	105	99	0.853	(0.811,0.897)	0.841	(0.783,0.903)	<0.001
	CAR	97	92	1.015	(0.963,1.068)			
NNRTI	DTG + RPV	275	262	0.793	(0.769,0.818)	0.728	(0.697,0.761)	<0.001
	CAR	278	260	1.090	(1.056,1.124)			
PI	DTG + RPV	133	119	0.821	(0.784,0.859)	0.802	(0.752,0.854)	<0.001
	CAR	136	127	1.024	(0.980,1.070)			
							P-Value Interaction Term[a]	p=0.001
Osteocalcin (µg/L)								
INSTI	DTG + RPV	105	98	0.776	(0.735,0.820)	0.855	(0.789,0.925)	<0.001
	CAR	97	91	0.909	(0.858,0.962)			
NNRTI	DTG + RPV	275	262	0.841	(0.813,0.870)	0.870	(0.829,0.912)	<0.001
	CAR	278	259	0.967	(0.935,1.000)			
PI	DTG + RPV	133	118	0.760	(0.723,0.800)	0.725	(0.676,0.777)	<0.001
	CAR	136	126	1.049	(0.999,1.102)			
							P-Value Interaction Term[a]	p<0.001
Procollagen 1 N-Terminal Propeptide (ug/L)								
All	DTG + RPV	513	479	0.855	(0.832,0.878)	0.845	(0.813,0.878)	<0.001
	CAR	511	478	1.011	(0.985,1.039)			
							P-Value Interaction Term[a]	p=0.677
Vitamin D (nmol/L)								
INSTI	DTG + RPV	105	98	0.826	(0.778,0.876)	0.882	(0.809,0.961)	0.004
	CAR	97	92	0.936	(0.880,0.996)			
NNRTI	DTG + RPV	275	261	0.824	(0.795,0.855)	0.984	(0.935,1.037)	0.550
	CAR	278	262	0.837	(0.807,0.869)			
PI	DTG + RPV	133	119	0.781	(0.739,0.825)	0.863	(0.800,0.930)	<0.001
	CAR	136	128	0.905	(0.859,0.954)			
							P-Value Interaction Term[a]	p=0.007

Data Source: 201636/201637 Table 3.543

a. P-value for interaction between treatment group and original ART third agent class.

Bone biomarkers were analyzed based on log transformed data.

Estimates were initially calculated from an ANCOVA model adjusting for original ART third agent class, age, sex, BMI category, smoking status and Baseline biomarker level.

If the interaction between third agent and treatment was significant at a 10% significance level in the pooled studies then the results were presented by third agent for the pooled studies and within each study.

Week 48 window was up to the end of on-treatment Early Switch Phase.

4.5. Pharmacokinetic/Pharmacodynamic Analyses

PK samples were collected at Weeks 4, 24, and 48, or at withdrawal during the Early Switch Phase of 201636 and 201637 for measurement of pre-dose (trough) concentrations (C0) of DTG and RPV for subjects in the DTG + RPV group. The pre-dose concentrations were summarized and used to investigate exposure-response relationships.

To evaluate the pre-dose DTG and RPV plasma concentrations and residual concentrations of EFV and NVP during the immediate post-switch period and over time, extra PK sampling was conducted at Weeks 2, 4, and 8 in approximately 20 subjects in the NNRTI subset who switched from an EFV or NVP containing regimen.

The results from the NNRTI subset showed that the DTG and RPV C0 increased from Week 2 through Week 4 post-switch and remained relatively constant from Week 4 to Week 48 following treatment with DTG + RPV. Residual concentrations of EFV and NVP decreased over the 4 week post-switch period.

The DTG and RPV C0 from Week 4 to Week 48 in the NNRTI subset with extra sampling were similar to the DTG and RPV C0 at Week 4, 24, and 48 in the larger subset of patients who switched from NNRTIs.

An exploration of plasma DTG and RPV C0avg (average of DTG or RPV C0 across Weeks 4, 24, and 48) and the most frequent AEs (nasopharyngitis, headache, upper respiratory tract infection, diarrhea, and back pain) and selected laboratory parameters (creatinine, GFR, urine albumin/creatinine, ALT, bilirubin, LDL and HDL) was performed. The results did not reveal any association between DTG or RPV exposures and these safety parameters.

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

Data from the pivotal studies conducted for the DTG/RPV FDC program and from studies conducted with the single entities are included in this section. Information from the single-entity studies are being provided where data from the DTG + RPV combination are either not available or are limited.

5.1. Intrinsic Factors

5.1.1. Gender, Age, Race

5.1.1.1. DTG + RPV

Data from studies with the DTG and RPV single entities do not suggest any effect of age, gender, or race on the safety profile of DTG/RPV FDC (beyond what might be expected for each subgroup).

In the 201636 and 201637 pooled analysis, there was no significant difference noted in the number of AEs reported post baseline between males (77%) and females (78%) in the DTG + RPV group. Events occurring in subjects <50 (76%) years and ≥50 (80%) years in the DTG + RPV group were similar (Data Source: 201636/201637 Table 3.801).

Some difference was observed in the number of AEs reported between races in the DTG + RPV group (Table 38); however the majority of subjects were white and there were relatively small numbers in the other groups. As observed for the pooled total population, for all race subgroups, subjects reported AEs most often from the infections and infestations SOC.

Table 38 Summary of Post-Baseline Adverse Event Incidence by Race during the Early Switch Phase for Pooled Data (Safety Population)

Race	DTG + RPV n/N (%)	CAR n/N (%)
African American /African	31/37 (84)	36/47 (77)
Asian	24/38 (63)	34/50 (68)
White	325/421 (77)	280/398 (70)
Other	15/17 (88)	14/16 (88)

Data Source: 201636/201637 Table 3.801

5.1.2. Hepatitis B and/or C Virus Co-Infection

5.1.2.1. DTG + RPV

DTG/RPV FDC has not been studied in patients with hepatitis B virus co-infection. In studies with the DTG and RPV single entities, a higher incidence of liver chemistry elevations were observed in patients co-infected with HBV and/or HCV.

In 201636 and 201637, subjects were excluded if they had evidence of HBV at screening, had an anticipated need for hepatitis C therapy, or for use of interferon therapy. Thus, data on the use of this 2-drug regimen in HBV or HCV co-infected patients from these studies are limited.

Available data are from a small total number of subjects positive for HCV at Baseline: DTG + RPV (n=29 [6%]) and CAR (n=40 [8%]). The changes from Baseline for ALT, AST, and bilirubin were comparable between the DTG + RPV and CAR groups (Data Source: 201636/201637 Table 3.839). There were a greater percentage of Grade 1 elevations of transaminases in the HCV co-infected subjects in both groups (Table 39). However, there were very few subjects with Grade 3 or 4 elevations in HCV co-infected subjects in either group. There was only 1 subject in each group with a Grade 3 or 4 elevation of ALT, and none with a Grade 3 or 4 elevation of AST or bilirubin.

Table 39 Summary of Maximum Post-Baseline Emergent Clinical Chemistry Toxicities by Baseline Hepatitis C Status for Selected Laboratory Parameters during the Early Switch Phase for Pooled Data (Safety Population)

	DTG + RPV		CAR	
	HCV Positive N=29 n (%)	HCV Negative N=484 n (%)	HCV Positive N=40 n (%)	HCV Negative N=471 n (%)
Alanine Aminotransferase				
Grade 1	4 (14)	31 (6)	5 (13)	17 (4)
Grade 2	0	8 (2)	1 (3)	3 (<1)
Grade 3	1 (3)	2 (<1)	1 (3)	1 (<1)
Grade 4	0	0	0	1 (<1)
Aspartate Aminotransferase				
Grade 1	3 (10)	22 (5)	4 (10)	12 (3)
Grade 2	0	5 (1)	2 (5)	6 (1)
Grade 3	0	2 (<1)	0	3 (<1)
Grade 4	0	1 (<1)	0	1 (<1)
Bilirubin				
Grade 1	2 (7)	15 (3)	1 (3)	9 (2)
Grade 2	2 (7)	9 (2)	3 (8)	15 (3)
Grade 3	0	0	0	11 (2)
Grade 4	0	0	0	2 (<1)

Data Source: 201636/201637 Table 3.560 and Table 3.839
Note: Borderline hepatitis C is included in hepatitis C.

5.1.2.2. DTG 50 mg Component

In an ART-naïve population from several studies of subjects treated with DTG + 2 NRTIs (ING112276, ING113086, ING114467, and ING114915), subjects with HBV and/or HCV co-infection at Baseline had a higher incidence of post-baseline-emergent Grade 2 to 4 liver chemistry toxicities compared with subjects who had neither infection (Table 40).

For ALT, the incidence of toxicities in subjects with hepatitis virus infection treated with DTG was lower than both the RAL and Atripla treated subjects, but similar to subjects treated with DRV +RTV (Table 40). The incidence of liver chemistry toxicities for subjects without hepatitis virus infection was similar in DTG, RAL, and Atripla groups, but lower in the DRV +RTV group. However, the percentage of subjects with the more severe Grade 3 to 4 elevations of ALT was low and comparable in all groups. Grade 2 to 4 elevations in bilirubin were low in all groups in both co-infected and non-infected subjects.

Table 40 Summary of ALT, AST, and Total Bilirubin Maximum Post-Baseline Emergent Toxicity, By Baseline Status for Co-Infection with Hepatitis B or C Virus – ART-Naïve Adults

	Baseline Status: Positive for HBV and/or HCV[a]				Baseline Status: Negative for HBV and HCV			
	Total DTG[b] N=116 n (%)	RAL[c] N=43 n (%)	Atripla[d] N=30 n (%)	DRV+RTV[e] N=20 n (%)	Total DTG[b] N=1100 n (%)	RAL[c] N=363 n (%)	Atripla[d] N=385 n (%)	DRV+RTV[e] N=222 n (%)
Alanine Aminotransferase (IU/L)								
Grades 1 to 4	40 (34)	20 (47)	11 (37)	5 (25)	140 (13)	62 (17)	64 (17)	12 (5)
Grades 2 to 4	18 (16)	10 (23)	7 (23)	2 (10)	37 (3)	14 (4)	17 (4)	4 (2)
Grades 3 to 4	6 (5)	2 (5)	0	1 (5)	10 (<1)	6 (2)	2 (<1)	3 (1)
Grade 1	22 (19)	10 (23)	4 (13)	3 (15)	103 (9)	48 (13)	47 (12)	8 (4)
Grade 2	12 (10)	8 (19)	7 (23)	1 (5)	27 (2)	8 (2)	15 (4)	1 (<1)
Grade 3	3 (3)	2 (5)	0	0	6 (<1)	4 (1)	1 (<1)	1 (<1)
Grade 4	3 (3)	0	0	1 (5)	4 (<1)	2 (<1)	1 (<1)	2 (<1)
Aspartate Aminotransferase (IU/L)								
Grades 1 to 4	37 (32)	21 (49)	10 (33)	4 (20)	176 (16)	69 (19)	63 (16)	18 (8)
Grades 2 to 4	16 (14)	6 (14)	6 (20)	2 (10)	50 (5)	18 (5)	18 (5)	7 (3)
Grades 3 to 4	3 (3)	1 (2)	2 (7)	1 (5)	23 (2)	9 (2)	9 (2)	2 (<1)
Grade 1	21 (18)	15 (35)	4 (13)	2 (10)	126 (11)	51 (14)	45 (12)	11 (5)
Grade 2	13 (11)	5 (12)	4 (13)	1 (5)	27 (2)	9 (2)	9 (2)	5 (2)
Grade 3	1 (<1)	1 (2)	2 (7)	1 (5)	17 (2)	7 (2)	7 (2)	2 (<1)
Grade 4	2 (2)	0	0	0	6 (<1)	2 (<1)	2 (<1)	0
Total Bilirubin (UMOL/L)								
Grades 1 to 4	6 (5)	5 (12)	0	0	71 (6)	27 (7)	3 (<1)	4 (2)
Grades 2 to 4	3 (3)	1 (2)	0	0	20 (2)	9 (2)	2 (<1)	1 (<1)
Grades 3 to 4	1 (<1)	0	0	0	3 (<1)	1 (<1)	1 (<1)	0
Grade 1	3 (3)	4 (9)	0	0	51 (5)	18 (5)	1 (<1)	3 (1)
Grade 2	2 (2)	1 (2)	0	0	17 (2)	8 (2)	1 (<1)	1 (<1)
Grade 3	1 (<1)	0	0	0	2 (<1)	1 (<1)	1 (<1)	0
Grade 4	0	0	0	0	1 (<1)	0	0	0

