Janssen Research & Development

Summary of Biopharmaceutic Studies and Associated Analytical Methods

Darunavir/Cobicistat 800/150-mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

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ABBREVIATIONS

ART	antiretroviral therapy
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{24h}	area under the plasma concentration-time curve over 24 hours
AUC_{∞}	area under the plasma concentration-time curve measured from time zero and extrapolated to infinity
AUC_{last}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
C_{0h}	predose plasma concentration
C_{24h}	24-hour plasma concentration
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COBI	cobicistat
CYP	cytochrome P450
DRV	darunavir
EDTA	ethylenediaminetetraacetic acid
EVG	elvitegravir
FDC	fixed-dose combination
FTC	emtricitabine
HIV-1	human immunodeficiency virus type 1
HPMC	hydroxypropyl methyl cellulose
LS	least square
MCC	microcrystalline cellulose
PK	pharmacokinetics
rtv	low-dose ritonavir
SD	standard deviation
SMCC	silicified microcrystalline cellulose
STR	single-tablet regimen
TDF	tenofovir disoproxil fumarate
t_{max}	time to reach maximum plasma concentration

SUMMARY OF BIOPHARMACEUTIC FINDINGS

The darunavir/cobicistat (DRV/COBI) fixed-dose combination (FDC) tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor. Cobicistat has recently been registered to be coadministered as a pharmacokinetic (PK) enhancer of DRV and atazanavir (ATV). The DRV/COBI 800/150-mg FDC tablet is dosed according to the same once-daily dose regimen as the single agents. The development program for the DRV/COBI 800/150-mg FDC tablet is therefore based on the clinical development programs for the DRV and COBI single agents; comprehensive clinical development programs have been conducted for the individual compounds. The PK bridging development program for this FDC tablet focused on the generation of additional clinical data to support the application.

In this Summary of Biopharmaceutic Studies and Associated Analytical Methods, data from a relative bioavailability study comparing DRV/COBI 800/150 mg coadministered as single agents with DRV/low-dose ritonavir (rtv) 800/100 mg coadministered as single agents, a relative bioavailability study comparing 2 candidate DRV/COBI 800/150-mg FDC tablet formulations with DRV/rtv 800/100 mg coadministered as single agents, and a bioequivalence study comparing the DRV/COBI 800/150-mg FDC tablet formulation with DRV/COBI 800/150 mg coadministered as single agents are presented in support of once-daily administration of the DRV/COBI 800/150-mg FDC tablet. Additionally, historical data on the effect of different food types on DRV PK when coadministered with rtv are presented in 1 study, and the effect of different food types on COBI PK when coadministered as the elvitegravir (EVG)/COBI/emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) single-tablet regimen (STR) are presented in 1 study. The bioanalytical methods and dissolution profiles supporting the DRV/COBI FDC are also summarized.

The data presented in this summary support the following main conclusions:

- The bioavailabilities of DRV administered as DRV/COBI 800/150-mg FDC candidate tablet formulations were comparable to DRV 800 mg when administered as a single agent with rtv 100 mg.
- With respect to DRV exposure, the intended commercial DRV/COBI 800/150-mg FDC tablet is bioequivalent to DRV/COBI 800/150 mg coadministered as single agents under fasted and fed conditions.
- In line with the single agent formulation for DRV, a food effect was observed for DRV when administered as the intended commercial DRV/COBI 800/150-mg FDC tablet. The mean maximum plasma concentration (C_{max}), area under the plasma concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), and area under the plasma concentration-time curve measured from time zero and extrapolated to infinity (AUC_{∞}) of DRV were increased 2.27-, 1.63-, and 1.70-fold, respectively, when the DRV/COBI FDC tablet was administered with a high-fat breakfast compared with administration under fasted conditions. It is therefore recommended that DRV/COBI 800/150-mg FDC tablets be taken with food.

- No food effect was observed for COBI exposure (C_{max}, AUC_{last}, and AUC_{∞}) when the DRV/COBI 800/150 mg FDC was administered with a high-fat breakfast, as compared with administration under fasted conditions.

1. BACKGROUND AND OVERVIEW

Darunavir (PREZISTA®, formerly known as TMC114) in combination with rtv is an HIV-1 protease inhibitor currently indicated for the treatment of HIV-1 infection in antiretroviral therapy (ART)-naïve and ART-experienced adults and pediatric patients 3 years of age and older. The dose regimen of DRV/rtv 800/100 mg daily (coadministered as single agents) is recommended in ART-naïve adults and ART-experienced adults with no DRV resistance-associated mutations and with a viral load of <100,000 HIV-1 RNA copies/mL and a CD4+ cell count of ≥100 cells/L at screening.

Cobicistat (formerly known as GS-9350) is a new chemical entity developed and registered by Gilead Sciences Inc. (Gilead) for use as a PK enhancer to increase systemic exposure of coadministered drugs metabolized by cytochrome P450 (CYP) 3A, including the HIV-1 integrase strand transfer inhibitor EVG, and the HIV protease inhibitors ATV and DRV. Cobicistat is a structural analog of rtv and a potent CYP3A inhibitor. Throughout its clinical development, COBI 150 mg once daily was generally safe and well tolerated, and boosted DRV, ATV, or EVG exposures to levels that were comparable to the boosting effect of coadministered rtv (refer to Summary of Clinical Efficacy in Module 2.7.3). Additionally, COBI 150 mg once daily is currently approved in the EU as part of an STR containing EVG, FTC, TDF, and COBI (STRIBILD®).

To reduce the pill burden of DRV-containing antiretroviral regimens, a DRV/COBI 800/150-mg FDC tablet has been developed. It is intended to be marketed for use in the same populations of HIV-1 infected subjects for which DRV/rtv 800/100 mg once daily is registered. Darunavir and COBI coadministered as single agents at a dose of 800/150 mg once daily was effective and generally safe and well tolerated in an ongoing Phase 3b study in HIV-1 infected ART-naïve adults and ART-experienced adults with no DRV resistance-associated mutations (study GS-US-216-0130, refer to the Summary of Clinical Efficacy in Module 2.7.3 and the Summary of Clinical Safety in Module 2.7.4). The clinical pharmacology information from this Phase 3b study is summarized in the Summary of Clinical Pharmacology Studies in Module 2.7.2.

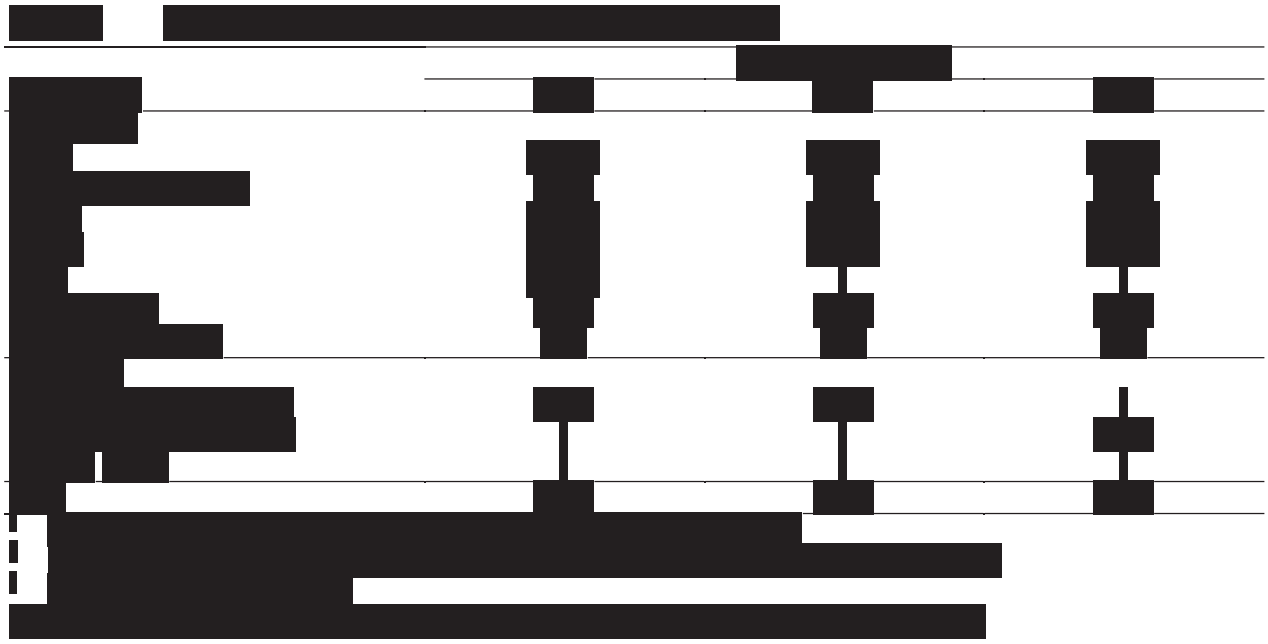
This Summary of Biopharmaceutic Studies and Associated Analytical Methods summarizes information from the 3 biopharmaceutic studies that have been conducted in healthy subjects to support the development of the DRV/COBI FDC tablet formulation intended for marketing, as well as 1 historical food effect study with DRV/rtv, and 1 historical food effect study with the EVG/COBI/FTC/TDF STR. One biopharmaceutic study compared the PK of DRV 800 mg when coadministered with COBI 150 mg as single agents with the PK of DRV 800 mg when coadministered with rtv 100 mg as single agents (GS-US-216-0115). A second study (TMC114IFD1001) compared the PK of DRV from 2 different DRV/COBI 800/150-mg FDC candidate tablet formulations (G003 and G004) with the PK of DRV 800 mg when coadministered with rtv 100 mg (administered as single agents). Although both FDC candidates showed acceptable DRV exposures, the G004 FDC tablet formulation was selected for further development based on other considerations, as outlined in Section 1.1.1. A pivotal bioequivalence study (TMC114IFD1003) was conducted to compare the PK of single-dose DRV and COBI from the DRV/COBI 800/150-mg G006 FDC tablet (identical to the G004 tablet

except for the nonfunctional color film coating) with the PK of DRV 800 mg coadministered with COBI 150 mg as single agents under fed and fasted conditions. The effect of a high-fat meal relative to fasting was also assessed with the FDC tablet in this study. Additionally, a study of different meal types (standard breakfast, high-fat breakfast, nutritional protein-rich drink, croissant with coffee) or fasted conditions on the PK of DRV 800 mg, when coadministered with rtv 100 mg as single agents, was conducted (TMC114-C143) to demonstrate that food type does not affect DRV exposure, which is also applicable to the DRV/COBI FDC. Likewise, historical data for the effect of different meal types (high-calorie/high-fat meal versus light meal) or fasting on COBI as part of the EVG/COBI/FTC/TDF STR are presented to demonstrate the lack of a clinically relevant food effect on COBI exposure.