From DTG single-entity submission ISO Table 2.910

a. There was only 1 subject with both HBV and HCV co-infection at Baseline; this individual was in the DTG arm of ING113086, and had a maximum post-baseline toxicity of Grade 2 for ALT and AST and of Grade 1 for bilirubin

b. Total DTG = combined total of all subjects from the DTG arms of ING112276, ING113086, ING114467, ING114915, all of whom received DTG 50 mg once daily (except for subjects in ING112276, who received either 10 mg, 25 mg, or 50 mg of DTG once daily) + 2 NRTIs

c. RAL = subjects from the RAL arm of ING113086, who received RAL 400 mg twice daily + 2 NRTIs
d. Atripla = subjects from the Atripla arm of ING114467, who received EFV/TDF/FTC once daily
e. DRV+RTV = subjects from the DRV+RTV arm of ING114915, who received DRV 800 mg + RTV 100 mg once daily + 2 NRTIs

Hepatitis B Virus Co-Infected Subjects

Across the clinical development program of DTG (as a single entity or as part of a FDC), there have been minimal numbers of subjects, and thus no specific analyses of DTG use in HBV-co-infected subjects is possible.

In the original DTG development program, 7 subjects were HBV co-infected and had clinically significant flares of liver chemistries and/or HBV IRIS: 2 subjects in ING113086 (DTG 1, RAL 1), 1 subject in ING112574, and 4 subjects in ING111762 (DTG 4, RAL 0). Of the cases identified on DTG, 5/7 were not on HBV active therapy at the time of liver chemistry elevation and 5/7 had HBV active therapy discontinued at the start of DTG therapy. All subjects had HIV virologic and immunologic responses to DTG. Three subjects (1 in ING112574, 2 in ING111762) restarted or continued DTG after or in conjunction with the start of HBV active therapy (e.g., TDF/FTC or entecavir). For all 3 of these cases, liver chemistries remain within normal limits after restart or continuation of DTG. From these data, it was concluded that if subjects are not receiving HBV active therapy at the start of potent HIV therapy, there is an increased risk for HBV IRIS or flare in the setting of HIV viral decline and immunologic improvement.

Hepatitis C Virus Co-Infected Subjects

For HCV-co-infected subjects, the risk for significant liver chemistry increases in the setting of HIV virologic and immunologic responses does not appear as profound as that identified for HBV, but HCV IRIS may also contribute to the findings across the clinical program. Across all studies and patient populations, comparable rates of liver chemistry elevations were noted in HCV-co-infected subjects across treatment groups.

Across all patient populations, safety data supports the administration of DTG in HIV-infected patients co-infected with HBC and/or HCV, with awareness of the need for appropriate HBV therapy and the possibility of HBV/HCV flares or IRIS after the start of DTG therapy.

5.1.2.3. RPV 25 mg Component

In the Phase III (C209 and C215) Week 96 pooled analysis in ART-naïve HIV-1-infected adult patients, approximately 9% of subjects were reported to be co-infected with HBV and/or HCV at Baseline or on-treatment.

As expected, a greater proportion of subjects with HBV and/or HCV co-infection experienced hepatic events of interest (33.3%) than subjects without co-infection (4.9%) in the RPV group (Table 41). These events were mostly abnormalities in AST and ALT reported in the investigations SOC. Similar results were observed in the control (EFV) group.

Table 41 Treatment-Emergent Hepatic Events of Interest by Hepatitis B and/or Hepatitis C Co-infection at Baseline (Phase III [C209 and C215] Week 96 Pooled Analysis)

System Organ Class Preferred term	RPV N=686		Control (EFV) N=682	
	Not Co-infected N=632 n (%)	Co-infected N=54 n (%)	Not Co-infected N=616 n (%)	Co-infected N=66 n (%)
Any hepatic event of interest	**31 (4.9)**	**18 (33.3)**	**36 (5.8)**	**20 (30.3)**
Investigations	**23 (3.6)**	**10 (18.5)**	**27 (4.4)**	**10 (15.2)**
AST increased	10 (1.6)	7 (13.0)	16 (2.6)	6 (9.1)
ALT increased	8 (1.3)	6 (11.1)	16 (2.6)	9 (13.6)
ALT abnormal	1 (0.2)	1 (1.9)	-	-
Hepatic enzyme increased	-	1 (1.9)	1 (0.2)	1 (1.5)
Transaminases increased	1 (0.2)	1 (1.9)	5 (0.8)	-
Blood ALP increased	-	-	3 (0.5)	1 (1.5)
Blood bilirubin increased	7 (1.1)	-	-	-
Blood bilirubin unconjugated increased	1 (0.2)	-	-	-
Liver function test abnormal	2 (0.3)	-	2 (0.3)	-
Hepatobiliary Disorders	**10 (1.6)**	**5 (9.3)**	**12 (1.9)**	**9 (13.6)**
Hepatic steatosis	2 (0.3)	1 (1.9)	-	3 (4.5)
Hepatitis	-	1 (1.9)	1 (0.2)	-
Hepatomegaly	1 (0.2)	1 (1.9)	3 (0.5)	1 (1.5)
Hepatotoxicity	-	1 (1.9)	-	-
Hyperbilirubinemia	1 (0.2)	1 (1.9)	1 (0.2)	-
Cholelithiasis	4 (0.6)	-	4 (0.6)	-
Cytolytic hepatitis	-	-	-	1 (1.5)
Hepatic cirrhosis	-	-	-	1 (1.5)
Hepatic function abnormal	1 (0.2)	-	-	3 (4.5)
Hepatitis acute	-	-	1 (0.2)	-
Hypertransaminasaemia	2 (0.3)	-	2 (0.3)	-
Infections and Infestations	**-**	**4 (7.4)**	**-**	**5 (7.6)**
Hepatitis B	-	2 (3.7)	-	1 (1.5)
Hepatitis C	-	2 (3.7)	-	4 (6.1)

From TMC278-C904-W96-Anal-Gen Display SAF.6

Review of the Grade 2-4 hepatic laboratory abnormalities for RPV-treated subjects with and without HBV and/or HCV co-infection indicated that Grade 2-4 increases in AST and ALT were seen at higher incidence in subjects with HBV and/or HCV co-infection (27.8% and 37.0%, respectively) than in subjects who were not co-infected (4.6% and 3.7%, respectively) (Table 42). Hyperbilirubinemia of at least Grade 2 was also seen at a higher incidence in subjects with HBV and/or HCV co-infection (9.3%) than in subjects who were not co-infected (3.7%), although due to the small proportion of subjects with HBV and/or HCV co-infection this observation should be treated with caution.

There was no obvious difference in the incidence of Grade 2-4 increases in AST and ALT between RPV and control (EFV) for non co-infected subjects or co-infected subjects. On control (EFV), Grade 2-4 increases in AST and ALT were seen for 21.2% and 31.8% of co-infected subjects and for 9.2% and 9.0% of non co-infected subjects.

Table 42 Treatment-emergent Hepatic Laboratory Abnormalities by Hepatitis B and/or Hepatitis C Co-infection at Baseline Reported in >=2% of Subjects in the RPV or Control Group (Phase III [C209 and C215] Week 96 Pooled Analysis)

Laboratory Parameter Abnormality, Worst Toxicity Grade	RPV N=686		Control (EFV) N=682	
	Not Co-infected N=632 n (%)	Co-infected N=54 n (%)	Not Co-infected N=616 n (%)	Co-infected N=66 n (%)
ALP, N'	**631**	**54**	**604**	**66**
Grade 1	17 (2.7)	5 (9.3)	76 (12.6)	12 (18.2)
Grade 2	1 (0.2)	-	8 (1.3)	2 (3.0)
Grade 3	-	-	1 (0.2)	-
AST, N'	**631**	**54**	**603**	**66**
Grade 1	98 (15.5)	12 (22.2)	113 (18.7)	13 (19.7)
Grade 2	21 (3.3)	7 (13.0)	39 (6.5)	8 (12.1)
Grade 3	8 (1.3)	4 (7.4)	12 (2.0)	3 (4.5)
Grade 4	-	4 (7.4)	4 (0.7)	3 (4.5)
ALT, N'	**631**	**54**	**604**	**66**
Grade 1	117 (18.5)	9 (16.7)	127 (21.0)	10 (15.2)
Grade 2	22 (3.5)	10 (18.5)	41 (6.8)	9 (13.6)
Grade 3	1 (0.2)	4 (7.4)	9 (1.5)	6 (9.1)
Grade 4	-	6 (11.1)	4 (0.7)	6 (9.1)
Hyperbilirubinaemia, N'	**631**	**54**	**604**	**66**
Grade 1	34 (5.4)	3 (5.6)	2 (0.3)	-
Grade 2	18 (2.9)	5 (9.3)	2 (0.3)	3 (4.5)
Grade 3	5 (0.8)	-	2 (0.3)	-

From TMC278-C904-W96-Anal-Gen Diplay SAF.35
N = number of subjects per treatment group; N' = number of subjects per test and treatment group; n = number of observations.

5.1.3. Hepatic Impairment

5.1.3.1. DTG + RPV

Subjects with severe hepatic impairment (Child-Pugh Grade C) were excluded from studies 201636 and 201637 investigating DTG + RPV. There is therefore no clinical data on the use of DTG + RPV in HIV-infected subjects with severe hepatic impairment.

The use of the individual components in severe hepatic impairment has also not been studied. Based on current labeling for the single entities, no dosage adjustment of DTG/RPV FDC will be required for patients with mild or moderate hepatic impairment (Child-Pugh Grade A or B).

5.1.3.2. DTG 50 mg Component

ING113097 was a Phase I, open-label, parallel-group, two-part, adaptive study to evaluate the PK and safety of single 50 mg doses of DTG in HIV-negative subjects with moderate hepatic impairment, compared with healthy control subjects matched for gender, age, and BMI.

DTG PK parameters were similar between subjects with moderate hepatic impairment and matched healthy controls. Thus, subjects with mild and moderate hepatic impairment do not require a dose adjustment.

A summary of the study design and main conclusions of ING113097 are provided in Table 1.

5.1.3.3. RPV 25 mg Component

In a Phase I, open-label, parallel, controlled, sequential trial (C130; TMC278-TiD6-C130) comparing 8 patients with mild hepatic impairment (Child-Pugh score A) to 8 matched controls, and 8 patients with moderate hepatic impairment (Child-Pugh score B) to 8 matched controls, the multiple dose exposure of RPV was 47% higher in patients with mild hepatic impairment and 5% higher in patients with moderate hepatic impairment. However, it may not be excluded that the pharmacologically active, unbound, rilpivirine exposure is significantly increased in moderate hepatic impairment.

No dose adjustment is suggested, but caution is advised in patients with moderate hepatic impairment. RPV has not been studied in patients with severe hepatic impairment (Child-Pugh score C).

A summary of the study design and main conclusions of C130 are provided in Table 1.

5.1.4. Renal Impairment

5.1.4.1. DTG + RPV

The DTG/RPV FDC or the single entities co-administered have not been studied in patients with renal impairment. In 201636 and 201637, there were no exclusionary criteria for subjects who were renally impaired. DTG has been studied in renally-impaired patients in ING113125 and data is provided below in Section 5.1.4.2.

Based on the prior data in renally-impaired subjects, combined with the lack of drug interactions, and the lack of new signs of renal compromise in studies 201636 and 201637 (see Section 3.1.2), no dosage adjustment of DTG/RPV FDC is required in patients with renal impairment.

5.1.4.2. DTG 50 mg Component

ING113125 was a Phase I, open-label, parallel-group study to evaluate the PK and safety of a single 50 mg dose of DTG in HIV-negative subjects with severe renal impairment (creatinine clearance <30 mL/min, not on dialysis), compared with healthy control subjects matched for gender, age, and BMI.

Severe renal impairment had a relatively moderate effect on DTG PK, reducing Cmax and AUC by around 23-40%, which is not considered clinically significant. In addition, there was overlap in exposure between the two groups, and 2/8 subjects with renal impairment had higher exposures than their matched controls. Similar results would be expected with the use of other methods for assessment of renal function.

Therefore, no dose adjustment is needed in INSTI-naïve subjects with mild to severe renal impairment (creatinine clearance of at least 30 mL/min, not on renal replacement therapy).

A summary of the study design and main conclusions of ING113125 are provided in Table 1.

5.1.4.3. RPV 25 mg Component

No data are currently available in patients with renal impairment. Since the renal clearance of RPV is negligible (<1% of total), a decrease in total body clearance is not expected, hence no dose adjustment is required.

5.2. Extrinsic Factors

5.2.1. Effect of Food

5.2.1.1. DTG + RPV

The results from 201674, a Phase I, 2-part relative oral bioavailability study of different fixed-dose combinations of DTG and RPV in fasted and fed healthy subjects, showed that co-administration of the DTG/RPV FDC tablets being investigated with a moderate- or high-fat meal increased both the AUC and Cmax of the DTG and RPV components.

In Part 1 (high-fat fed state), the AUC (0-∞) and Cmax of DTG following administration of various FDC tablets were comparable to those following the reference DTG single agent co-administered with RPV. The AUC (0-∞) and Cmax of RPV following administration of various FDC tablets were comparable to or ranged from 8% lower to 10% higher (depending on the FDC tablet) than those of the reference RPV single agent co-administered with DTG.

In Part 2 (fasted state), the AUC(0-∞) and Cmax of DTG from the various FDC tablets were 5 to 19% lower than for the reference DTG single entity co-administered with RPV. The AUC(0-∞) and Cmax of RPV were comparable to or up to 1% lower to 10% higher (depending on the FDC tablet) than those of the reference RPV single entity co-administered with DTG. In Part 2, co-administration of the various FDC tablets with a moderate-fat meal increased the DTG AUC(0-∞) by 74 to 87% and Cmax by 75 to 88%, and RPV AUC(0-∞) was increased by 38 to 57% and Cmax by 74 to 94%.

A cross-cohort comparison (Parts 1 and 2) showed that co-administration of the FDC tablets with a high-fat meal increased DTG AUC(0-∞) by 71 to 87% and Cmax by 71 to 85%, and RPV AUC(0-∞) was increased 68 to 72% and Cmax by 73 to 117%. These

results support the recommendation that DTG/RPV FDC should be given with a meal, as is currently recommended for the RPV single entity.

There were no deaths or SAEs reported during the study. No clinically significant changes in clinical laboratory values, vital signs, or ECGs were reported. Two subjects were withdrawn from the study due to AEs of tooth abscess and ALT increase. The single doses of DTG/RPV 50 mg/25 mg FDC tablets as well as co-administration of the single agents were safe and well-tolerated.

Further information on this study can be found in m.2.7.1 Section 2.3.1.1.

5.3. Drug Interactions

5.3.1. DTG + RPV

DTG and RPV have been shown not to interact with each other.

LAI116181 is a Phase I, open-label, crossover study to evaluate the PK and safety of GSK1265744 and RPV, and DTG and RPV in healthy adults. The study showed that the PK parameters of each drug alone were similar to those when given in combination, demonstrating a lack of interaction between RPV and DTG. In this study, DTG 50 mg and RPV at 25 mg were generally well tolerated in healthy subjects. All AEs were Grade 1, with the exception of 3 AEs (insomnia, catheter site inflammation, and toothache), which were Grade 2. No subject became pregnant, died, or experienced a SAE, Grade 3/4 AE, or AE leading to premature discontinuation of investigational product during the study. One subject on GSK1265744 and RPV developed a Grade 4 CPK elevation that was attributed to strenuous exercise. No other clinically significant changes in clinical laboratory values, vital signs, or ECGs were observed during the study. Additional PK data from this study can be found in m2.7.2.

DTG is primarily metabolized by UDP glucuronosyltransferase (UGT1A1, UGT1A3, UGT1A9) and in minor part by CYP3A4. RPV is primarily metabolized by CYP3A.

No specific studies have been conducted looking at how the DTG/RPV FDC might interact with other drugs. Any interactions that have been identified with the individual components DTG and RPV may occur with the DTG/RPV FDC.

5.3.2. DTG 50 mg Component

5.3.2.1. Effect of DTG on Other Drugs

Based on in vitro and in vivo data, DTG had low propensity to cause drug interactions except for drugs that are OCT-2 substrates with narrow therapeutic windows. A comprehensive review of all DDI data with DTG is provided in m2.7.2 Section 3.6.1.2.

5.3.2.1.1. Dofetilide and Pilsicainide

Co-administration of DTG with dofetilide has the potential to increase dofetilide plasma concentration via the inhibition of the OCT-2 transporter and result in potential life-threatening toxicity caused by high dofetilide concentration, and as such, is

contraindicated. For this reason, co-administration has not been studied and was prohibited in all clinical studies.

Pilsicainide is another anti-arrhythmic agent with a narrow therapeutic window that is cleared in part by OCT-2. Accordingly, it is also contraindicated for use with DTG.

5.3.2.1.2. Metformin

Co-administration of DTG with metformin has the potential to increase metformin plasma concentration (study 201167). A dose adjustment of metformin should be considered when starting and stopping co-administration of DTG with metformin, to maintain glycemic control.

A summary of the study design and main conclusions of 201167 are provided in Table 1.

5.3.2.2. Effect of Other Drugs on DTG

DTG is eliminated mainly through metabolism by UGT1A1. DTG is also a substrate of UGT1A3, UGT1A9, CYP3A4, P-gp, and BCRP; therefore drugs that induce those enzymes or transporters may theoretically decrease DTG plasma concentration and reduce the therapeutic effect of DTG.

Co-administration of DTG and other drugs that inhibit UGT1A1, UGT1A3, UGT1A9, CYP3A4, and/or P-gp may increase DTG plasma concentration.

Co-administration of antacids containing polyvalent cations decreased DTG plasma concentration. DTG is recommended to be administered 2 hours before or 6 hours after taking antacid products containing polyvalent cations or products containing calcium or iron. If administered with food, DTG can be taken at the same time as calcium or iron supplements.

Rifampicin and carbamazepine (study 200901) decrease the DTG concentration. Co-administration of the metabolic inducers phenytoin, phenobarbital and St. John's wort also has the potential to decrease DTG plasma concentration due to enzyme induction. The recommended DTG adult dose is 50 mg twice daily when co-administered with these products. Alternative products should be used where possible for INSTI-resistant patients.

5.3.3. RPV 25 mg Component

A comprehensive review of all DDI data with RPV is provided in m2.7.2 Section 3.6.2.1.

5.3.3.1. Effect of RPV on Other Drugs

RPV 25 mg once daily is not likely to have a clinically relevant effect on the exposure of medicinal products metabolized by CYP enzymes or transported by P-gp.

There is limited information available on the potential for a pharmacodynamic interaction between RPV and drugs that prolong the QTc interval of the electrocardiogram. In a study of healthy subjects (C131), supratherapeutic doses of rilpivirine (75 mg once daily

and 300 mg once daily) have been shown to prolong the QTc interval of the electrocardiogram; this was not observed with the RPV 25 mg dose (C152). RPV should be used with caution when co-administered with a drug with a known risk of torsades de pointes. A summary of the study design and main conclusions of C131 and C152 are provided in Table 1.

5.3.3.2. Effect of Other Drugs on RPV

Medicinal products that induce or inhibit CYP3A may affect the clearance of RPV. Co-administration of RPV and medicinal products that induce CYP3A (e.g., rifampin, carbamazepine) may result in decreased plasma concentrations of RPV, which could potentially reduce the therapeutic effect of RPV. RPV should not be used in combination with strong CYP3A inducers. Co-administration of RPV and medicinal products that inhibit CYP3A (e.g., ketoconazole, boosted PIs) may result in increased plasma concentrations of RPV.

RPV should not be used in combination with proton pump inhibitors (increase gastric pH) as co-administration may cause significant decreases in RPV plasma concentrations. This may result in loss of therapeutic effect of RPV. The combination of RPV and H2 receptor antagonists or antacids (increase gastric pH) should be used with caution as co-administration may cause significant decreases in RPV plasma concentrations. H2-receptor antagonists should only be administered at least 12 hours before or at least 4 hours after RPV, and antacids should only be administered at least 2 hours before or at least 4 hours after RPV.

5.4. Use in Pregnancy and Lactation

5.4.1. Non-Clinical Data (Reprotoxicity Studies)

5.4.1.1. DTG + RPV

No nonclinical reprotoxicity studies have been conducted with DTG + RPV.

5.4.1.2. DTG 50 mg Component

There were no effects on fertility or early embryonic development in rats orally administered DTG at ≤1000 mg/kg/day in males or females (S-349572-TF-063-L). The NOAEL was 1000 mg/kg/day, which corresponds to ~44X above the anticipated human exposure for a 50 mg once daily dose, based on exposures achieved in the 1-month rat toxicity study.

No adverse effects on fetal development were observed in pregnant rats orally administered DTG at ≤1000 mg/kg/day. The NOAEL for maternal and fetal toxicity was 1000 mg/kg/day, which corresponds to ~50X above the anticipated human exposure for a 50 mg once daily or twice dose, respectively.

In an embryo fetal development study in rabbits, DTG was orally administered at 40, 200, or 1000 mg/kg/day to pregnant rabbits. Suppressed body weight gain (13.6% on gestation Day 19), decreased food consumption (up to 53%) and scant or no feces/urine

associated with the decreased food consumption were noted in the 1000 mg/kg/day dams. The NOAEL was 200 mg/kg/day for maternal general toxicity (~0.35X the anticipated human exposure for a 50 mg once daily dose) and 1000 mg/kg/day for maternal reproductive function and embryo fetal development (0.74X the anticipated human exposure for a 50 mg once daily dose).

In summary, based on animal data, DTG is not anticipated to increase the risk of adverse developmental (or reproductive) outcomes in humans when used in accordance with dosing information in the product label.

For a complete discussion of the effects of DTG on reproductive and developmental toxicity see m2.4.

5.4.1.3. RPV 25 mg Component

There were no effects of RPV on fertility (NC124) or early embryonic development (NC125) in male rats at doses ≤1600 mg/kg/day (oral administration) or female rats at doses ≤400 mg/kg (oral administration). The NOAEL was ≥1600 mg/kg in male rats and ≥400 mg/kg in female rats which corresponds to at least 35 times the exposure of RPV 25 mg once daily in humans.

The results of the embryo-fetal developmental studies in rats (NC105) and rabbits (NC130) demonstrated the absence of a potential for teratogenicity. The maternal and fetal NOAELs in rats were established at 40 mg/kg/day. In rabbits, the maternal NOAEL was ≥20 mg/kg/day and the fetal NOAEL was 10 mg/kg/day. The exposures at NOAEL for embryo-fetal toxicity are at least 15 times higher than the exposure of RPV 25 mg once daily in humans.