1.1. Formulation Development

1.1.1. Overview and Rationale



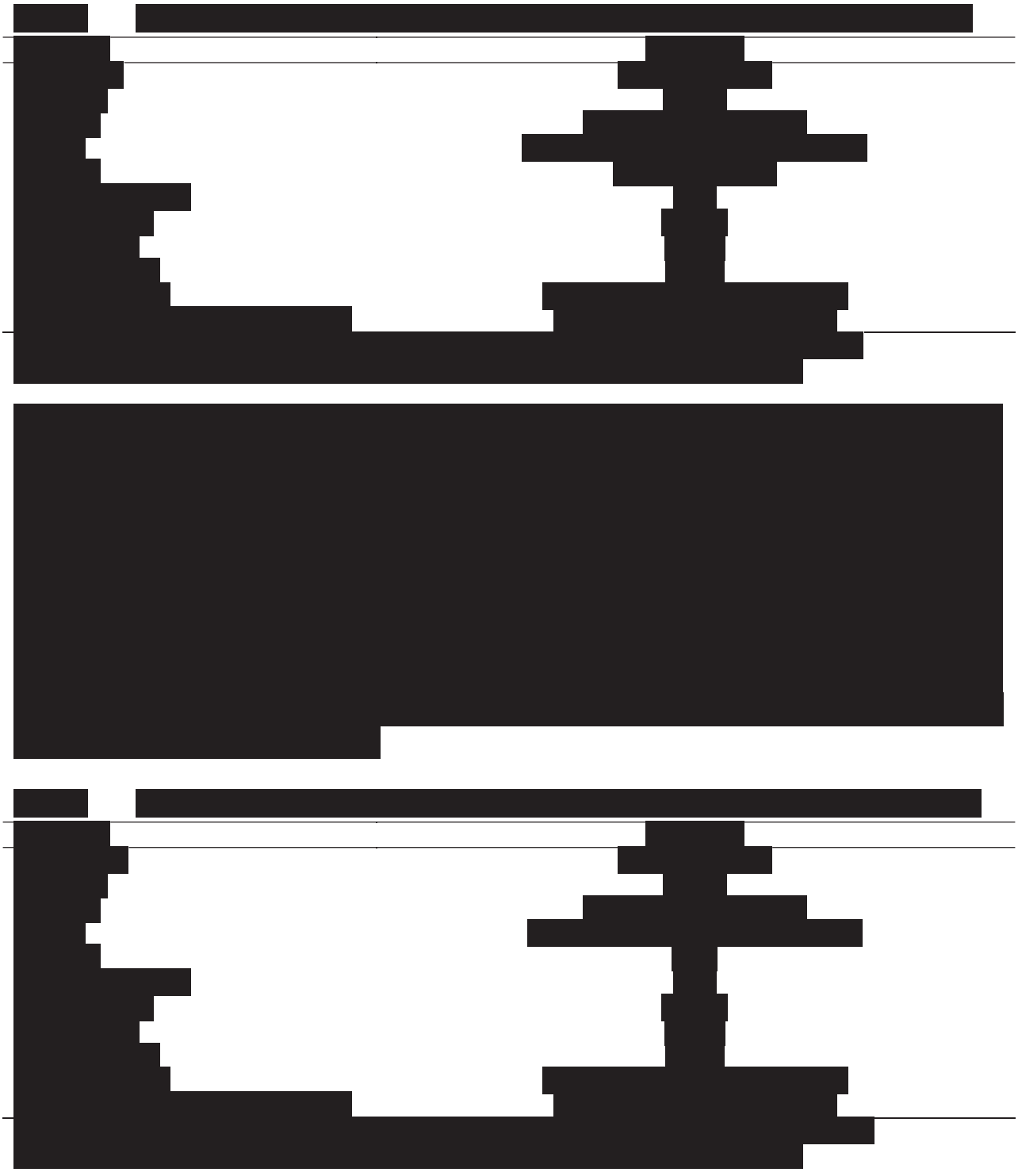


1.1.2. In Vitro Release of DRV/COBI FDC Tablets

1.1.2.1. Dissolution Evaluation Methods and Specifications







1.1.2.2. Dissolution Profiles of DRV and COBI in DRV/COBI FDC Tablets





1.2. Biopharmaceutic Studies

1.2.1. Overview and Rationale

An overview of the 5 completed clinical biopharmaceutic studies (GS-US-216-0115, TMC114IFD1001, TMC114IFD1003, TMC114-C143, GS-US-236-0105) evaluating the bioavailability of DRV and/or COBI as single agents, COBI as part of the EVG/COBI/FTC/TDF STR, or DRV and COBI coadministered as the DRV/COBI 800/150-mg FDC tablet formulations is presented in Appendix 2. More details are given in Section 2, in the tabular listing of all clinical studies (Module 5.2), in the synopses (Module 2.7.6), and in the study reports (Module 5.3). A tabular listing of these studies, together with information on the dosage form, formulation number, and dose, is provided in Table 6.

The effect of concomitant food intake on the oral bioavailability of the DRV/COBI FDC G006 tablet was also investigated in study TMC114IFD1003, and the effect of different meal types and fasted conditions on the oral bioavailability of DRV, coadministered with rtv, as single agents was investigated in study TMC114-C143. The effect of different meal types and fasted conditions on the oral bioavailability of COBI administered as the EVG/COBI/FTC/TDF STR tablet was investigated in study GS-US-236-0105.

Table 6: Clinical Biopharmaceutic Studies, Including Information on Dosage Form, Formulation Number, and Dose

Clinical Study Number (Abbreviated Number)	Dosage Form	Formulation Number	Dose
Relative Oral Bioavailability:			
GS-US-216-0115	2 x DRV 400-mg tablet + 1 x rtv 100-mg tablet	F030 (DRV)	800/100 mg
(Section 2.1.1)	2 x DRV 400-mg tablet + 1 x COBI 150-mg tablet	F030 (DRV)	800/150 mg
TMC114IFD1001	2 x DRV 400-mg tablet + 1 x rtv 100-mg tablet	F030 (DRV)	800/100 mg
(Section 2.1.2)	1 x DRV/COBI 800/150-mg FDC tablet	G003	800/150 mg
	1 x DRV/COBI 800/150-mg FDC tablet	G004	800/150 mg
Pivotal Bioequivalence:			
TMC114IFD1003	2 x DRV 400-mg tablet + 1 x COBI 150-mg tablet	F030 (DRV)	800/150 mg
(Section 2.2.1)	1 x DRV/COBI 800/150-mg FDC tablet	G006	800/150 mg
Food Effect:			
TMC114IFD1003 (Section 2.2.1)	1 x DRV/COBI 800/150-mg FDC tablet	G006	800/150 mg
TMC114-C143 (Section 2.3.1)	1 x DRV 400-mg tablet + 1 x rtv 100-mg tablet[a]	F014	400/100 mg[a]
GS-US-236-0105 (Section 2.3.2)	1 x EVG/COBI/FTC/TDF 150/150/200/300 mg FDC tablet single dose	FDC	150/150/200/ 300 mg

[a] DRV was given as a single dose of 400 mg and rtv was given at 100 mg bid from 2 days before until 2 days after DRV administration.

Source: Module 5.3.1.2/GS-US-216-0115-CSR; Module 5.3.1.1/TMC114IFD1001-CSR; Module 5.3.1.2/TMC114IFD1003-CSR; Module 5.3.1.1/TMC114-C143-CRR; Module 5.3.1.1/GS-US-236-0105

A total of 250 subjects were treated in the 5 completed biopharmaceutic studies summarized in this document, as shown in Table 7.

Table 7: Numbers of Subjects Treated in Completed Biopharmaceutic Studies

Type of Study (Study Number)	Number of Studies	Population	Number of Subjects
Relative oral bioavailability (GS-US-216-0115; TMC114IFD1001)	2	Healthy subjects	69 (36 + 33)
Pivotal bioequivalence/Food effect (TMC114IFD1003)	1	Healthy subjects	133
Food effect (TMC114-C143; GS-US-236-0105)	2	Healthy subjects	48 (24 + 24)
Total	5	-	250

Source: Module 5.3.1.2/GS-US-216-0115-CSR; Module 5.3.1.1/TMC114IFD1001-CSR; Module 5.3.1.2/TMC114IFD1003-CSR; Module 5.3.1.1/TMC114-C143-CRR; Module 5.3.1.1/GS-US-236-0105

1.2.1.1. Relative Bioavailability

DRV (as a single agent) is approved for use in combination with low-dose rtv, which acts as a booster of DRV exposure. COBI (as a single agent) is registered as a booster of DRV. An FDC of the 2 single agents (DRV and COBI) reduces the pill burden. To support the FDC development, 1 biopharmaceutic study was conducted to compare the oral bioavailability of DRV when DRV 800 mg was coadministered with COBI 150 mg as single agents versus DRV when DRV 800 mg was coadministered with rtv 100 mg as single agents (study GS-US-216-0115) (see Section 2.1.1), and a second study was conducted to compare the oral bioavailabilities of DRV and COBI after administration of 2 different candidate DRV/COBI FDC oral formulations that were considered for use during clinical development (study TMC114IFD1001) (Section 2.1.2). In the latter study (study TMC114IFD1001), 2 DRV/COBI 800/150-mg FDC tablet formulations (G003 and G004) were compared with DRV 800 mg and rtv 100 mg coadministered as single agents. The only differences between these 2 FDC tablet formulations were the type of binder used (SMCC/MCC versus SMCC-only for G003 and G004, respectively) and the tablet weight (1,545 mg and 1,648 mg for G003 and G004, respectively) (Table 1). As both FDC tablet formulations provided comparable exposure, the G004 FDC tablet was selected for further development because it closely aligns with the DRV 800-mg tablet formulation and employs the simplest drug product composition.

1.2.1.2. Bioequivalence

One pivotal bioequivalence study (TMC114IFD1003) was conducted to compare the DRV/COBI 800/150-mg G006 FDC tablet (identical to the G004 tablet except for the nonfunctional coating color) with DRV/COBI 800/150 mg administered as single agents under fed and fasted conditions (see Section 2.2.1).

1.2.1.3. Food Effect

In study TMC114IFD1003, the effect of concomitant food intake (high-fat breakfast) on the oral bioavailability of the DRV/COBI 800/150-mg G006 FDC tablet was also investigated (see Section 2.2.1). In study TMC114-C143, the effect of different meal types (standard breakfast, high-fat breakfast, nutritional protein-rich drink, croissant with coffee) and fasted conditions on the oral bioavailability of DRV, when a single dose of DRV 400 mg (F014 tablet) was coadministered with rtv 100 mg twice daily as single agents, was investigated to demonstrate that food type does not affect DRV exposure, which also applies to the DRV/COBI FDC (see

Section 2.3.1). In study GS-US-236-0105, the effect of different meal types (high-calorie/high-fat meal versus light meal) or fasting on COBI when a single dose of the EVG/COBI/FTC/TDF 150/150/200/300 mg STR was administered was investigated to demonstrate the lack of a clinically relevant food effect on COBI exposure (see Section 2.3.2).

1.2.2. Critical Aspects of Methods Used

In all 5 studies summarized in this Summary of Biopharmaceutic Studies and Associated Analytical Methods, randomization was used to minimize bias in the assignment of subjects to treatment groups, thereby enhancing the validity of statistical comparisons across treatment groups. All studies had an open-label, randomized, crossover design, which is a widely accepted means of comparing the PK of different formulations. The crossover design allowed for intrasubject comparison. A washout period of at least 4 days between successive sessions of drug intake was considered sufficient to avoid carryover effects considering the elimination half-life of DRV (15 to 19 hours), rtv (approximately 4 hours), and COBI (3 to 4 hours). In studies TMC114IFD1001 and GS-US-216-0115, dosing for 10 days was considered sufficient to achieve steady-state for all compounds, and ensured maximum inhibition of CYP3A. In study TMC114IFD1003, only single doses of each study drug were administered for the evaluation of bioequivalence and food effect. In study TMC114-C143, single doses of DRV coadministered with multiple doses of rtv were used to evaluate the effect of different types of food or fasting on DRV PK in the presence of rtv. In study GS-US-236-0105, single doses of the EVG/COBI/FTC/TDF STR were administered.

For DRV, pairwise comparisons between 2 treatments for C_{max} and area under the plasma concentration-time curve (AUC) values in the biopharmaceutic studies were based on least square (LS) means ratios and their 90% confidence intervals (CIs). Equivalence between treatments or absence of food effect were concluded if the 90% CIs were within 80.00% to 125.00%.[1]

1.3. Bioanalytical Methods

1.3.1. Introduction

All plasma assays for unchanged drug were validated according to the applicable guidelines, and all acceptance criteria as specified in the guidelines were met (EMA Guideline on Bioanalytical Method Validation).[2] An overview of the validation parameters for each method used in studies in which DRV and COBI were coadministered is provided in Appendix 3, including a link to each method validation report. An overview of the analytical methods that were used for each clinical study where DRV and COBI were coadministered is provided in Appendix 4. An overview of the validation parameters for methods used in the historical studies with DRV and rtv is provided in Appendix 5, with a list of which clinical studies used each method. The in-study method validation parameters are part of the individual clinical study reports.

1.3.2. Measurement of Unchanged Drug in Plasma

1.3.2.1. DRV

In studies TMC114IFD1001 and GS-US-216-0115, DRV was analyzed using analytical method BA1119, validated at [redacted]. This method was based on analytical method BA819, validated at Janssen Research and Development, and was partially validated after transfer to [redacted]. Briefly, 50 µL of plasma was precipitated with acetonitrile, and analyzed on a Waters XBridge 3 cm x 4.6 mm, 3.5 µm C18 column. Detection was performed on an API-4000 mass spectrometer. Further details are available in Module 5.3.1.4/TMC114-BA1119.

In study TMC114IFD1003, DRV was analyzed using analytical method BA10396, validated at [redacted]. This method was based on analytical method BA819 validated at Janssen Research and Development and analytical method BA1389 validated at [redacted]. The method was validated for analysis of DRV in the presence of COBI. Briefly, 50 µL of plasma was precipitated with acetonitrile, and analyzed on a Waters XBridge 3 cm x 4.6 mm, 3.5 µm C18 column. Detection was performed on an API-4000 mass spectrometer. Further details are available in Module 5.3.1.4/TMC114-BA10396.

In study GS-US-216-0130, DRV was analyzed using analytical method BA10243, validated at [redacted]. This method was based on analytical method BA819 validated at Janssen Research and Development and analytical method BA1389 validated at [redacted]. The method was validated for analysis in potassium ethylenediaminetetraacetic acid (EDTA) plasma. Briefly, 50 µL of plasma was precipitated with acetonitrile, and analyzed on a Waters XBridge 3 cm x 4.6 mm, 3.5 µm C18 column. Detection was performed on an API-4000 mass spectrometer. Further details are available in Module 5.3.1.4/TMC114-BA10243.

1.3.2.2. COBI

In studies GS-US-216-0115, TMC114IFD1001, TMC114IFD1003, GS-US-216-0130, and GS-US-236-0105, COBI was analyzed using analytical method [redacted], validated at [redacted]. Briefly, 50 µL of plasma was extracted using solid-phase extraction on an Oasis HLB (30 µm, 10 mg) column. Elution was done with acetonitrile:water:formic acid (90:10:0.1/v:v:v). Samples were analyzed on a Waters XBridge 50 mm x 2.1 mm, 3.5 µm C18 column. Detection was performed on an API-4000 mass spectrometer. Further details are available in Module 5.3.1.4/[redacted].

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The clinical biopharmaceutic studies that support the indication for which marketing approval is requested are summarized in this section and listed in Appendix 2. Supplementary information about these studies is provided in the tabular listing of all clinical studies (Module 5.2), in the synopses (Module 2.7.6) and in the study reports (Module 5.3).

The following sections provide a summary of the information obtained in the 5 biopharmaceutic studies that were conducted to support development of the intended commercial DRV/COBI FDC tablet. Throughout this document, references to plasma concentrations refer to total concentrations (bound and unbound) and references to drug exposure refer to the AUC_{24h}, unless stated otherwise.

2.1. Relative Bioavailability Studies

2.1.1. Study GS-US-216-0115: Relative Bioavailability and PK of DRV Following Coadministration of DRV With COBI or With rtv

GS-US-216-0115-CSR

Module 5.3.1.2/GS-US-216-0115-CSR

2.1.1.1. Objective

To evaluate the relative oral bioavailability and PK of DRV 800 mg when coadministered with COBI 150 mg as single agents versus DRV 800 mg when coadministered with rtv 100 mg as single agents.

2.1.1.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-period crossover study to investigate the oral bioavailability of DRV 800 mg when coadministered with either COBI 150 mg or rtv 100 mg, both of which are CYP3A inhibitors (ie, PK boosters of DRV).

The study population consisted of 33 healthy subjects. All subjects received multiple oral doses of study medication in each of 2 sessions in a randomized order:

- Treatment A (test): 2 DRV 400-mg commercial tablets (F030) and 1 COBI 150-mg tablet once daily for 10 days;
- Treatment B (reference): 2 DRV 400-mg commercial tablets (F030) and 1 rtv 100-mg capsule once daily for 10 days.

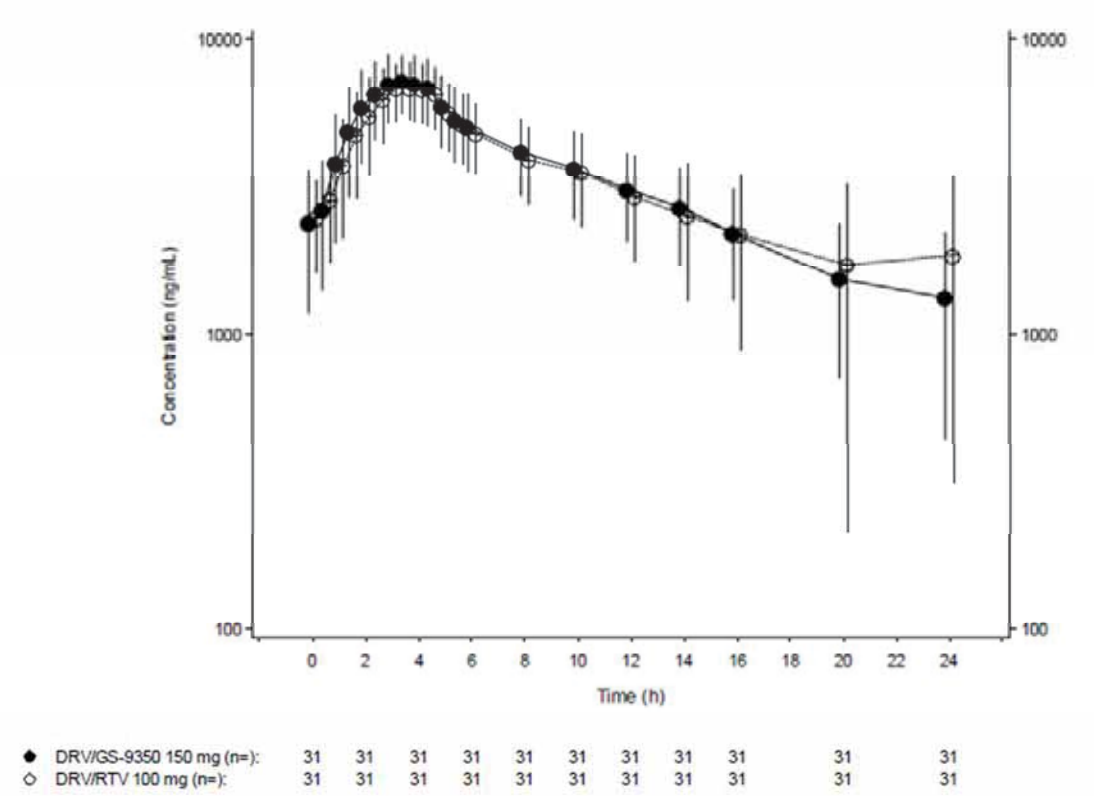
All treatments were taken under fed conditions within 5 minutes after a standardized breakfast. Treatments were separated by a washout period of at least 4 days.

2.1.1.3. Results

2.1.1.3.1. DRV PK

The mean (standard deviation [SD]) DRV plasma concentration-time curves obtained after administration of DRV with COBI were similar to those obtained after administration of DRV with rtv (Figure 1).

Figure 1: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Administration of DRV 800 mg Once Daily With Either COBI 150 mg Once Daily or rtv 100 mg Once Daily (Day 10) (Study GS-US-216-0115)



Source: Module 5.3.1.2/GS-US-216-0115-CSR/Figure 10-3

The LS means ratios for predose (C_{0h}) and 24-hour (C_{24h}) plasma concentrations of DRV when DRV was coadministered with COBI relative to DRV coadministered with rtv were 89% and 69%, respectively; the lower bound 90% CIs were below 80.00% whereas the upper bound 90% CIs were within 125.00% (Table 8). The C_{max} and AUC_{24h} values for DRV when DRV was coadministered with COBI were comparable to DRV coadministered with rtv; the 90% CIs were contained within the 80.00% to 125.00% bounds. The median time to reach maximum plasma concentration (t_{max}) was 3.0 hours for DRV both when coadministered with COBI and when coadministered with rtv.

To evaluate the ability of COBI versus rtv to boost DRV and to provide similar or lower variability in DRV PK, the degree of fluctuation and swing in peak-to-trough values were assessed. Comparable peak-to-trough variability was seen for DRV irrespective of whether the boosting agent was COBI (mean [SD], 1.99 [0.446]) or rtv (mean [SD], 1.81 [0.512]).

Differences in swing were noted when DRV was boosted with COBI (mean [SD], 8.12 [8.735]) compared with rtv (mean [SD], 4.60 [3.574]); however, the lower swing with rtv may be attributed to the increase in DRV trough when DRV was coadministered with rtv.

The increase in DRV plasma concentration between 20 and 24 hours postdose (C_{20h} and C_{24h}, respectively) occurred more frequently with DRV/rtv (19/31, 61.3%) than with DRV/COBI (7/32, 21.9%).

Table 8: PK Parameters of DRV Following Administration of DRV 800 mg Once Daily With COBI 150 mg Once Daily or With rtv 100 mg Once Daily (Day 10) (Study GS-US-216-0115)

	Mean (SD); t_{max}: Median (Q1; Q3)		Test/Reference Least Square Means Ratio, % (90% CI)
Parameter	**Test**	**Reference**	
	DRV/COBI 800/150 mg qd	**DRV/rtv 800/100 mg qd**	
N	31	31	
t_{max}, h	3.00 (2.72; 3.50)	3.00 (3.00; 4.00)	-
C_{0h}, ng/mL	2,396 (1,215)	2,484 (852)	89.39 (80.36; 99.44)
C_{24h}, ng/mL[a]	1,333 (890)	1,867 (1,555)	69.43 (59.02; 81.68)
C_{max}, ng/mL	7,737 (1,689)	7,464 (1,517)	103.36 (100.34; 106.48)
AUC_{24h}, ng.h/mL[b]	81,084 (25,151)	79,987 (27,200)	101.78 (97.40; 106.36)

N=maximum number of subjects with data; qd=once daily.

[a] Reported as $C_{\#}$.

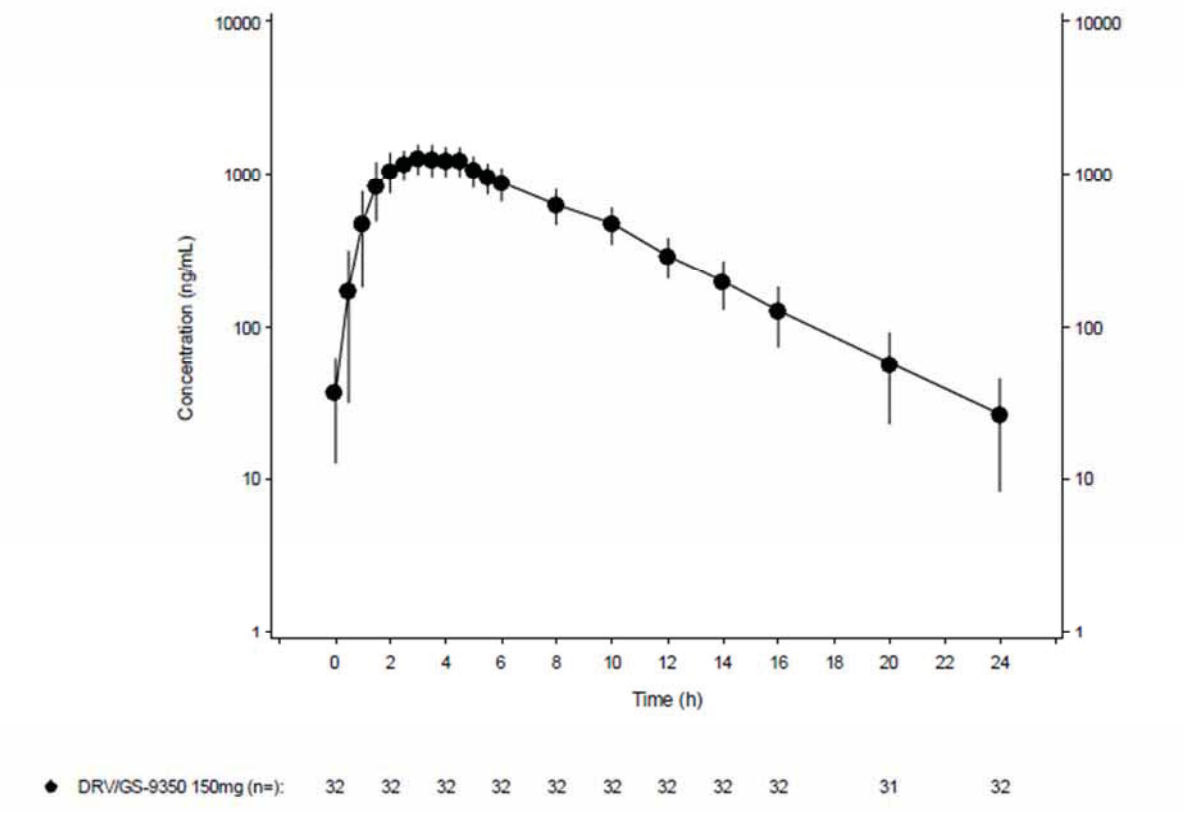
[b] Reported as $AUC_{\#}$.