5.4.2. Human Pregnancy Data

5.4.2.1. DTG + RPV

Through the data cut-off date for the Week 48 analysis ([redacted]), 3 subjects became pregnant, all while taking DTG + RPV (Table 43). One subject was in the DTG + RPV group and became pregnant during the Early Switch Phase; 2 subjects were in the CAR group and became pregnant during the Late Switch Phase (i.e., after switching to DTG + RPV). One pregnancy resulted in a live birth with no apparent congenital anomalies, the outcome of one is pending, and one was electively terminated with no apparent congenital anomaly present.

Table 43 Listing of Pregnancies Reported in Either Study 201636 or Study 201637 (Safety Population)

Subject ID	Age (yrs)[a]	Treatment (Start Date/ Stop Date)	Dose (mg)	Date of LMP/ EDD	TTO Positive Pregnancy Test	Outcome	Week of Gestation	Other Medical Conditions / Comments	Contra-ceptive Method	Duration of Exposure
[redacted]	3[redacted]	DTG + RPV (30-Jul-[redacted]/ 02-Sep- a*)	50 mg/ 25 mg	22-JUL- a* / 07-Apr- b* (actual)	Day 35[b]	Live birth via cesarean delivery; no apparent congenital anomalies; APGAR scores were 8 and 9; neonate measured 48.0 cm	37 weeks + 1 day	Concomitant products included lopinavir + ritonavir, tenofovir disoproxil fumarate, lamivudine + zidovudine	Male condom	34 days
[redacted]	3[redacted]	DTG + RPV[c] (27-Jul-[redacted]/ 16-Aug- a*)	50 mg/ 25 mg	04-Jul- a* / 08-Apr- b*	Day 391[d]	Pending	-	Concomitant products included atazanavir, lamivudine, and abacavir sulphate	Male condom/ spermicide	33 days
[redacted]	3[redacted]	DTG + RPV[e] (02-Aug- [redacted]/ 26-Sep- a*	50 mg/ 25 mg	Unknown / Unknown	Day 394[f]	Abortion induced on Day 406; no apparent congenital anomaly present	Unknown	Subject reported an IUD was inserted to induce abortion by a gynecologist on Day 406; Concomitant products included emtricitabine + tenofovir disoproxil fumarate and nevirapine	Unknown	29 days

Data Source: 201636/201637 Listing 4, Listing 8, Listing 16, and Listing 74; GSK Global Clinical Safety database
EDD = estimated delivery date; LMP = last menstrual period; TTO = time to onset

a. Age at Screening.
b. Based on duration of DTG + RPV exposure; the subject was withdrawn from study on Day 42
c. Subject received CAR through Day 357, then switched to DTG + RPV
d. Based on date of study drug withdrawal and date of withdrawal visit (both on Day 391)
e. Subject received CAR through Day 364, then switched to DTG + RPV
f. Based on investigator narrative of last date of DTG + RPV dose; subject was withdrawn from study on Day 451

a*: The year
b*: Following year

5.4.2.2. DTG 50 mg Component

As of [redacted], a total of 39 pregnancies occurred in patients receiving DTG therapy as part of the DTG MAH-sponsored clinical development program. One of the 39 reports involved a male subject receiving DTG containing ART (i.e., a partner pregnancy) and 1 involved a twin pregnancy. The partner pregnancy was reported in study ING114467. The participating male subject was receiving DTG 50 mg + ABC/3TC once daily. The pregnancy had a normal outcome.

An additional 13 pregnancies have been reported where the patient received DTG as a component of TRIUMEQ (DTG/ABC/3TC) as part of a MAH-sponsored clinical study.

Pregnancy outcomes reported for the 38 cases involving female subjects with direct administration of DTG and the 13 cases exposed to TRIUMEQ are presented in Table 1.

Due to patient selection and withdrawal criteria for MAH-sponsored studies; cases involving female patients with direct exposure to investigational product (either DTG or DTG/ABC/3TC) would have involved exposure to investigational product during the first trimester, which would not have extended to the second trimester.

Table 44 Pregnancy Outcomes Reported Following Exposure to DTG during MAH-Sponsored Clinical Studies

Outcome	Cases from DTG Clinical Studies	Cases from DTG/ABC/3TC clinical studies	Total
Live infant, no apparent congenital anomaly	21	5	26
Live infant, congenital anomaly	1	-	1
Spontaneous abortion, no apparent congenital anomaly	4	1	5
Elective termination	10	3	13
Pregnancy ongoing	1	2	5
Pregnancy outcome unknown/lost to follow-up	2	2	4
Total	39a	13	52

a. Includes 1 twin pregnancy – hence 38 pregnancies but 39 outcomes

Few cases resulted in an adverse pregnancy outcome (e.g., spontaneous abortion or ectopic pregnancy), and were comparable for DTG, RAL, and Atripla. One case involved a congenital anomaly. A double-outlet right ventricle and ventricular septal defect was found on ultrasound in a 31-week gestation fetus. The mother's antiretroviral regimen consisted of DTG, ABC, and RTV-boosted atazanavir. Surgery was performed following delivery; however, the infant died on their fourth day of life due to post-operative complications. The congenital anomaly was considered by the Investigator to be unrelated to investigational product. The 5 spontaneous abortions all occurred at less than 12 weeks of gestation. None of the cases resulting in an adverse pregnancy outcome were considered reasonably attributable to investigational product by the reporting investigators.

DTG should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

5.4.2.3. RPV 25 mg Component

In the 2 Phase III studies (C209 and C215), 5 pregnancies were reported during treatment with RPV after drug exposure ranging from 59 days to approximately 16 months. Four subjects subsequently discontinued the study. The fifth subject was a male whose partner became pregnant and therefore, discontinuation of the study medication was not applicable. This partner delivered a healthy baby girl. Of the 4 female subjects who became pregnant, 1 subject gave birth prematurely to a baby girl by Caesarean section; the baby, who was born approximately 4 weeks prematurely, had nasal flaring and indrawing lower chest, but reported to be healthy with no anomalies. Another subject gave birth by Caesarean section to a healthy baby boy. There was no information available regarding the outcome of the third pregnancy. The fourth subject experienced a spontaneous abortion during her first trimester, approximately 1 month after her last dose of study medication. It was reported the spontaneous abortion was without complications and no fetus abnormalities were noted. This was the first pregnancy for this subject.

RPV in combination with a background regimen was evaluated in the RPV treatment arm of study TMC114HIV3015, in 19 pregnant women during the second and third trimesters and postpartum. The PK data demonstrate that total exposure (AUC) to RPV as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). Virologic response was preserved throughout the study period. No mother-to-child transmission occurred in all 10 infants born to the mothers who completed the study and for whom the HIV status was available. RPV was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of RPV in HIV-1-infected adults.

RPV should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

5.4.2.4. Antiretroviral Pregnancy Registry

Due to limitations of spontaneous reporting, the Antiretroviral Pregnancy Registry (APR) provides the best source of cumulative information regarding use of DTG and RPV during pregnancy post marketing.

The APR is an international registry that monitors prenatal exposures to antiretroviral drugs to detect a potential increase in the risk of birth defects through a prospective exposure-registration cohort. Clinicians register pregnant women with prenatal exposures to any ARV before the outcome of pregnancy is known, report data on exposure throughout pregnancy, and provide birth outcome data. Registration is voluntary and confidential. Defects are reviewed by a teratologist, and all data are reviewed semi-annually by an independent Advisory Committee. Exposure is classified and analyzed by the earliest trimester of exposure to each individual ARV medication. Birth defect prevalence (any pregnancy outcome >20 weeks of gestation with a defect/live birth) is compared with both internal and external comparator groups. The external comparators used are two population-based surveillance systems – Metropolitan

Atlanta Congenital Defects Program (MACDP) by CDC and the Texas Birth Defects Registry (TBDR); and internal comparators include exposures to other drugs and exposures in the second/third trimester of pregnancy relative to first trimester exposures when organogenesis occurs. Statistical inference is based on exact methods for binomial proportions. APR has 80% power and a Type 1 error rate of 5% to detect doubling of risk for overall birth defects. For specific defects, the power varies with the population's frequency of the defect and the size of the exposed group.

5.4.2.4.1. DTG 50 mg Component

TIVICAY was added to the list of the ARVs monitored by the APR on 21 August 2012. As of 31 July 2016, there were 83 pregnancies with prenatal exposure to TIVICAY reported to the APR; 41 during first trimester and 42 during second/third trimester. Two birth defects were observed in the first trimester group, and one birth defect was observed in the second/third trimester group.

There are limited human data on DTG use and safety in pregnancy, so no definitive conclusions can be made.

5.4.2.4.2. RPV 25 mg Component

The MAH for RPV has reported appropriate cases to the APR since 30 July 2007. The most recent interim report from the APR, issued December 2016, reviewed data through 31 July 2016, based on prospective reports of over 17371 live births with pregnancy exposure, including 347 cases with exposure to RPV. Of these 347 cases, 1 birth defect was reported after RPV exposure during the first trimester of pregnancy, and 1 birth defect was reported after RPV exposure during the second/third trimester of pregnancy. For RPV, sufficient numbers of first trimester exposures are available to allow detection of at least a two-fold increase in risk of overall birth defects. No such increases have been detected to date.

5.5. Clinical Pharmacology Bioequivalence Study in Adults

201676 was a Phase I open-label randomized two-way crossover study that evaluated the bioequivalence between the DTG/RPV FDC 50 mg/25 mg tablet formulation compared with co-administration of the separate tablet formulations of DTG 50 mg and RPV 25 mg in healthy adult volunteers in the fed state. There were 118 subjects randomized in this study.

Bioequivalence was confirmed in terms of both DTG and RPV for the FDC tablet formulation of DTG/RPV 50 mg/25 mg compared with separate tablet formulations of DTG 50 mg plus RPV 25 mg, when administered after a moderate-fat meal. The safety results showed that dosing with the DTG/RPV FDC tablet and separate DTG and RPV tablets did not lead to any noted differences in reported AEs or laboratory changes, and both treatments were well tolerated.

Further information on this study can be found in m.2.7.1 Section 2.1.1.1.

5.6. Cerebrospinal Fluid Penetration

5.6.1. DTG 50 mg Component

ING116070 was a Phase IIIb single-arm study to evaluate the safety, efficacy, and PK in the central nervous system and plasma of DTG 50 mg once daily in combination with ABC/3TC FDC in HIV-infected ART-naïve adult subjects over 96 weeks.

This study confirmed that DTG is present in the CSF with average concentrations in the CSF of 16.2 ng/mL at Week 2 and 12.6 ng/mL at Week 16, ranging from 3.7 to 23.2 ng/mL. DTG concentrations were similar to the unbound DTG concentrations in plasma, with statistically significant correlations between DTG CSF and plasma concentrations. CSF:plasma concentration ratio of DTG ranged from 0.12% to 2.04%. The DTG concentration observed in the CSF at both Week 2 and Week 16 exceeded the in vitro IC50 against wild-type viruses (0.2 ng/mL) for all subjects, suggesting that DTG is able to achieve therapeutic concentrations in the CSF. The regimen of DTG 50 mg once daily with ABC/3TC demonstrated good tolerability in this study, with a safety profile comparable to that observed in other studies with DTG + ABC/3TC.