Source: Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-3 and Table 10-4

2.1.1.3.2. COBI PK

The mean (SD) plasma concentrations of COBI after coadministration with DRV 800 mg increased rapidly to a maximum at approximately 3.5 hours and then declined over 24 hours (Figure 2).

Figure 2 Mean (SD) Plasma Concentration-Time Profiles of COBI Following Administration of DRV/COBI 800/150 mg Once Daily (Day 10) (Study GS-US-216-0115)



Source: Module 5.3.1.2/GS-US-216-0115-CSR/Figure 10-1

The PK of COBI following 10 days of coadministration with DRV are summarized in Table 9.

Table 9: PK Parameters of COBI Following Administration of DRV/COBI 800/150 mg Once Daily (Day 10) (Study GS-US-216-0115)

Parameter	Mean (SD); t_{max}: Median (Q1; Q3)
N	32
t_{max}, h	3.50 (3.00; 4.00)
C_{24h}, ng/mL[a]	27.0 (18.8)
C_{last}, ng/mL	27.0 (18.8)
C_{max}, ng/mL	1,376 (268)
AUC_{24h}, ng.h/mL[b]	10,370 (2,147)
$t_{1/2,term}$, h	3.4 (0.6)

C_{last}=last observed quantifiable plasma concentration; N=maximum number of subjects with data.
[a] Reported as $C_{\#}$.
[b] Reported as $AUC_{\#}$.
Source: Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-1

2.1.1.3.3. RTV PK

The PK of rtv following 10 days of coadministration with DRV are summarized in Table 10.

Table 10: PK Parameters of rtv Following Administration of DRV/rtv 800/100 mg Once Daily (Day 10) (Study GS-US-216-0115)

Parameter	Mean (SD); t_{max}: Median (Q1; Q3)
N	31
t_{max}, h	4.08 (4.00; 4.50)
C_{24h}, ng/mL[a]	60.1 (40.5)
C_{last}, ng/mL	60.1 (40.5)
C_{max}, ng/mL	1,159 (448)
AUC_{24h}, ng.h/mL[b]	6,694 (2,218)
$t_{1/2,term}$, h	7.3 (2.4)

C_{last}=last observed quantifiable plasma concentration; N=maximum number of subjects with data.
[a] Reported as $C_{\#}$.
[b] Reported as $AUC_{\#}$.
Source: Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-2

2.1.1.4. Conclusion

Exposure (C_{max} and AUC_{24h}) of DRV when coadministered with COBI was comparable to exposure of DRV when coadministered with rtv; the 90% CIs for the LS means ratios were contained within the 80.00% to 125.00% bounds. The LS means ratios for C_{0h} and C_{24h} values of DRV were 89% and 69%, respectively. Exposure of COBI was comparable to what has been observed in other studies.

2.1.2. Study TMC114IFD1001: Relative Oral Bioavailability of DRV/COBI 800/150 mg Administered as 2 Different FDC Tablet Formulations Compared With DRV/rtv 800/100 mg Administered as Single Agents

TMC114IFD1001

Module 5.3.1.1/TMC114IFD1001-CSR

2.1.2.1. Objective

To compare the oral bioavailability of DRV/COBI 800/150 mg administered as 2 different FDC tablet formulations (G003 and G004) with DRV/rtv 800/100 mg coadministered as single agents.

2.1.2.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-period crossover study to investigate the oral bioavailability of DRV/COBI 800/150 mg administered as 2 different FDC tablet formulations compared with DRV/rtv 800/100 mg coadministered as single agents. The 2 FDC formulations are identical in formulation except for the binder (SMCC/MCC in G003 resulting in a 1,500-mg tablet and SMCC-only in G004 resulting a 1,600-mg tablet).

The study population consisted of 36 healthy subjects. All subjects received multiple oral doses of study medication in each of 3 sessions in a randomized order:

- Treatment A (reference): 2 DRV 400-mg commercial tablets (F030) and 1 rtv 100-mg tablet once daily for 10 days;
- Treatment B (test): 1 DRV/COBI 800/150-mg FDC tablet (G003) once daily for 10 days;

! Treatment C (test): 1 DRV/COBI 800/150-mg FDC tablet (G004) once daily for 10 days.

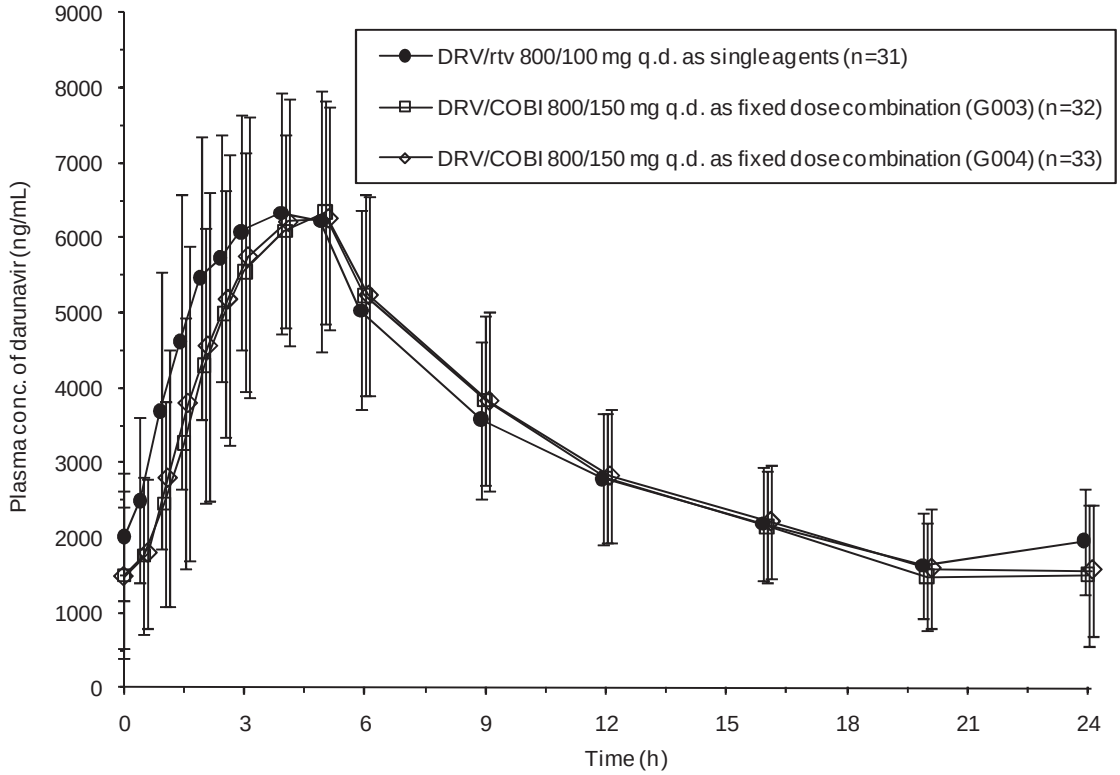
All treatments were taken under fed conditions within 30 minutes after a standardized breakfast. Treatments were separated by a washout period of at least 7 days.

2.1.2.3. Results

2.1.2.3.1. DRV PK

The mean (SD) DRV plasma concentration-time curves obtained with the 2 DRV/COBI FDC tablet formulations were similar to the reference DRV tablet F030 that was coadministered as a single agent with rtv (Figure 3).

Figure 3: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Administration of 2 Different FDC Tablet Formulations of DRV/COBI 800/150 mg Once Daily (G003 and G004) Compared With DRV/rtv 800/100 mg Once Daily Coadministered as Single Agents (Day 10) (Study TMC114IFD1001)



Source: Module 5.3.1.1/TMC114IFD1001-CSR/Figure 2

The LS means ratio for the minimum plasma concentration (C_{min}) of DRV with the DRV/COBI G003 FDC tablet relative to the reference DRV tablet (F030) coadministered with rtv as a single agent was 69% (Table 11). The LS means ratios for C_{max} and AUC_{24h} of DRV with the DRV/COBI G003 FDC tablet were comparable to DRV coadministered with rtv as a single agent; the 90% CIs were contained within the 80.00% to 125.00% bounds.

The LS means ratio for DRV C_{min} with the DRV/COBI G004 FDC tablet relative to the reference DRV tablet coadministered with rtv as a single agent was 74%. The C_{max} and AUC_{24h} values for DRV with the DRV/COBI G004 FDC tablet were comparable to DRV coadministered with rtv as a single agent; the 90% CIs were contained within the 80.00% to 125.00% bounds. The median t_{max} was 4.0 hours for the DRV/COBI G004 FDC tablet and DRV as a single agent tablet coadministered with rtv; t_{max} was 5.0 hours for the DRV/COBI G003 FDC tablet.

A higher DRV C_{24h} relative to C_{20h} was more frequent with DRV/rtv (28/32, 87.5%) than for either of the DRV/COBI FDC formulations (G003: 12/33, 36.4% and G004: 13/32, 40.6%).

Table 11: PK Parameters of DRV Following Administration of 2 Different FDC Tablet Formulations of DRV/COBI 800/150 mg (G003 and G004) Compared With DRV/rtv 800/100 mg Coadministered as Single Agents (Day 10) (Study TMC114IFD1001)

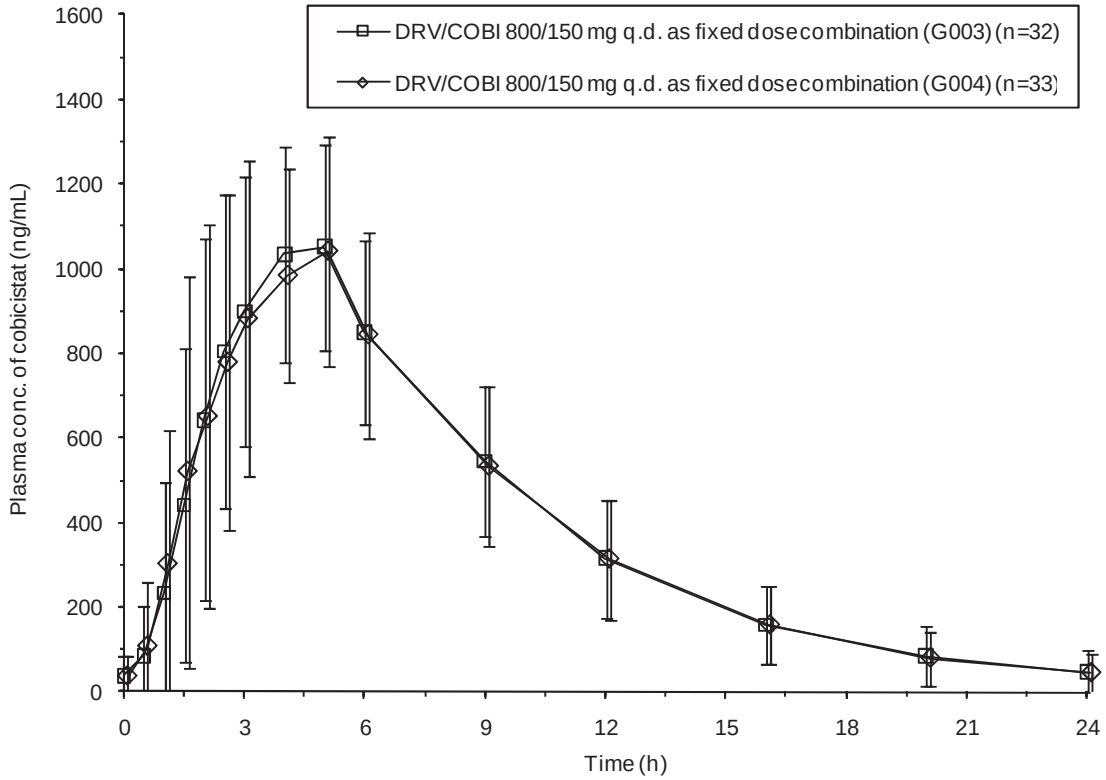
	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
Parameter	**Test**	**Reference**	
	DRV/COBI 800/150 mg FDC qd (G003)	**DRV/rtv 800/100 mg qd**	
N	33	32	
t_{max}, h	5.0 (2.5-6.0)	4.0 (1.5-5.0)	-
C_{0h}, ng/mL	1,504 (1,114)	2,015 (852.3)	-
C_{min}, ng/mL	1,167 (786.6)	1,540 (610.7)	69.28 (59.59; 80.56)
C_{max}, ng/mL	6,666 (1,287)	6,973 (1,527)	96.69 (92.48; 101.09)
AUC_{24h}, ng.h/mL	74,780 (19,750)	78,410 (20,910)	96.80 (92.04; 101.80)
	DRV/COBI 800/150 mg FDC qd (G004)	**DRV/rtv 800/100 mg qd**	
N	33	32	
t_{max}, h	4.0 (1.5-5.0)	4.0 (1.5-5.0)	-
C_{0h}, ng/mL	1,478 (933.8)	2,015 (852.3)	-
C_{min}, ng/mL	1,224 (680.6)	1,540 (610.7)	73.78 (63.41; 85.84)
C_{max}, ng/mL	6,917 (1,394)	6,973 (1,527)	99.90 (95.52; 104.47)
AUC_{24h}, ng.h/mL	76,490 (20,900)	78,410 (20,910)	98.72 (93.83; 103.87)

N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 7, Table 8, Table 9, and Supporting Data Display PK10

2.1.2.3.2. COBI PK

The mean (SD) COBI plasma concentration-time curves obtained with the 2 DRV/COBI FDC tablet formulations (G003 and G004) were comparable (Figure 4).