5.6.2. RPV 25 mg Component

No data are currently available on CSF penetration from the RPV single-entity development program. However, a PK study by Mora-Peris et al. [Mora-Peris, 2014] assessing RPV exposure in plasma and sanctuary site compartments in 13 HIV-infected males who switched from TDF/FTC/NVP to TDF/FTC/RPV reported a mean RPV CSF concentration of 0.8 ng/ml (95% CI 0.7-1.0) at Day 60, representing a mean CSF:plasma percentage ratio of 1.4% (95% CI 1.2% -1.6%). Individual RPV CSF concentrations were above the EC50 in all subjects and above the EC90 in 85% of the subjects. HIV-1 RNA in the CSF was undetectable (<5 c/mL) in all patients. Higher concentrations of RPV in the CSF were weakly associated with higher plasma RPV Ctrough at Day 60 (P=0.072), without significant associations with any other patient characteristic or pharmacokinetic parameter. This association however requires cautious interpretation due to the small sample size within this study.

5.7. Overdose

5.7.1. DTG + RPV

There is limited experience of overdose with DTG + RPV. Across 201636 and 201637, there were 3 subjects who had a protocol-defined overdose (any tablet intake exceeding the randomized daily number of tablets for study treatment). One subject took an extra dose of both DTG and RPV on a single day. A second subject took extra doses of both DTG and RPV over a 7 day period. The third subject was reported to have taken 2 tablets of DTG. No adverse events were reported at the time of the overdose in these subjects. The third subject reported “general discomfort” a week following the overdose, but this was Grade 1, considered unrelated to study treatment, and resolved the same day. These events are not considered clinically significant overdoses of DTG and RPV. All 3 subjects were retrained on compliance with taking their study treatment following the event.

There is no specific treatment for overdose with DTG/RPV FDC. If overdose occurs, patients should be treated supportively, with appropriate monitoring, vital signs, ECG (QT interval), and observations of the clinical status of the patient, as necessary.

As DTG and RPV are both highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis. Administration of activated charcoal may be used to aid in removal of unabsorbed active substance.

5.7.2. DTG 50 mg Component

Single daily doses of DTG up to 250 mg have been administered orally to healthy subjects in clinical pharmacology study ING111856; no unexpected adverse effects were reported for DTG during this study. The effects of higher doses are not known.

A summary of the study design and main conclusions of ING111856 are provided in Table 1.

5.7.3. RPV 25 mg Component

Cases of intentional or accidental acute overdose with RPV were not reported during clinical trials. Systematic examination of the effects of high drug exposure have been performed in 2 trials. In trial C131, subjects received a supratherapeutic dose of RPV (300 mg once daily) for 11 days, which was generally well tolerated (mean Cmax = 1665 ±398.1 ng/mL). In trial C112, subjects received RPV 150 mg once daily with DRV/RTV 800/100 mg for 11 days (mean Cmax = 1860 ±673 ng/mL), which was also generally well tolerated. In comparison, the mean Cmax value as observed in HIV-infected subjects at a 25 mg once daily dose was 134 ±72 ng/mL (pooled data pharmacokinetic substudies of the Phase III [C209 and C215] trials).

There is no specific antidote for overdose with RPV. General measures to maintain or support the basic vital functions should be taken in case of deliberate or accidental overdosage, i.e., monitoring of vital signs and ECG (QT interval) and the clinical status of the patient. Administration of activated charcoal may also be used to aid in removal of unabsorbed active substance. Since RPV is highly protein bound, dialysis is unlikely to result in significant removal of the active substance.

5.8. Drug Abuse

5.8.1. DTG + RPV

No studies have been performed to investigate the potential for drug abuse with DTG/RPV FDC; however the Sponsor does not consider there is a potential for misuse of DTG/RPV FDC for illegal purposes.

5.8.2. DTG 50 mg Component

The Sponsor does not consider that there is a potential for misuse of DTG for illegal purposes.

The INSTI class of compounds has no known drug abuse potential. The mechanism of action for DTG does not involve receptors or neurotransmitters known to be involved in drug dependence. In secondary pharmacology evaluations, DTG did not significantly bind to any receptors or ion channels that would be considered relevant to abuse liability (including monoamine oxidase A and B, cannabinoid CB1 or CB2, nicotinic cholinergic, dopamine D1 or D2, dopamine transporter, GABA A or GABA B, glutamate NMDA, opiate, serotonin 5-HT1, 5-HT2, or 5-HT3).

No effects related to DTG administration on central and peripheral nervous system or body temperature were noted in preclinical studies, even following dosing withdrawal in different preclinical species including nonhuman primates. The results from a quantitative whole body autoradiography study in rats indicated that the ability of DTG or metabolites to cross the blood brain barrier in rats was limited.

Considering that: a) DTG is not centrally active, b) there is clear evidence that the compound has very low blood brain barrier penetration, c) mechanistically it does not interact with neurotransmitters/receptors involved in the drug-dependence mechanism, and d) preclinical and extensive clinical data generated are not indicative of an abuse liability, the likelihood of abuse liability for DTG is considered extremely low and further studies are not necessary.

5.8.3. RPV 25 mg Component

No systematic examination of the abuse potential of RPV has been performed in nonclinical and clinical trials. Based on the pharmacology and mechanism of action of RPV, it is considered highly unlikely that RPV has the potential for abuse. There have been no reports of RPV dependence from any clinical trial.

5.9. Withdrawal and Rebound

5.9.1. DTG + RPV

No studies have been performed to investigate the potential for withdrawal and rebound effects with DTG/RPV FDC. However, the Sponsor does not consider that there is a potential for this type of effect with DTG/RPV FDC.

5.9.2. DTG 50 mg Component

No studies have been performed to investigate the potential for withdrawal and rebound effects with DTG. However, the Sponsor does not consider that there is a potential for this type of effect with DTG.

This class of compounds has no known drug withdrawal or rebound potential. No effect related to DTG administration on central and peripheral nervous system or body temperature was noted in preclinical studies, even following dosing withdrawal in different preclinical species including nonhuman primates. The results from a quantitative whole body autoradiography study in rats indicated that the ability of DTG or metabolites to cross the blood brain barrier in rats was limited.

5.9.3. RPV 25 mg Component

Trials or systematic analyses to evaluate the potential withdrawal and rebound effects of RPV have not been conducted.

Safety parameters (AEs, clinical laboratory parameters, ECG, vital signs, and physical examinations, including skin examinations) were examined during washout periods and during follow up periods after last intake of study medication. This showed that the overall safety and tolerability profile of RPV was not negatively impacted by interruption or permanent discontinuation of treatment. These findings suggest that serious withdrawal and rebound effects are unlikely to result from the interruption or permanent discontinuation of RPV administration.

5.10. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

5.10.1. DTG + RPV

As no clinically-significant drug interaction is expected between DTG and RPV, the combination is not expected to impact differently than any individual component, which are all anticipated to not have any detrimental effect upon the ability to drive, operate machinery, or mental ability (as described in Section 5.10.2 and Section 5.10.3).

Across 201636 and 201637, there was a single AE of road traffic accident reported (DTG + RPV group) (Data Source: 201636/201637 Table 3.845). This was a Grade 1 event (verbatim text: motorbike fall) that was reported on Day 331, was considered non-serious and not related to study treatment.

Table 45 Summary of Adverse Events That May Alter Ability to Drive or Operate Machinery during the Early Switch Phase for Pooled Data (Safety Population)

System Organ Class Preferred term	DTG + RPV N=513 n (%)	CAR N=511 n (%)
Psychiatric Disorders		
Insomnia	17 (3)	10 (2)
Sleep disorder	4 (<1)	0
Nervous System Disorders		
Dizziness	15 (3)	1 (<1)
Somnolence	4 (<1)	0
Syncope	2 (<1)	0
Disturbance in attention	1 (<1)	0
Balance disorder	1 (<1)	0
Presyncope	1 (<1)	0
Visual field defect	1 (<1)	0
Loss of consciousness	0	1 (<1)
Epilepsy	0	1 (<1)
General Disorders and Administration Site Conditions		
Fatigue	11 (2)	6 (1)
Malaise	3 (<1)	0
Ear and Labyrinth Disorders		
Vertigo	7 (1)	5 (<1)
Eye Disorders		
Vision blurred	2 (<1)	0
Diplopia	1 (<1)	1 (<1)
Visual acuity reduced	1 (<1)	0
Visual impairment	0	1 (<1)

Data Source: 201636/201637 Table 3.040

5.10.2. DTG 50 mg Component

Studies investigating the effects of DTG on the ability to drive or use machines have not been performed. This class of compounds has no known effects on ability to drive or operate machinery or impairment of mental ability.

AEs were reported in controlled clinical studies that may influence a patient's ability to drive or operate machinery, or that may impact upon mental ability (e.g., dizziness, headache, somnolence, disturbance in attention, lethargy, fatigue), however, the incidence of these adverse events in DTG-treated subjects were similar when compared with groups taking EFV-, RAL- or DRV-containing regimens, with the exception of dizziness, which occurred less frequently in the overall group that received DTG compared with those who had received EFV.

In a pooled analysis of studies ING114467, ING113086, ING112276, ING114915 and ING116070, traffic accidents were reported as AEs for 4 of 1,131 (<1%) of the ART-

naïve population taking DTG, and were reported in ING111762 for 1/357 (<1%) of the ART-experienced (INSTI-naïve) population taking DTG.

Overall, given the pharmacology of DTG and available clinical evidence, there is no detrimental effect anticipated on the ability to drive or operate machinery, or on mental ability.

5.10.3. RPV 25 mg Component

Studies investigating the effects of RPV on the ability to drive or use machines have not been performed. Table 46 lists the AEs from the Phase III (C209 and C215) Week 96 pooled analysis in ARV-treatment HIV-1-infected adult patients that may have a potential impact on the ability to drive or operate machinery.

Table 46 Overview of Treatment-Emergent Adverse Events That May Alter Ability to Drive or Operate Machinery (Phase III [C209 and C215] Week 96 Pooled Analysis)

System Organ Class Preferred Term	RPV N=686 n (%)	Control (EFV) N=682 n (%)
Nervous System Disorders		
Dizziness	70 (10.2)	202 (29.6)
Somnolence	30 (4.4)	51 (7.5)
Disturbance in attention	7 (1.0)	17 (2.5)
Presyncope	2 (0.3)	-
Loss of consciousness	1 (0.1)	-
Syncope	1 (0.1)	6 (0.9)
Depressed level of consciousness	-	2 (0.3)
Dizziness postural	-	1 (0.1)
Syncope vasovagal	-	2 (0.3)
General Disorders and Administration Site Conditions		
Fatigue	39 (5.7)	60 (8.8)
Sluggishness	-	1 (0.1)
Ear and Labyrinth Disorders		
Vertigo	6 (0.9)	20 (2.9)
Vertigo positional	1 (0.1)	2 (0.3)
Eye Disorders		
Vision blurred	3 (0.4)	8 (1.2)
Visual disturbance	1 (0.1)	1 (0.1)
Diplopia	-	1 (0.1)
Psychiatric Disorders		
Confusional state	1 (0.1)	3 (0.4)
Disorientation	-	4 (0.6)
Mental status changes	-	1 (0.1)

From TMC278-C904-W96-Anal-Gen Display SAF.7

6. POST-MARKETING DATA

DTG/RPV FDC is not currently approved or marketed in any country.

This section provides an overview of any significant post-marketing information for DTG and RPV. An overview of post-marketing information describing the use of DTG and RPV together is also provided.

The continued review of data from post-marketing clinical experience with DTG and RPV and the original clinical trial data, has resulted in well-established safety profiles for DTG- and RPV-containing products. The resulting safety profile for each product is maintained and summarized in the Company's corresponding Reference Safety Information and Country Prescribing Information.

A data cut-off data of [redacted] has been used for this section.

6.1. DTG 50 mg Component

DTG is indicated in adults and adolescents above 12 years of age for the treatment of HIV-1 infection, as part of cART. DTG was approved in the US on 12 August 2013 and in the EU on 20 January 2014. As of 16 January 2017, DTG has been approved in the US, all EU member states, and Japan, as well as over 85 further countries.

Depression and suicidal behaviors were upgraded from an important potential risk to an important identified risk, and added to the Global Data Sheet (GDS)/RSI as a labeled adverse reaction in [redacted]. Myalgia and arthralgia were also added to the GDS/RSI as a labeled adverse reaction in [redacted].

No other significant safety concerns or risks have been identified from marketing experience through to [redacted] for DTG.

As calculated from Intercontinental Medical Statistics (IMS) Health Sales Data available to [redacted], the best estimate of total post-marketing exposure for TIVICAY (DTG single entity) based on a 50 mg once-daily dose is 223,630 patient-years.

6.2. RPV 25 mg Component

RPV is indicated, in combination with other ARV medicinal products, for the treatment of HIV-1 infection in ARV treatment-naïve patients 12 years of age and older. In most countries, including the US and Europe, this indication is further restricted to patients with a viral load ≤100,000 copies/mL. RPV was approved in the US on 20 May 2011 and in the EU on 28 November 2011. As of 16 January 2017, RPV is approved in the US, all EU member states and Japan, as well as over 85 additional countries.

No significant safety concerns or risks have been identified from marketing experience through to 16 January 2017 for RPV.

Based on the 33,750,614 tablets of EDURANT distributed by the Company (from launch to 31 December 2016), the estimated exposure is 92,468 patient-years.

6.3. DTG + RPV

This section provides an overview of literature describing the use of DTG and RPV together, and any post-marketing reports on the Global Safety databases that report the use of DTG and RPV together.

6.3.1. Literature

Review of the literature has identified a number of conference abstracts, posters, and papers that describe the use of DTG and RPV as dual therapy. A summary of these is provided below and in Table 47.

Five studies [Capetti, 2016; Diaz, 2016; Grabmeier-Pfistershammer, 2016; Palacios, 2016; Gantner, 2016] provide additional information on 472 patients who have used DTG and RPV together as dual therapy. The patients in these studies are similar to those enrolled in the two Phase III clinical trials (201636 and 201637). The majority of these patients were ART-experienced with their viral load suppressed at the time of switch to DTG + RPV.

Capetti et al. [Capetti, 2016] describe subjects who were enrolled in an observational multicenter cohort in Italy named TivEdo (TIVICAY plus EDURANT Observational cohort) during a 12-month period. There were only two inclusion criteria: being HIV-1 antibody positive and having started DTG + RPV. The patients were evaluated (visit and blood work) about 4 weeks after starting DTG + RPV and subsequently at Months 3, 6 and 12. No data were collected after Week 48. There were 132 patients enrolled in the cohort and followed for a median of 24 months (mean 33 months). The median age was 51.8 (range 2[redacted]-7[redacted]), 31.7% were female, and 10% were non-caucasian. Fifty seven (43.2%) had had at least one failure with a previous antiretroviral regimen. The main reason for switch to DTG + RPV was simplification (53.0%), followed by toxicity (34.8%), drug-drug interactions with anti-HCV therapy (5.3%), persistent low-level viremia (3.0%), non-adherence (2.3%), and viral failure (1.6%); 40.1% of subjects switched from an INSTI (RAL)-containing regimen.

At Baseline, 67 patients (45.5%) had reverse transcriptase mutations, of which 46 had mutations to NRTIs alone, 1 to NNRTIs alone, and 13 to both, including 6 to RPV. Also, 69 (44.7%) subjects had PI mutations, 1 had full INSTI resistance, and 8 (6.1%) subjects had never had genotyping. The patient with full INSTI resistance was taking DTG twice daily, having no other choice due to drug interactions and resistance.

The number of subjects who had a viral load >50 c/ml decreased from Baseline (n=16) to Week 4 (n=3). At Week 24, only 1 patient had viral rebound without mutations due to missed drug refill (11030 c/ml). Of the 50 patients who had 48 weeks of follow-up, 4 patients had 1-49 c/ml and 45 patients had no virus detected (0 c/ml). The subject described above at Week 24 had another treatment interruption, with 14770 c/ml. This patient, who frequently interrupted therapy, accumulated reverse transcriptase mutations 138Q and 181C, while the integrase gene was unaffected. None of the patients with baseline resistance to RPV (n=6) failed, all having 48-week follow-up. The authors stated that no viral failures were observed in the short term, while the proportion of patients with any detectable viremia decreased by 50% from Baseline.

One patient discontinued DTG + RPV at Week 24 due to headache (and insomnia), 1 for drug interaction (with proton pump inhibitor used to treat gastro-esophageal reflux) and 1 died after Week 24 from illicit drug abuse. Serum creatinine, urinary proteins, and estimated GFR were assessed. The median variation in serum creatinine was +0.1 (IQR + 0.23 to -0.18, range + 0.47 to – 0.31) and the median estimated GFR decline was 10.3 ml/min (from 87.4 to 77.1). One patient had mild proteinuria at Baseline that resolved spontaneously by Week 24.

PK analysis of both drug's Ctrough performed in 9 subjects revealed suboptimal concentrations of RPV in 4 subjects and low concentrations in general (<20-38 ng/ml), while DTG median level was 445 ng/ml (range 334-1112).

The authors noted that the small pill size was appreciated by patients. Overall they concluded that DTG + RPV was safe, well-tolerated with only one drop out due to tolerability issues, and effective, controlling viral replication in all patients who took the therapy, with 90.9% of the sub-group who had 48-week follow-up fully suppressed.

Diaz et al. [Diaz, 2016] describe an ongoing cohort study of heavily pretreated patients with multiple virological failures and resistance mutations who were switched to a once daily regimen of DTG + RPV. Those with resistance to INSTIs or RPV were excluded. Follow-up visits were scheduled at 4, 12, 24 and 36 weeks after switching. Thirty-eight (38) patients were included. At Baseline, median age was 53.4 years and 34% were female. Median nadir and current CD4+ cell count were 179 and 592 cells/mm^3, respectively. Patients had received ART for a median 19.4 years with exposure to a median of 3.6 drug families (100% NRTI, 89.5% NNRTI, 97.4% PI, 61.7% INSTI, 10.5% T20, 10.5% CCR5 receptor antagonist; 87% NRTI+NNRTI+PI, 52.6% NRTI+NNRTI+PI+INSTI). Previous failures were documented to 1 or more regimens including NRTI (100%), PI (71%), NNRTI (68.4%), and INSTI (8.1%). Patients with primary ART mutations were: 64.7% to NRTI, 37% to NNRTI, and 31.6% to PI. No INSTI-associated mutations were detected. Median time of undetectable HIV RNA viral load with current regimens was 6.7 years. Patients were taking a median 4.3 pills before switching.

One patient (2.6%) left the study due to GI toxicity, and another one because of drug interaction with omeprazole. HIV-1 RNA remained below 37 c/mL in 100% (38/38) at Week 4, and 97% (33/34) at Week 24. CD4 count remained stable after switching (median 633 cells/mm3 at Week 24). There was a statistical improvement in triglycerides and liver tests, with no changes in total, HDL, and LDL-cholesterol. CKD-EPI estimated GFR decreased from 85 to 74 mL/min/1.73m^2 (95% CI 5.1-16.6, p=0.0002) at Week 24. The authors concluded that switching to a simple, dual regimen of DTG + RPV in heavily pretreated, multiply-failed, suppressed HIV-infected patients is safe and highly efficacious.

Grabmeier-Pfistershammer et al. [Grabmeier-Pfistershammer, 2016] describe a single center retrospective analysis of 45 chronically HIV-1-infected patients started on DTG + RPV in the last 3 years. Two patients (both with a very low baseline viral load) were ART-naïve and so excluded by the authors from further analysis. Forty-three (43) patients were ART-experienced and switched from a current cART. All were suppressed

at the time of switching. Reasons for changing treatment were mainly adverse events of their current regimen, predominately affecting the renal function (21/43), or treatment simplification (7/43). Median time on treatment is reported as 11 months (1-29 months). Three patients prematurely stopped treatment due to adverse events after 3 weeks to 5 months (not further specified), and 40/43 patients remained on DTG + RPV until the end of the observation time. No virologic failure occurred, and all patients were below level of quantification at the end of the observation time. The authors concluded that in this small, single center analysis, DTG + RPV dual therapy seems efficient and well-tolerated in a maintenance scenario.

Palacios et al. [Palacios, 2016] describe an open-label, non-controlled, multicenter study in Spain. Patients who switched from any regimen to DTG + RPV over a 12-month period were included. A total of 105 patients started DTG + RPV; 82 (78.1%) were virologically suppressed, 22 (20.9%) non-virologically suppressed (8 failures and 14 restart of ART), and there was 1 patient who was ART-naïve, who the authors did not include in the analysis. Of enrolled patients, 70.5% were male, mean age was 51.9 years, mean time of HIV infection was 214.7 months (IQR 140.4 – 288.9 months), and mean time on prior ART was 37.0 months (IQR 7.8 – 68.2 months). The most frequent reasons for switching were toxicity or intolerance (41.9%), convenience (27.6%), and drug interaction (17.1%). Prior regimens were based on PI (56.9%), INSTI (26.5%), or NNRTI (16.7%). At the time of this analysis, 85 patients had completed 24 weeks and all were still taking the same regimen. Eighty-two (96.5%) of them had an undetectable viral load; the 3 cases with detectable viral load (532, 316 and 75 c/ml) were not considered virologic failures. Mean CD4 cell count increased (622 vs 552 cell/µl; p=0.008), and a mean decrease in fasting triglycerides (-34.6 mg/dl; p=0.005) and glomerular filtration (-5.2 ml/min; p=0.004) were observed, with no changes detected in total cholesterol, HDL-cholesterol, LDL-cholesterol, creatinine, and ALT. No patient stopped DTG + RPV due to an adverse event. The authors concluded that DTG + RPV is effective and safe in a cohort of patients with long time of HIV infection and prior ART.

Gantner et al. [Gantner, 2016] describe a multicenter and retrospective study in the Dat'AIDS cohort, in which patients with a viral load <50 c/ml were started on DTG + RPV. A total of 152 patients started DTG + RPV mainly due to adverse events (47%) and simplification of treatment (30%). The median duration of follow-up after switch was 36 weeks (IQR 25-50). The cumulative percentages of patients without virological or therapeutic failure on DTG + RPV at Week 24 were 99.3% and 89.8%, respectively. There were 19 (13%) patients who discontinued DTG + RPV due to adverse events (mainly neurological). Three virological failures (defined as 2 consecutive HIV RNA >50 c/ml or 1 HIV-RNA >1000 c/ml) were identified. In 2 of the patients, the viral load came back to undetectable while they remained on DTG + RPV; patient 1 (Week 38, 1147 c/ml, wild strain), patient 2 (Week 39, 130 and 51 c/ml, wild strain). The third patient had intensification of treatment (Week 15, 1259 c/ml, no genotype). At Week 24, only a significant increase in creatinine was noted (11.1 + 5.4µmol/l; p<0.001). ALT remained normal. Pharmacological assays of DTG and RPV were performed in 23 patients; all results were above the IC90 of the two molecules and were consistent with the expected concentrations. The authors concluded that these data, in patients who are virologically suppressed, suggest that the combination of DTG + RPV could be an effective and well tolerated option for maintenance therapy.

Two further studies, describe a smaller number of subjects using DTG + RPV together. **Togami** et al. [Togami, 2016] describe 27 Japanese HIV-1-infected patients using DTG + RPV who were identified from a retrospective review of medical records. The majority were male (26/27) and mean age was 57 years. Median duration of regimen was 323 days (3-404 days). Twenty-five (25) of 27 patients were reported to have continued using DTG + RPV. Two patients had switched to another ARV combination regimen because of low drug susceptibility and drug interactions. HIV viral load was reported as being less than the detection limit for all patients after starting DTG + RPV. No specific safety information was reported.