Figure 4 Mean (SD) Plasma Concentration-Time Profiles of COBI Following Administration of 2 Different FDC Tablet Formulations of DRV/COBI 800/150 mg (G003 and G004) (Day 10) (Study TMC114IFD1001)



Source: Module 5.3.1.1/TMC114IFD1001-CSR/Figure 4

The mean systemic exposure (C_{max} and AUC_{24h}) of COBI was comparable for the DRV/COBI G003 and G004 FDC tablets (Table 12). The median t_{max} was 4.0 hours for both formulations.

Table 12: PK Parameters of COBI Following Administration of 2 Different FDC Tablet Formulations of DRV/COBI 800/150 mg (G003 and G004) (Day 10) (Study TMC114IFD1001)

Parameter	Mean (SD); t_{max}: Median (Range)	
	DRV/COBI 800/150 mg qd G003	DRV/COBI 800/150 mg qd G004
N	33	33
t_{max}, h	4.0 (2.0-5.0)	4.0 (1.0-5.0)
C_{0h}, ng/mL	39.3 (44.7)	36.3 (47.2)
C_{min}, ng/mL	34.0 (37.8)	31.9 (40.1)
C_{max}, ng/mL	1,136 (233)	1,158 (250)
AUC_{24h}, ng.h/mL	9,386 (2,666)	9,314 (2,652)
$C_{ss,av}$, ng/mL	391 (111)	388 (111)

$C_{ss,av}$=average plasma concentration at steady-state; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 11

2.1.2.3.3. RTV PK

The PK of rtv following 10 days of coadministration with DRV are summarized in Table 13.

Table 13: PK Parameters of rtv Following Multiple-Dose Administration of DRV/rtv 800/100 mg (Day 10) (Study TMC114IFD1001)

Parameter	Mean (SD); t_{max}: Median (Range)
	DRV/rtv 800/100 mg qd
N	32
t_{max}, h	5.0 (4.0-6.0)
C_{0h}, ng/mL	54.8 (32.9)
C_{min}, ng/mL	37.5 (21.1)
C_{max}, ng/mL	728 (299)
AUC_{24h}, ng.h/mL	5,310 (2,101)
$C_{ss,av}$, ng/mL	221 (87.5)

$C_{ss,av}$=average plasma concentration at steady-state; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 10

2.1.2.4. Conclusion

Exposure (C_{max} and AUC_{24h}) of DRV with each of the 2 different DRV/COBI 800/150-mg FDC tablet formulations (G003 and G004) was comparable to that of DRV coadministered with rtv as a single agent; the 90% CIs for the LS means ratios were contained within the 80.00% to 125.00% bounds. The LS means ratio for the C_{min} of DRV was 69% for the G003 tablet and 74% for the G004 tablet; the lower bound 90% CIs were below 80.00% whereas the upper bound 90% CIs were within 125.00%. Exposure of COBI was comparable for the G003 and G004 tablets.

2.2. Comparative Bioavailability and Bioequivalence

2.2.1. Study TMC114IFD1003: Pivotal Bioequivalence Study of DRV Following Coadministration With COBI as an FDC Formulation or as Single Agents, Under Fasted and Fed Conditions

TMC114IFD1003

Module 5.3.1.2/TMC114IFD1003-CSR

2.2.1.1. Objective

To assess the bioequivalence of DRV following coadministration of DRV with COBI as an 800/150 mg-FDC tablet (G006) compared with administration of each component as single agents (2 DRV commercial 400-mg tablets [F030] and 1 COBI commercial 150-mg tablet) under fasted and fed conditions, and to assess the effect of a high-fat breakfast on the exposure of DRV and COBI when administered as the DRV/COBI G006 FDC tablet.

2.2.1.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-panel, crossover study to investigate the oral bioequivalence of DRV/COBI 800/150 mg administered as the G006 FDC tablet formulation compared with DRV/COBI 800/150 mg administered as 2 DRV 400-mg tablets (F030) and 1 COBI 150-mg tablet. The effect of food (high-fat breakfast) on the oral bioavailability of the DRV/COBI G006 FDC tablet was also investigated.

The study population consisted of 133 healthy subjects divided into 3 panels of 74, 40, and 19 (treated) subjects. Within each panel, subjects received single oral doses of DRV/COBI FDC or DRV/COBI coadministered as single agents in each of 2 sessions in a randomized order:

Panel 1:

- Treatment A (reference): 2 DRV 400-mg commercial tablets (F030) and 1 COBI 150-mg commercial tablet, fasted;
- Treatment B (test): 1 DRV/COBI 800/150-mg FDC tablet (G006), fasted.

Panel 2:

- Treatment C (reference): 2 DRV 400-mg commercial tablets (F030) and 1 COBI 150-mg commercial tablet, fed (standardized breakfast);
- Treatment D (test): 1 DRV/COBI 800/150-mg FDC tablet (G006), fed (standardized breakfast).

Panel 3:

- Treatment E (reference): 1 DRV/COBI 800/150-mg FDC tablet (G006), fasted;
- Treatment F (test): 1 DRV/COBI 800/150-mg FDC tablet (G006), fed (high-fat breakfast).

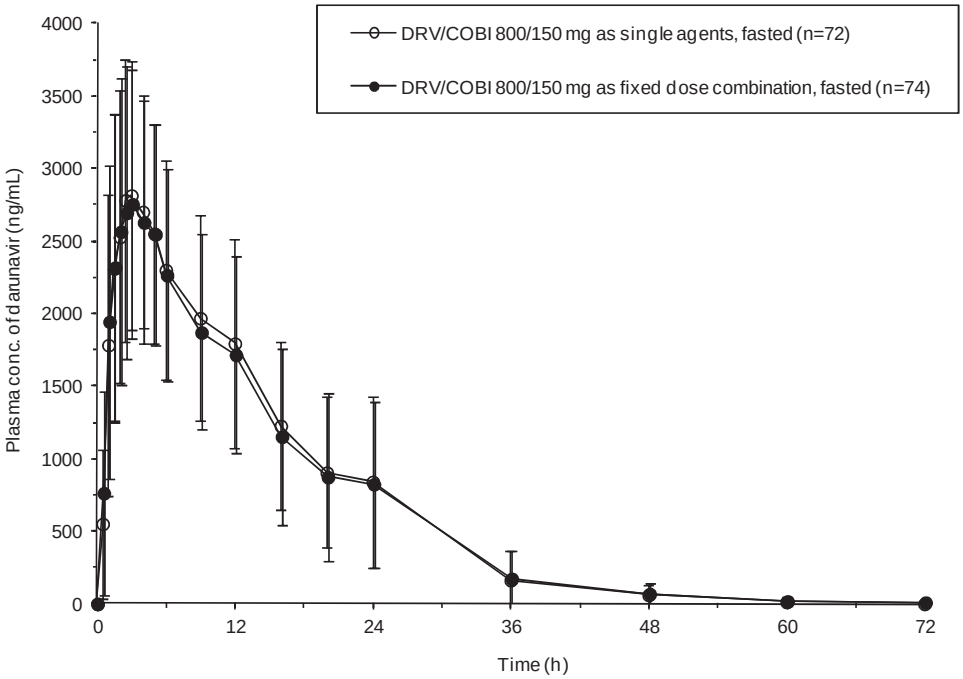
Treatments were separated by a washout period of at least 7 days.

2.2.1.3. Results

2.2.1.3.1. DRV PK

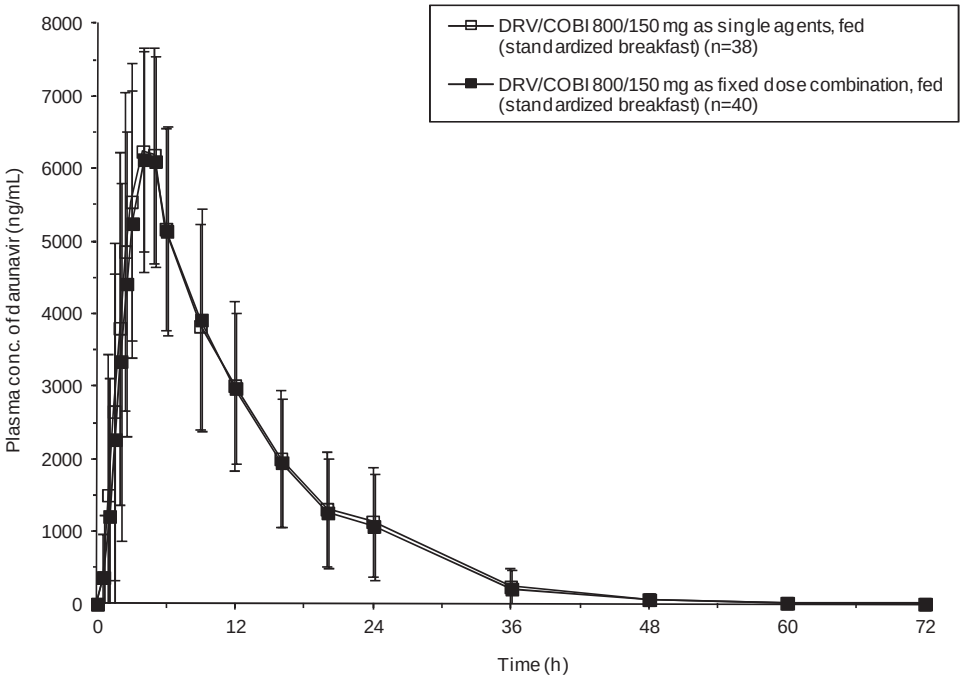
The mean (SD) DRV plasma concentration-time curves obtained after administration of the DRV/COBI 800/150-mg G006 FDC tablet were comparable to those obtained after administration of DRV/COBI 800/150 mg as single agents under both fasted (Figure 5) and fed (Figure 6) conditions.

Figure 5: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Single-Dose Administration of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fasted Conditions (Study TMC114IFD1003)



Source: Module 5.3.1.2/TMC114IFD1003-CSR/Figure 3

Figure 6: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Single-Dose Administration of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fed Conditions (Study TMC114IFD1003)



Source: Module 5.3.1.2/TMC114IFD1003-CSR/Figure 5

The LS means ratios for DRV exposure (C_{max}, AUC_{last}, AUC_{∞}) were comparable following administration of DRV and COBI as the DRV/COBI G006 FDC tablet and as single agents under both fasted and fed conditions; the 90% CIs were contained within the 80.00% to 125.00% bounds (Table 14). Under fasted conditions, median t_{max} was 3.0 hours for both the FDC tablet and DRV coadministered with COBI as a single agent. Under fed conditions, the median t_{max} of DRV was 4.0 hours for both the FDC tablet and DRV coadministered with COBI as a single agent.