Saling et al. [Saling, 2016] describe an observational retrospective study conducted in an inner-city HIV clinic, in which 14 patients received DTG + RPV after failing a previous regimen. Six out of 14 were African American, 6 were Caucasian, and 7 were male. Prior to the switch, 4 regimens were NNRTI-based, 5 PI-based, 6 INSTI-based, and 11 had a regimen containing a 2-NRTI backbone. Half of the patients had developed resistance to their previous regimens, with 4 patients having 2-class resistance and 3 resistant only to NRTIs. Nine patients had intolerance to their prior regimens. Patients had a combined total of 599 weeks of viral load <20 c/ml on DTG + RPV. No adverse events were identified. The authors concluded that this combination is both safe and well tolerated in patients who had experienced adverse events to their previous ART. DTG + RPV seems very efficacious in suppressing HIV viral load in those with prior resistance.

Ruiz et al. [Ruiz, 2016] and **Gubavu** et al. [Gubavu, 2015] report a total of 15 patients across their studies who received DTG + RPV. However no further information on these patients was reported.

Review of this information in a real-world setting has not identified any new risks or adverse drug reactions from that observed in the two Phase III clinical trials (201636 and 201637) of DTG + RPV. Across the studies, a high level of virological success was observed, and the number of AEs reported across the studies was low, suggesting that the use of DTG + RPV as a dual therapy is both efficacious and well tolerated in the real world. Where AEs were reported, these were consistent with the established safety profile for DTG and RPV.

Table 47 Summary of Articles Reporting Use of DTG and RPV as Dual Therapy

Article	Study design	Number on DTG + RPV Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Capetti et al. [Capetti, 2016] Full article Italy	Observational multicenter cohort TivEdO (TIVICAY plus EDURANT Observational Cohort).	132 patients on DTG +RPV 16 patients baseline viral load >50c/ml 67 patients (45.5%) had reverse transcriptase mutations – 46 to NRTIs alone, 1 to NNRTIs alone and 13 to both, including 6 to RPV. 69 (44.7%) had PI mutations, one had full INSTI resistance. 8 (6.1%) subjects had never had genotyping.	Median follow up 24 months	At Week 24 – 1 subject had viral rebound without mutations due to missed drug refill. At Week 48 (n=50): >50 c/ml: 1/50 (viral load 14770 c/ml). 1-49 /ml: 4/50: No virus detected: 45/50:	Subject with viral load >50 c/ml at Week 48 had frequently interrupted therapy – acquired RT mutations 138Q and 181C, integrase gene not affected. At baseline - 1 subject had low-level resistance to RPV, 1 intermediate resistance and 4 high-level resistances. None of the six failed. All had 48 week follow up information.	1 patient discontinued due to headache and insomnia; 1 patient discontinued due to DDI, 1 patient died after Week 24 from illicit drug abuse.	Median variation in serum creatinine was +0.1 (IQR + 0.23 to– 0.18, range + 0.47 to– 0.31) and the median estimated GFR decline was 10.3 ml/min (from 87.4 to 77.1).

Article	Study design	Number on DTG + RPV Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Diaz et al. [Diaz, 2016] Conference abstract	Ongoing cohort study	38 patients on DTG + RPV Heavily treatment experienced, multiple virological failures and resistance mutations. On complex suppressive therapy. Patients were fully suppressed at baseline. Patients with primary ART mutations were: 64.7% to NRTI, 37% to NNRTI, and 31.6% to PI. No INSTI-associated mutations were detected. Patients with resistance to DTG or RPV were excluded.	Follow up visits scheduled up to 36 weeks	Viral load <37 c/ml in 38/38 (100%) at Week 4, in 33/34 (97%) at Week 24.	-	1 patient discontinued due to GI toxicity. 1 patient withdrew due DDI with omeprazole.	Statistical improvement in triglycerides and liver tests, with no changes in total, HDL and LDL-cholesterol. CKD-EPI estimated GFR decreased from 85 to 74 mL/min/1.73m2 (95% CI 5.1-16.6, p=0.0002) at Week 24.

Article	Study design	Number on DTG + RPV Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Grabmeier-Pfistershammer et al. [Grabmeier-Pfistershammer, 2016] Conference abstract	Single centre, retrospective analysis	45 patients on DTG + RPV 43 treatment experienced, virologically suppressed at time of switch. 2 patients were treatment-naïve with very low baseline viral load – they were excluded from further analysis.	Median duration on treatment: 11 mths (range: 1-29 mths)	No virological failure. All patients below level of quantification at end of observation time.		3 patients discontinued due to AEs (not specified) after 3 weeks to 5 months.	
Palacios et al. [Palacios, 2016] Conference poster Spain	Open-label, non-controlled, multicentre	105 patients on DTG + RPV 78.1% virologically suppressed. 104 treatment experienced patients, 1 treatment-naïve (not included in analysis).	-	At Week 24, 82/85 (96.5%) were suppressed. 3 patients not suppressed – viral load 532, 316, and 75 c/ml, not considered virological failures.	-	No patient stopped due to AEs.	At Week 24 a mean decrease in fasting triglycerides (-34.6 mg/dL; p=0.005) and glomerular filtration (-5.2 mL/min; p=0.004) were observed, with no significant changes detected in total cholesterol, HDL-c, LDL-c, creatinine or ALT.

Article	Study design	Number on DTG + RPV Baseline characteristics	Follow up period / duration of treatment	Efficacy	Resistance	Adverse events	Investigations
Gantner et al. [Gantner, 2016] Poster	Multicentric, retrospective, cohort on Dat'AIDS cohort.	152 patients on DTG + RPV Patients with viral load <50 c/mL	Median duration of follow up: 36 weeks	At Week 24, percentage of patients without virological or therapeutic failure was 99.3% and 89.3%, respectively. 3 virological failures (2 consecutive viral loads >50 c/ml or 1 viral load >1000 c/ml).	-	12 discontinued due to AEs (noted as mainly neurological).	At Week 24, significant increase in creatinine noted (11.1 +/- 5.4 μmol/L; p<0.001). ALT remained normal.
Ruiz et al. [Ruiz, 2016] Conference abstract	Retrospective study; switch from triple to dual therapy.	4 patients on DTG + RPV Experienced HIV patients	-	-	-	-	-
Togami et al. [Togami, 2016] Conference abstract Japan	Retrospective review of medical records	27 patients on DTG + RPV	Median duration of treatment: 323 days (range 3 – 404 days)	Viral load reported as less than detection for all patients	-	-	-

Article	**Study design**	**Number on DTG + RPV** **Baseline characteristics**	**Follow up period / duration of treatment**	**Efficacy**	**Resistance**	**Adverse events**	**Investigations**
Gubavu et al. [Gubavu, 2015] Conference abstract	Monocentric ongoing study, subjects receiving DTG as monotherapy or dual therapy	11 patients on DTG + RPV Treatment experienced	-	-	-	-	-
Saling et al. [Saling, 2016] Conference abstract	Observational retrospective study in inner city HIV clinic	14 patients on DTG + RPV Half had developed resistance to their previous regimens, with four patients having 2 class-resistance and 3 resistant only to NRTIs.	-	Combined total of 599 weeks of viral load ≤20 c/ml	-	No AEs identified.	-

6.3.2. Post-Marketing Case Reports

A total of 5 spontaneous or post-marketing cases were identified on the GSK Global Clinical Safety database up to [redacted].

Three of these 5 cases describe the 3 patients who developed virological failure after taking DTG + RPV in the study by Gantner et al. [Gantner, 2016], which are described under Section 6.3.1. No further information in addition to that presented above was provided for these patients.

The fourth case, reported by a sale representative, describes information on a poster at a conference. A 5[redacted] year old female experienced drug-induced psychosis, insomnia, hallucinations, persecutory delusions, anxiety, irritability, restlessness, and a suicide attempt approximately 3 months after switching from etravirine and raltegravir to DTG + RPV. She was admitted to hospital and started on risperidone and clonazepam. She was switched back to etravirine and raltegravir; clinical improvement was observed and she was discharged from hospital. The patient had been treated for 5 years with antidepressants and benzodiazepines for anxiety and depressive symptoms.

The final case, reported by a nurse, concerns a 5[redacted] year old female, who experienced hair loss after starting DTG + RPV. The patient stopped DTG + RPV and then rechallenged it at a later date and the hair loss reappeared. Information on the time to onset and duration of alopecia were not provided, making the case difficult to assess.

A review of these five cases has not identified any significant new safety information for DTG or RPV. Depression, including suicidal ideation and behaviors, particularly in patients with a pre-existing history of depression or psychiatric illness is included in the GDS for DTG. Similarly, depression and depressed mood are included in Company Core DataSheet (CCDS) for RPV.

7. SAFETY CONCLUSIONS

Pivotal studies 201636 and 201637 evaluated the safety and efficacy of the new combination of DTG + RPV for the treatment of HIV-1 infection in ART-experienced adult patients, with viral load suppressed to <50 c/mL, and who are switching from their current 3-drug ART regimen (CAR). The goal of the DTG/RPV FDC program is to develop a FDC tablet of this 2-drug regimen. The 48-week data from studies 201636 and 201637 support the proposition that DTG + RPV is an effective and well tolerated regimen for the maintenance of HIV-1 suppression. This NRTI-sparing regimen has the potential to avoid short- and long-term toxicities seen with this class.

Key findings from the safety data for 201636 and 201637 are as follows:

- Over 48 weeks, the safety data from the two identical, randomized, open-label Phase III studies of subjects switching to DTG + RPV are consistent with current labeling and the known safety profile for the single entities. No new adverse drug reactions were observed.

- Greater proportions of subjects in DTG + RPV group compared with those in the CAR group reported AEs (77% vs 71%), drug-related AEs (19% vs 2%), and AEs leading to withdrawal (4% vs <1%), which is expected when comparing an open-label switch arm to subjects continuing their current tolerated treatment.
- There was no difference in the incidence of serious drug-related AEs, which was low for both treatment groups (<1% of subjects in each group).
- There was no evidence for an increased risk of rash with or without systemic symptoms with DTG + RPV compared with CAR. Serious rash was not observed in this study, including no reports of Stevens Johnson syndrome, toxic epidermal necrolysis, or erythema multiforme.
- The psychiatric AE profile for DTG + RPV was comparable to the known safety profile for the single entities. Psychiatric AEs leading to withdrawal, while the most common SOC with withdrawals, each occurred in less than 5 (<1%) subjects in the DTG + RPV group.
- There was no evidence for an increased risk of renal toxicity or hepatic toxicity for DTG + RPV compared with CAR.
- There were no clinically significant differences in the changes in lipid profile between the 2 groups.

Additional safety findings relevant to the DTG/RPV FDC program are as follows:

- The results of DEXA scans in Study 202094, supported by the bone biomarker data in studies 201636 and 201637, suggest a potential benefit of improving bone health in switching from a TDF-containing 3-drug antiretroviral regimen to a regimen of DTG + RPV.
- The data reported in publications from over 400 patients using DTG and RPV together support the efficacy and safety profile observed in the 201636 and 201637 Phase III trials.