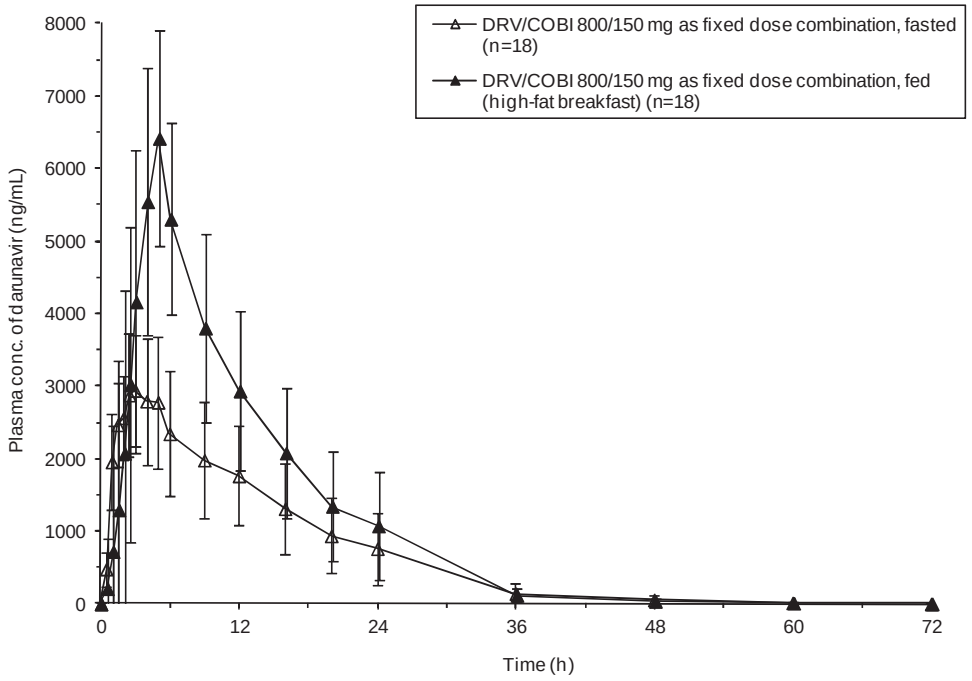
Table 14: PK Parameters of DRV Following Single-Dose Administration of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fasted and Fed Conditions (Study TMC114IFD1003)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Fasted		
	DRV/COB1 800/150 mg FDC (G006)	**DRV 800 mg (F030) and COBI 150 mg**	
N	74	72	
t_{max}, h	3.00 (1.00-12.00)	3.00 (1.00-12.00)	-
C_{max}, ng/mL	3,087 (927)	3,129 (933)	98.59 (93.72; 103.73)
AUC_{last}, ng.h/mL	46,329 (18,476)	47,326 (18,314)	96.20 (90.98; 101.71)
AUC_{∞}, ng.h/mL	46,291 (18,781)	47,668 (18,689)	96.00 (90.30; 102.07)
$t_{1/2term}$, h	7.6 (3.5)	7.2 (3.3)	-
	Fed (Standardized Breakfast)		
	DRV/COB1 800/150 mg FDC (G006)	**DRV 800 mg (F030) and COBI 150 mg**	
N	40	38	
t_{max}, h	4.03 (1.50-9.05)	4.00 (1.00-9.00)	-
C_{max}, ng/mL	6,773 (1,343)	6,979 (1,201)	96.76 (93.06; 100.60)
AUC_{last}, ng.h/mL	78,942 (26,709)	81,483 (27,540)	97.71 (93.08; 102.57)
AUC_{∞}, ng.h/mL	78,811 (27,304)	79,836 (26,913)	97.81 (92.85; 103.05)
$t_{1/2term}$, h	6.7 (3.4)	5.5 (1.6)	-
	DRV/COB1 800/150 mg FDC (G006)		
	Fed (High-Fat Breakfast)	**Fasted**	
N	18	18	
t_{max}, h	4.50 (1.50-6.00)	3.00 (1.00-5.07)	-
C_{max}, ng/mL	7,053 (1,057)	3,173 (859)	227.09 (205.75; 250.63)
AUC_{last}, ng.h/mL	75,258 (21,632)	47,356 (17,723)	163.18 (144.90; 183.78)
AUC_{∞}, ng.h/mL	76,165 (22,090)	43,985 (13,548)	170.20 (148.50; 195.06)
$t_{1/2term}$, h	6.6 (3.2)	6.8 (3.1)	-

N=maximum number of subjects with data; $t_{1/2term}$=terminal elimination half-life.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 12, Table 13, Table 16, Table 17, Table 20, and Table 21

The maximum concentration for DRV was lower, and occurred, earlier when the DRV/COBI FDC tablet was administered under fasted conditions compared with administration with a high-fat breakfast (Figure 7). A faster decline in plasma concentrations was observed under fed conditions than under fasted conditions. The LS means ratios for C_{max}, AUC_{last}, and AUC_{∞} of DRV were 227%, 163%, and 170%, respectively, when the DRV/COBI FDC tablet was administered with a high-fat breakfast compared with administration under fasted conditions (Table 14). The median t_{max} of DRV with the DRV/COBI G006 FDC tablet formulation was 3.0 hours under fasted conditions and 4.5 hours with a high-fat breakfast.

Figure 7: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Single-Dose Administration of a DRV/COBI 800/150 mg FDC Tablet Formulation (G006) Under Fasted Versus Fed (High-Fat Breakfast) Conditions (Study TMC114IFD1003)

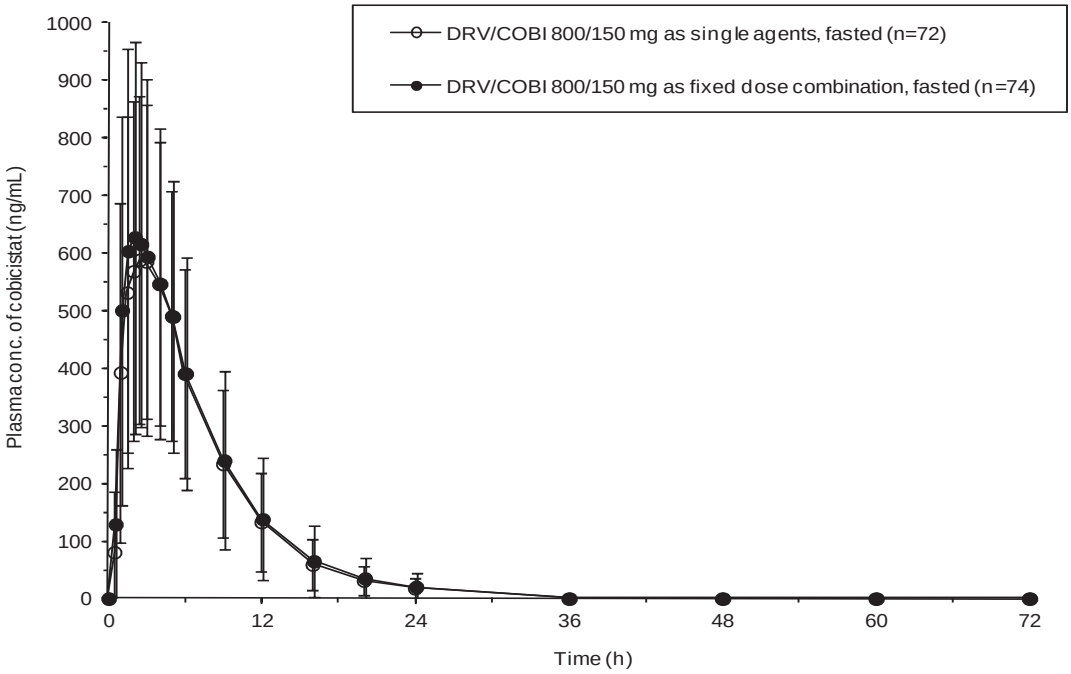


Source: Module 5.3.1.2/TMC114IFD1003-CSR/Figure 7

2.2.1.3.2. COBI PK

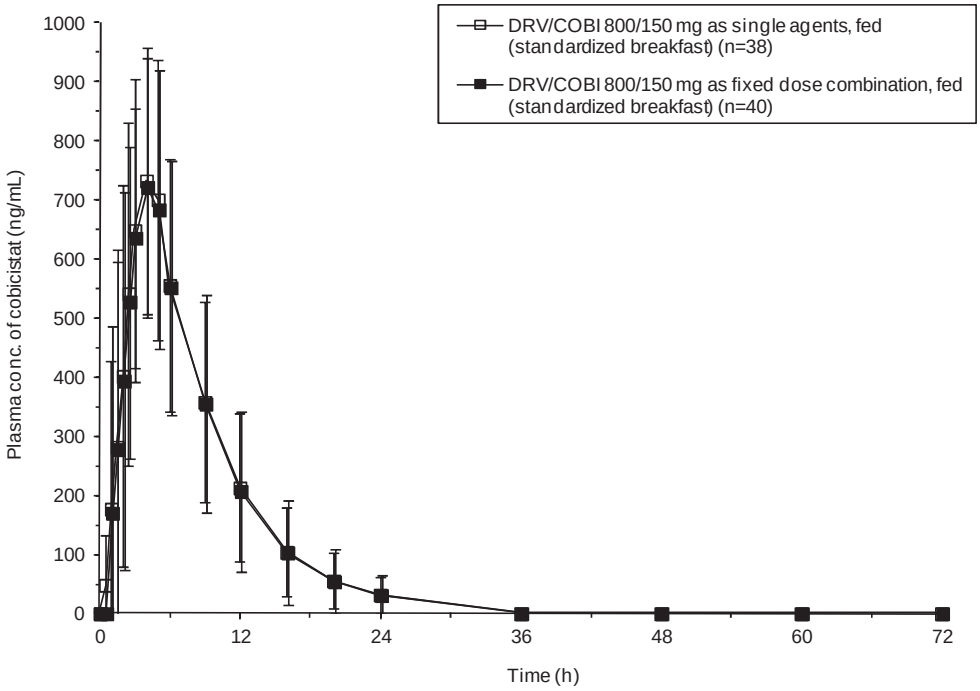
The mean (SD) COBI plasma concentration-time curves obtained after administration of the DRV/COBI 800/150-mg G006 FDC tablet were comparable to those obtained after administration of DRV/COBI 800/150 mg as single agents under both fasted (Figure 8) and fed (Figure 9) conditions.

Figure 8: Mean (SD) Plasma Concentration-Time Profiles of COBI Following Single-Dose Administration of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fasted Conditions (Study TMC114IFD1003)



Source: Module 5.3.1.2/TMC114IFD1003-CSR/Figure 4

Figure 9: Mean (SD) Plasma Concentration-Time Profiles of COBI Following Single-Dose Administration of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fed Conditions (Study TMC114IFD1003)



Source: Module 5.3.1.2/TMC114IFD1003-CSR/Figure 6

The LS means ratios for COBI exposure (C_{max}, AUC_{last}, and AUC_{∞}) were comparable following administration of DRV and COBI as the DRV/COBI FDC tablet and as single agents under both fasted and fed conditions; the 90% CIs were all within the 80.00% to 125.00% bounds (Table 15). Under fasted conditions, the median t_{max} of COBI was 2.0 hours for the DRV/COBI FDC tablet and 2.5 hours for COBI coadministered with DRV as a single agent. Under fed conditions, the median t_{max} of COBI was 4.0 hours for both the FDC tablet and for COBI coadministered with DRV as a single agent.

Table 15: PK Parameters of COBI Following Single-Dose Administration of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fasted and Fed Conditions (Study TMC114IFD1003)

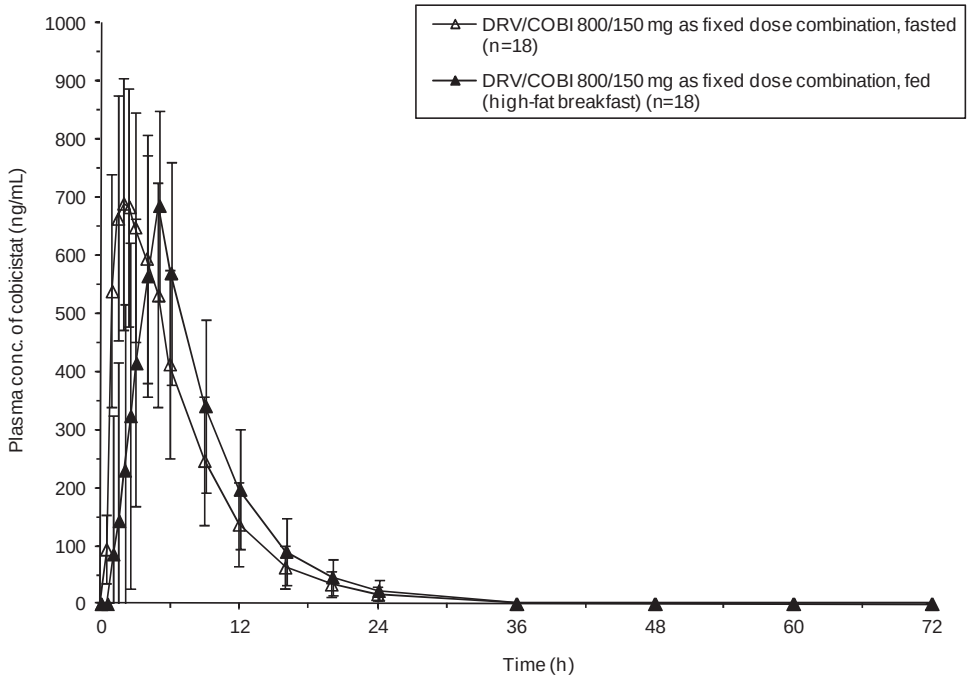
Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Fasted		
	DRV/COBI 800/150 mg FDC (G006)	**DRV800 mg (F030) and COBI 150 mg**	
N	73	72	
t_{max}, h	2.00 (1.00-5.03)	2.50 (1.00-5.03)	-
C_{max}, ng/mL	697 (339)	664 (301)	103.40 (94.25; 113.44)
AUC_{last}, ng.h/mL	5,219 (3,051)	4,962 (2,493)	101.20 (91.77; 111.61)
AUC_{∞}, ng.h/mL	5,448 (3,005)	5,106 (2,474)	104.33 (94.85; 114.77)
$t_{1/2term}$, h	3.9 (0.8)	4.0 (0.9)	-
	Fed (Standardized Breakfast)		
	DRV/COBI 800/150 mg FDC (G006)	**DRV800 mg (F030) and COBI 150 mg**	
N	40	38	
t_{max}, h	4.00 (1.00-5.02)	3.99 (1.00-5.03)	-
C_{max}, ng/mL	819 (221)	823 (208)	97.65 (93.77; 101.70)
AUC_{last}, ng.h/mL	6,285 (2,735)	6,401 (2,745)	97.82 (94.65; 101.10)
AUC_{∞}, ng.h/mL	6,388 (2,779)	6,511 (2,784)	97.77 (94.60; 101.05)
$t_{1/2term}$, h	3.8 (0.8)	3.9 (0.9)	-
	DRV/COBI 800/150 mg FDC (G006)		
	Fed (High-Fat Breakfast)	**Fasted**	
N	18	18	
t_{max}, h	4.98 (1.00-6.00)	2.00 (0.98-4.00)	-
C_{max}, ng/mL	769 (174)	741 (222)	106.02 (98.34; 114.29)
AUC_{last}, ng.h/mL	5,491 (1,425)	5,459 (1,959)	103.83 (96.32; 111.93)
AUC_{∞}, ng.h/mL	5,526 (1,478)	5,532 (1,967)	104.31 (96.45; 112.82)
$t_{1/2term}$, h	3.9 (0.7)	3.9 (0.7)	-

N=maximum number of subjects with data; $t_{1/2term}$=terminal elimination half-life.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 14, Table 15, Table 18, Table 19, Table 22, and Table 23

The shape of the COBI plasma concentration-time curves was similar when the DRV/COBI FDC tablet was administered under fasted conditions and when it was administered with a high-fat breakfast (Figure 10). Maximum plasma concentrations of COBI were similar under both conditions, but were reached earlier under fasted conditions compared with administration after a high-fat breakfast. The LS means ratios for COBI exposure (C_{max}, AUC_{last}, and AUC_{∞}) were comparable when the DRV/COBI FDC tablet was administered with a high-fat breakfast or under fasted conditions; the 90% CIs were all within the 80.00% to 125.00% bounds (Table 15).

The median t_{max} of COBI with the DRV/COBI FDC tablet formulation was 2.0 hours under fasted conditions and 5.0 hours with a high-fat breakfast.

Figure 10: Mean (SD) Plasma Concentration-Time Profiles of COBI Following Single-Dose Administration of a DRV/COBI 800/150 mg FDC Tablet Formulation (G006) Under Fasted Versus Fed (High-Fat Breakfast) Conditions (Study TMC114IFD1003)



Source: Module 5.3.1.2/TMC114IFD1003-CSR/Figure 8

2.2.1.4. Conclusion

Exposure (C_{max} and AUC_{24h}) of DRV with the DRV/COBI G006 FDC tablet was bioequivalent to the exposure of DRV coadministered with COBI as a single agent under both fasted and fed (standardized breakfast) conditions; the 90% CIs for the LS means ratios were contained within the 80.00% to 125.00% bounds. The LS means ratios for C_{max}, AUC_{last}, and AUC_{∞} of DRV were 227%, 163%, and 170%, respectively, when the DRV/COBI FDC tablet was administered with a high-fat breakfast compared with administration under fasted conditions.

Exposure of COBI with the DRV/COBI FDC tablet was comparable to COBI coadministered with DRV as a single agent under both fasted and fed (standardized breakfast) conditions; the 90% CIs for the LS means ratios were contained within the 80.00% to 125.00% bounds for all comparisons. Exposure of COBI with the DRV/COBI FDC tablet was comparable following administration with a high-fat breakfast and under fasted conditions; the 90% CIs for the LS means ratios were contained within the 80.00% to 125.00% bounds.

2.3. Food Effect Studies

2.3.1. Study TMC114-C143: Effect of Food on Bioavailability of DRV Coadministered With rtv

TMC114-C143

Module 5.3.1.1/TMC114-C143-CRR

2.3.1.1. Objective

To assess the effect of different meal types on DRV PK following coadministration of DRV/rtv 400/100 mg.

2.3.1.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-panel, 3-way crossover study to investigate the effect of food and different types of meals on the bioavailability of a single dose of DRV (400 mg, tablet formulation F014) coadministered with multiple doses of rtv 100 mg twice daily. The study population consisted of 24 healthy subjects divided equally into 2 panels. In 3 sessions, Panel 1 received Treatments A, B, and C, and Panel 2 received Treatments A, D, and E. For all treatments, a single dose of 400 mg DRV was administered, and rtv 100 mg twice daily was given from 2 days before until 2 days after administration of DRV. Darunavir was taken immediately after 1 of 4 types of meals at breakfast, or under fasted conditions, as follows:

- Standard breakfast (Treatment A): 4 slices of bread, 1 slice of ham, 1 slice of cheese, butter, jelly, and 2 cups of coffee or tea with milk and/or sugar, if desired. Kcal: 533, fat: 21 g, carbohydrates: 67 g, protein: 19 g;
- Fasted conditions (Treatment B): fasted for at least 10 hours before drug administration, water intake was allowed up to 2 hours prior to drug administration;
- High-fat breakfast (Treatment C): 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese and 240 mL of whole milk. Kcal: 928, fat: 56 g, carbohydrate: 65 g, protein: 41 g;
- Nutritional protein-rich drink (Ensure®, 8 fl. oz.) (Treatment D): Kcal: 250, fat: 8.4 g, carbohydrate: 33.4 g, protein: 10.5 g;
- Croissant with coffee (Treatment E): Kcal: 240, fat: 12 g, carbohydrate: 28 g, protein: 5 g.

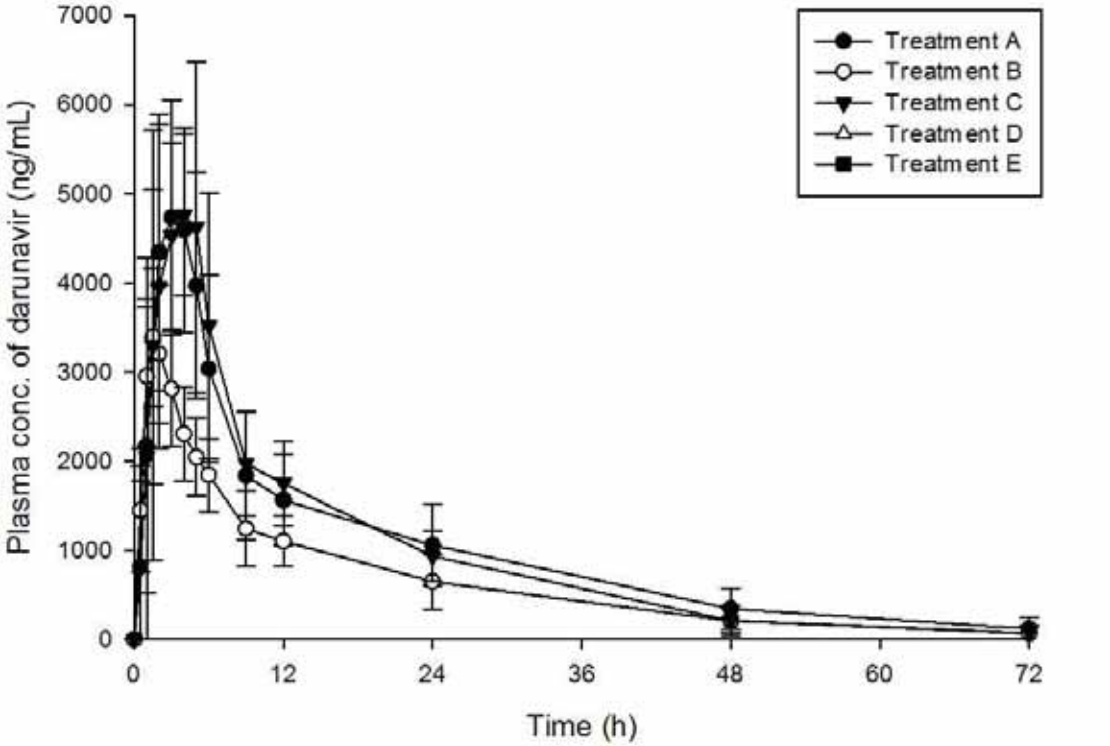
Treatments were separated by a washout period of at least 7 days.

2.3.1.3. Results

2.3.1.3.1. DRV PK

The mean DRV plasma concentration-time curves obtained after administration of DRV/rtv with different meal types is shown in Figure 11. The mean plasma concentration-time profiles of DRV were comparable for all administrations under fed conditions (Treatments A, C, D, and E). Compared with these treatments, administration of DRV under fasted conditions (Treatment B) resulted in a lower mean DRV plasma concentration-time profile.

Figure 11: Mean Plasma Concentration-Time Profiles of DRV Following a Single Oral Dose of DRV 400 mg, Coadministered With rtv 100 mg Twice Daily, With Different Meal Types (Study TMC114-C143)



Treatment A=standard breakfast; Treatment B=fasted conditions; Treatment C=high-fat breakfast; Treatment D=nutritional protein-rich drink; Treatment E=croissant and coffee.
Source: Module 5.3.1.1/TMC114-C143-CRR/Figure 2

The LS means ratios for DRV exposure (C_{max}, AUC_{last}) following a high-fat breakfast, nutritional protein-rich drink, or croissant and coffee relative to a standard breakfast were all close to 100%; the 90% CIs were contained within the 80.00% to 125.00% bounds for all comparisons (Table 16). The LS means ratios for DRV C_{max} and AUC_{last} under fasted conditions relative to a standard breakfast were 69% and 70%, respectively. Median t_{max} was 3.0 hours for all treatments except fasted conditions (1.5 hours).