8. APPENDIX

Appendix Table 1 Summary of Completed Safety Studies that were Previously Submitted as Part of the TIVICAY or EDURANT Registration and are Considered "Supportive" Single-Entity Studies for the Safety Assessment of the DTG/RPV FDC Submission

Study No. (Component) Document Identifier Status	Short Description of Study	Conclusion(s)
201102 (DTG) Status: Complete	Phase I, open-label, crossover study to evaluate the drug interaction between DTG and daclatasvir in healthy adult subjects	Plasma exposure of daclatasvir did not appear to be meaningfully affected when co-administered with DTG compared with daclatasvir administered alone. Co-administration of DTG 50 mg q24h with daclatasvir 60 mg q24h increased DTG AUC(0-τ), Cmax, and Cτ by approximately 33%, 29%, and 45%, respectively, compared with DTG administered alone. DTG and daclatasvir can be co-administered without dose adjustment.
ING111604 (DTG) Status: Complete	Phase I, open-label, single sequence, drug interaction study to evaluate plasma DTG and tenofovir PK in healthy adult subjects	PK parameters of DTG and TDF during combination therapy were similar to those when either drug was given alone, demonstrating no drug interaction. Therefore these two drugs can be taken together without dose adjustment.
ING111855 (DTG) Status: Complete	Double-blind study to evaluate the PK of an oral contraceptive containing norgestimate and ethinyl estradiol when co-administered with DTG to healthy adult female subjects	Co-administration with DTG had no effect on the PK of norelgestromin and ethinyl estradiol in healthy female subjects receiving Ortho-Cyclen. DTG and common oral contraceptives can be co-administered without dose adjustment.
ING115697 (DTG) Status: Complete	Phase I, open-label, randomized, two-cohort, two-period, one-way study to evaluate the effect of boceprevir and telaprevir on DTG PK in healthy adult subjects	Co-administration of DTG with BCV had no effect on plasma exposure of DTG. Co-administration of DTG with TVR resulted in increased DTG plasma exposures: AUC(0-τ), Cmax, Cτ, increased by 25%, 19%, 37%, respectively. Co-administration of BCV or TVR with DTG had no clinically significant effect on DTG PK. Plasma BCV and TVR PK data for the DTG-TVR combination treatment were similar to historical TVR data, indicating no effect of DTG on BCV or TVR exposure.

Study No. **(Component)** **Document Identifier** **Status**	**Short Description of Study**	**Conclusion(s)**
ING115698 (DTG) Status: Complete	Phase 1, open label, two-period drug interaction study to assess steady state plasma methadone enantiomer PK following co-administration of methdadone QD with DTG 50 mg twice daily in opiate-dependent, HIV seronegative adult subjects	Co-administration of methadone with repeat dose of 50 mg DTG had no effect on total, R-, and S-methadone pharmacokinetics. Co-administration of methadone with repeat dose of 50 mg DTG had no effect on methadone induced PD markers. No dose adjustment in methadone is required when given in combination with DTG.
ING116070 (DTG) Status: Complete	Single-arm study of the safety, efficacy and central nervous system and plasma PK of DTG 50 mg QD in combination with ABC/3TC FDC over 96 weeks in HIV-1-infected ART-naive adult subjects	DTG concentrations observed in CSF at both Week 2 and Week 16 exceed the in vitro IC_{50} against wild-type viruses (0.2 ng/mL) for all subjects suggesting that DTG is able to achieve therapeutic concentrations in the CSF. DTG concentrations were similar to the unbound DTG concentrations in plasma, with statistically significant correlations between DTG CSF and plasma, (both total and unbound) concentrations. A regimen of DTG + ABC/3TC was effective in decreasing CSF HIV-1 RNA levels.

Appendix Table 2 Description of Pivotal Efficacy and Safety Studies

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)
201636 (SWORD-1)	65 centers: Spain: 16, US: 14, Canada: 6, , France: 5, Germany: 5, Russia: 5, Belgium: 4, Italy: 4, Taiwan: 3, Australia: 2, Netherlands: 2, UK: 2, Argentina: 1	14 April 2015 Ongoing LSLV for Week 48: 16 September 2016. Data cut-off for Week 48: [redacted]	Non-inferior antiviral activity of switching to DTG + RPV once daily compared to continuation of CAR over 48 weeks in HIV-1-infected ART-experienced subjects	148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected adults with plasma HIV-1 RNA <50 c/mL. CAR for at least 6 months prior to Screening with 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	DTG 50 mg + RPV 25 mg oral tablets once daily with a meal or CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	ITT-E Population: DTG + RPV: 252 CAR: 256	DTG + RPV: 58F; 194M; 43.6 (2[redacted]-7[redacted]) years CAR: 51F; 205M; 43.6 (2[redacted]-7[redacted]) years	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E Population
201637 (SWORD-2)	60 centers: Spain: 15, US: 13, Canada: 7, Germany: 5, France: 6, Russia: 4, Taiwan: 4, Australia: 3, Argentina: 3, Italy: 2, UK: 1	21 April 2015 Ongoing LSLV for Week 48: 16 September 2016. Data cut-off for Week 48: [redacted]	Non-inferior antiviral activity of switching to DTG + RPV once daily compared to continuation of CAR over 48 weeks in HIV-1-infected ART-experienced subjects	148-week, Phase III, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-1-infected adults with plasma HIV-1 RNA <50 c/mL. CAR for at least 6 months prior to Screening with 2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV)	DTG 50 mg + RPV 25 mg oral tablets once daily with a meal or CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	ITT-E Population: DTG + RPV: 261 CAR: 255	DTG + RPV: 62F; 199M; 43.3 (2[redacted]-7[redacted]) years CAR: 57F; 198M; 43.2 (2[redacted]-6[redacted]) years	Proportion of subjects with plasma HIV-1 RNA <50 c/mL at Week 48 (Snapshot algorithm) in ITT-E Population

Protocol No.	No. Study Centers Location(s)	Study Start; Enrolments Status and Date; Total Enrolment /Target Enrolment	Study Objectives	Study Design	Diagnosis; Key Inclusion Criteria	Treatment Details (Drug; Dose; Form; Route; Frequency; Duration)	No. of Subjects by Group Entered/ Completed	Gender M/F; Mean Age (Range)	Primary Endpoint(s)
202094 (DEXA)	32 centers: Argentina, Belgium, Canada, Spain, UK, US	11 June 2015 Ongoing LSLV for Week 48: 16 September 2016. Data cut-off for Week 48: [redacted]	Change in from Baseline in total hip BMD at 48 weeks following switch from ART regimen containing TDF to DTG + RPV compared to continued therapy with the TDF-containing regimen	Open-label, parallel group sub-study of the 2 identical pivotal, Phase III, randomized, multicentre, parallel-group, non-inferiority studies, 201636 and 201637	HIV-1-infected adults screened and eligible for either 201636 or 201637 and received a TDF-containing regimen	Same treatment 201636 or 201637: DTG 50 mg + RPV 25 mg oral tablets once daily with a meal or CAR (2 NRTIs + INSTI, NNRTI, or PI/r (or unboosted ATV))	DTG + RPV: 53 CAR: 49	DTG + RPV: 27F; 26M 42.6 (2[redacted], 6[redacted]) years CAR: 26F; 23M 44.8 (2[redacted], 7[redacted]) years	Percentage change from baseline at Week 48 in total hip BMD as assessed by areal density in g/cm^2

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2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration**	**Total No. of Subjects by Group Entered/ Completed**	**Study Reporting Status/ Type of Report / Location of Report**
Biopharmaceutic Studies						
201674	To evaluate the relative bioavailability in the fed and fasted states of a single dose of DTG 50 mg and RPV 25 mg as a FDC tablet compared to co-administered of a single dose of the single-entity DTG and RPV products [Part 1] To evaluate the effect of food on the bioavailability of selected FDC formulation(s) of DTG and RPV [Part 2]	Relative oral bioavailability of different fixed dose combinations of DTG and RPV	Healthy adult subjects in fasted and fed states	DTG (clinical image) 50 mg; tablet; oral; single dose RPV (EDURANT) 25 mg; tablet; oral; single dose DTG + RPV tablets, DTG 50 mg, RPV 25 mg; tablet; oral; single dose (Product Code AS) DTG + RPV tablets, DTG 50 mg, RPV 25 mg; tablet; oral; single dose (Product Code AM) DTG + RPV tablets, DTG 50 mg, RPV 25 mg; tablet; oral; single dose (Product Code AQ) DTG + RPV tablets, DTG 50 mg, RPV 25 mg; tablet; oral; single dose (Product Code AK) DTG + RPV tablets, DTG 50 mg, RPV 25 mg; tablet; oral; single dose (Product Code AU)	Part 1: 27 Treated 24 Completed Part 2: 36 Treated 35 Completed	Completed CPSR 5.3.1.2

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration**	**Total No. of Subjects by Group Entered/ Completed**	**Study Reporting Status/ Type of Report / Location of Report**
201676	To evaluate the bioequivalence between an FDC tablet formulation of DTG 50 mg and RPV 25 mg vs. co-administration of the separate tablet formulations of DTG 50 mg plus RPV 25 mg, in the fed state	Randomized, open-label, 2-period, single-dose crossover study	Healthy adult subjects	Reference Treatment = DTG 50 mg tablet (clinical image) plus a single EDURANT 25 mg tablet Test Treatment = DTG and RPV FDC tablets, 50 mg/25 mg (Product Code AW)	118 Enrolled 113 Completed	Completed CPSR 5.3.1.2
Patient PD and PK/PK Study Reports						
202094	To evalute the change in BMD assessed by areal density in total hip at 48 weeks following switch of subjects from an ART regimen containing TDF to DTG + RPV once daily compared to continued therapy with the TDF-containing regimen	Open-label, parallel-group study (sub-study of two identical parent studies 201636 and 201637)	HIV-infected, ART-experienced adult subjects	NA (subjects did not receive study treatment as part of this sub-study; refer to 201636 and 201637 for treatment details of parent studies)	102 Enrolled 92 Ongoing	Ongoing Week 48 ACSR 5.3.4.2

2.7.6 Synopses of Individual Studies

Study Identifier (Identifier of Study Report)	**Study Objective(s)**	**Study Design**	**Healthy Subjects or Diagnosis of Patients**	**Treatment Details (Test Product(s); Dosage Regimen; Route; Duration**	**Total No. of Subjects by Group Entered/ Completed**	**Study Reporting Status/ Type of Report / Location of Report**
Efficacy and Safety Studies: Controlled Clinical Studies Pertinent to the Claimed Indication						
201636	To demonstrate the non-inferior antiviral activity of switching to DTG plus RPV once daily comopared to continuation of CAR over 48 weeks	Phase III, 148-week, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-infected, ART-experienced adult subjects	Test Treatment = DTG 50 mg; tablet; oral; once daily + RPV 25 mg; tablet; oral; once daily with a meal Reference Treatment = Continue CAR; regimen and dosing varies; could be boosted PI (or ATV unboosted) + 2 NRTIs; NNRTI + 2 NRTIs; or INI + 2 NRTIs	510 Randomized and exposed 483 Ongoing	Ongoing Week 48 Full CSR 5.3.5.1
201637	To demonstrate the non-inferior antiviral activity of switching to DTG plus RPV once daily compared to continuation of CAR over 48 weeks	Phase III, 148-week, randomized, open-label, active-controlled, multicenter, parallel-group, non-inferiority study	HIV-infected, ART-experienced adult subjects	Test Treatment = DTG 50 mg; tablet; oral; once daily + RPV 25 mg; tablet; oral; once daily with a meal vs. Reference Treatment = Continue CAR; regimen and dosing varies; could be boosted PI (or ATV unboosted) + 2 NRTIs; NNRTI + 2 NRTIs; or INI + 2 NRTIs	518 Randomized and exposed 481 Ongoing	Ongoing Week 48 Full CSR 5.3.5.1

ACSR = abbreviated clinical study report; ART = antiretroviral therapy; ATV = atazanavir; BMD = bone mineral density; CAR = current antiretroviral regimen; CPSR = clinical pharmacology study report; CSR = clinical study report; DTG = dolutegravir; FDC = fixed-dose combination; HIV = human immunodeficiency virus; INI = integrase inhibitor; NA = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleotide analogue reverse transcriptase inhibitor; PI = protease inhibitor; q24h = every 24 hours; RPV = rilpivirine; TDF = tenofovir disoproxil fumarate