Table 16: PK Parameters of DRV Following a Single Oral Dose of DRV 400 mg, Coadministered With rtv 100 mg Twice Daily, Administered With Different Meal Types (Study TMC114-C143)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B: Fasted Conditions	**Treatment A: Standard Breakfast**	
N	12	23	
t_{max}, h	1.5 (1.0-3.0)	3.0 (1.5-5.0)	-
C_{max}, ng/mL	3,609 (775)	5,326 (1,148)	69.37 (62.4; 77.1)
AUC_{last}, ng.h/mL	46,750 (11,137)	71,929 (21,675)	70.39 (62.6; 79.2)
$t_{1/2term}$, h	14.1 (6.3)	14.6 (4.8)	-
	Treatment C: High-Fat Breakfast	**Treatment A: Standard Breakfast**	
N	12	23	
t_{max}, h	3.0 (1.5-5.0)	3.0 (1.5-5.0)	-
C_{max}, ng/mL	5,908 (1,687)	5,326 (1,148)	110.2 (97.9; 124)
AUC_{last}, ng.h/mL	68,675 (15,266)	71,929 (21,675)	104.4 (96.0; 114)
$t_{1/2term}$, h	12.7 (4.5)	14.6 (4.8)	-
	Treatment D: Nutritional Protein-Rich Drink	**Treatment A: Standard Breakfast**	
N	10	23	
t_{max}, h	3.0 (1.5-4.0)	3.0 (1.5-5.0)	-
C_{max}, ng/mL	5,545 (1,245)	5,326 (1,148)	98.89 (86.0; 114)
AUC_{last}, ng.h/mL	80,270 (28,211)	71,929 (21,675)	99.84 (88.4; 113)
$t_{1/2term}$, h	21.0 (9.6)	14.6 (4.8)	-
	Treatment E: Croissant With Coffee	**Treatment A: Standard Breakfast**	
N	11	23	
t_{max}, h	3.0 (1.5-4.0)	3.0 (1.5-5.0)	-
C_{max}, ng/mL	5,363 (959)	5,326 (1,148)	98.86 (87.7; 111)
AUC_{last}, ng.h/mL	76,732 (26,330)	71,929 (21,675)	97.88 (86.7; 110)
$t_{1/2term}$, h	17.1 (5.6)	14.6 (4.8)	-

N=maximum number of subjects with data; $t_{1/2term}$=terminal elimination half-life.
Source: Module 5.3.1.1/TMC114-C143-CRR/Table 8, Table 9, Table 10, Table 11, and Table 12

2.3.1.3.2. RTV PK

The PK of rtv, coadministered with DRV, administered with different types of meals are summarized in Table 17. Administration of rtv in the presence of DRV resulted in comparable rtv PK when DRV/rtv was taken immediately after a nutritional protein-rich drink or after a croissant with coffee. Compared to these treatments, the absorption of rtv was lower after administration of DRV/rtv under fasted conditions, after a standard breakfast, and after a high-fat breakfast.

Table 17: PK Parameters of rtv 100 mg Twice Daily, Coadministered With a Single Dose of DRV 400 mg, Administered With Different Meal Types (Study TMC114-C143)

	Mean (SD); t_{max}: Median (Range)				
Parameter	**Treatment A: DRV/rtv 400/100 mg (Standard Breakfast)**	**Treatment B: DRV/rtv 400/100 mg (Fasted Conditions)**	**Treatment C: DRV/rtv 400/100 mg (High-Fat Breakfast)**	**Treatment D: DRV/rtv 400/100 mg (Nutritional Protein-Rich Drink)**	**Treatment E: DRV/rtv 400/100 mg (Croissant With Coffee)**
N	23	12	12	10	11
t_{max}, h	4.0 (1.5-9.0)	2.0 (1.0-4.0)	5.0 (1.5-6.0)	4.0 (3.0-4.0)	4.0 (3.0-4.0)
C_{max}, ng/mL	1,827 (679)	2,044 (982)	1,522 (689)	3,335 (742)	3,236 (847)
AUC_{12h}, ng.h/mL	11,424 (4,326)	12,500 (5,454)	9,197 (3,256)	17,189 (4,019)	18,521 (4,784)

N=maximum number of subjects with data.
rtv 100 mg twice daily was given from 2 days before until 2 days after administration of DRV.
Source: Module 5.3.1.1/TMC114-C143-CRR/Table 13

2.3.1.4. Conclusion

Exposure (C_{max} and AUC_{last}) of DRV was decreased when administered under fasted conditions compared with a standard breakfast; the 90% CIs for the LS means ratios were below the 80.00% to 125.00% bounds. Relative to a standard breakfast, exposure of DRV with all other meal types (high-fat breakfast, nutritional protein-rich drink, or croissant with coffee) was comparable; for all comparisons, the 90% CIs for the LS means ratios were contained within the 80.00% to 125.00% bounds.

2.3.2. Study GS-US-236-0105: Effect of Food on Bioavailability of EVG, COBI, FTC, and TDF Administered Together as an STR Tablet

GS-US-236-0105

Module 5.3.1.1/GS-US-236-0105

2.3.2.1. Objective

To assess the effect of food on the PK of EVG, FTC, TDF, and COBI when administered together as a single tablet.

2.3.2.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-period, 6-way crossover study to investigate the effect of 2 different fed conditions (high-calorie/high-fat meal or light meal) versus fasted conditions on the PK of a single dose of the EVG/COBI/FTC/TDF 150/150/200/300 mg STR tablet. The study population consisted of 24 healthy subjects divided into 1 of 6 treatment sequences in which the following treatments were administered:

! Treatment A: EVG/COBI/FTC/TDF 150/150/200/300 mg (1 STR tablet), administered as a single dose in the morning under fasted conditions;

- Treatment B: EVG/COBI/FTC/TDF 150/150/200/300 mg (1 STR tablet), administered as a single dose in the morning under fed conditions (light meal);
- Treatment C: EVG/COBI/FTC/TDF 150/150/200/300 mg (1 STR tablet), administered as a single dose in the morning under fed conditions (high-calorie, high-fat meal).

Treatments were separated by a washout period of at least 7 days.

2.3.2.3. Results

2.3.2.3.1. COBI PK

The COBI exposure parameters C_{max}, AUC_{last}, and AUC_{∞} were bioequivalent following a light meal compared with fasted conditions. For the high-calorie/high-fat meal condition, C_{max}, AUC_{∞}, and AUC_{last}, were decreased by 27%, 19%, and 20% relative to the light meal condition and were decreased by 24%, 17%, and 18% relative to the fasted condition. These lower values in COBI exposures did not result in lower EVG exposures.

2.3.2.3.2. EVG PK

Relative to fasted conditions, EVG C_{max}, AUC_{∞}, and AUC_{last} were increased by 22%, 34%, and 36%, respectively, when the STR tablet was administered following a light meal and were increased by 56%, 87%, and 91%, respectively, following a high-calorie/high-fat meal. Elvitegravir C_{max}, AUC_{∞}, and AUC_{last} were increased by 28%, 39%, and 40%, respectively, when the STR was administered with a high-calorie/high-fat meal relative to a light meal.

2.3.2.3.3. FTC PK

Mean FTC C_{max}, AUC_{∞}, and AUC_{last} estimates and median FTC t_{max} estimates were similar under all treatment conditions. All 90% CIs were contained within the 80% to 125% bounds.

2.3.2.3.4. Tenofovir PK

Relative to fasted conditions, tenofovir AUC_{∞} and AUC_{last} were increased by 24% and 25%, respectively, following a light meal and by 23% and 25%, respectively, following a high-calorie/high-fat meal. AUC estimates were bioequivalent between the 2 fed conditions (ie, light meal versus high-calorie/high-fat meal). Tenofovir C_{max} was increased by 20% with a light meal relative to fasted conditions, but was similar between the high-calorie/high-fat meal and fasted conditions. Tenofovir C_{max} was decreased by 14% with a high calorie/high fat meal relative to a light meal.

2.3.2.4. Conclusion

The effect of food on COBI did not affect EVG exposure. The difference in EVG exposure with a light meal and a high-calorie/high-fat meal was not considered to be clinically significant. Tenofovir and FTC exposures in the presence of food were consistent with the established PK profiles of tenofovir and FTC.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

An overview table of all bioavailability parameters across biopharmaceutic and clinical pharmacology studies in which DRV and COBI were coadministered is provided in Module 2.7.2/Appendix 2 and Appendix 3.

3.1. Relative Bioavailability of DRV

3.1.1. Impact of Formulation Changes

The exposure of DRV when DRV/COBI 800/150 mg once daily was coadministered as single agents was compared with the exposure of DRV when DRV/rtv 800/100 mg once daily was coadministered as single agents in study GS-US-216-0115 (Section 2.1.1). The mean AUC_{24h} and C_{max} of DRV were comparable when DRV was coadministered with COBI and with rtv (LS means ratios of 102% and 103%, respectively) (Table 18). The mean C_{0h} and C_{24h} values of DRV were lower when DRV was coadministered with COBI than with rtv; the LS mean ratios were 89% and 69%, respectively (ie, decreased by 11% and 31%, respectively). The median t_{max} was unchanged for both treatments.

In study TMC114IFD1001, the bioavailability of DRV when coadministered with COBI as 2 different FDC tablet formulations (G003 and G004) following multiple doses of DRV/COBI 800/150 mg once daily was compared with the bioavailability of DRV 800 mg once daily (as the 400-mg commercial tablet F030) when coadministered with rtv 100 mg once daily as single agents (Section 2.1.2). As in study GS-US-216-0115, relative to DRV/rtv 800/100 mg coadministered as single agents, the mean exposure (C_{max} and AUC_{24h}) of DRV with the 2 FDC tablet formulations (G003 and G004) was comparable. Furthermore, similar to study GS-US-216-0115, the C_{min} value of DRV was lower when DRV was coadministered with COBI than when DRV was coadministered with rtv, with an LS means ratio of 69% (ie, decreased by 31%) for the G003 FDC tablet and 74% (ie, decreased by 26%) for the G004 FDC tablet. No relevant differences were observed for median t_{max} between the 2 FDC tablets and the DRV single agent tablet F030.

Based on the results of study TMC114IFD1001, both formulation candidates (G003 and G004) were deemed acceptable. However, the FDC G004 tablet was selected for further development because it closely aligned with the DRV 800-mg tablet formulation and employed the simplest drug product composition. For commercial reasons, the color film coating of the FDC G004 tablet was changed from white to pink, yielding the G006 FDC tablet. Except for the nonfunctional tablet coating, the G004 and G006 FDC tablets are identical. Based on the results of study TMC114IFD1003 (Section 2.2.1). The DRV/COBI G006 FDC tablet was bioequivalent to DRV/COBI coadministered as single agents under both fasted and fed (standardized breakfast) conditions. For DRV C_{max}, AUC_{last}, and AUC_{∞}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds (Table 18). No relevant differences were observed for the median t_{max} of DRV between the DRV/COBI G006 FDC tablet and DRV/COBI administered as single agents. Based on the results of this study, the G006 FDC tablet was selected as the intended commercial FDC tablet formulation of DRV/COBI.

Table 18: Pairwise Comparison of DRV Formulations (Fasted or Fed Conditions) (Studies GS-US-216-0115, TMC114IFD1001, and TMC114IFD1003)

Parameter	Test Geometric Mean	Reference Geometric Mean	Test/Reference Least Square Means Ratio, % (90% CI)
	DRV/COBI Single Agents 800/150 mg	**DRV/rtv Single Agents 800/100 mg**	
GS-US-216-0115	**(Fed)**	**(Fed)**	
N	31	31	
C_{max}, ng/mL	7,538	7,293	103.36 (100.34; 106.48)
AUC_{24h}, ng.h/mL	77,390	76,036	101.78 (97.40; 106.36)
	DRV/COBI FDC (G003) 800/150 mg	**DRV/rtv Single Agents 800/100 mg**	
TMC114IFD1001	**(Fed)**	**(Fed)**	
N	32	31	
C_{max}, ng/mL	6,487	6,709	96.69 (92.48; 101.09)
AUC_{24h}, ng.h/mL	71,860	74,240	96.80 (92.04; 101.80)
	DRV/COBI FDC (G004) 800/150 mg	**DRV/rtv Single Agents 800/100 mg**	
TMC114IFD1001	**(Fed)**	**(Fed)**	
N	33	31	
C_{max}, ng/mL	6,702	6,709	99.90 (95.52; 104.47)
AUC_{24h}, ng.h/mL	73,290	74,240	98.72 (93.83; 103.87)
	DRV/COBI FDC (G006) 800/150 mg	**DRV/COBI Single Agents 800/150 mg**	
TMC114IFD1003	**(Fasted)**	**(Fasted)**	
N	74	72	
C_{max}, ng/mL	2,950	2,992	98.59 (93.72; 103.73)
AUC_{last}, ng.h/mL	42,831	44,525	96.20 (90.98; 101.71)
AUC_{∞}, ng.h/mL	43,058	44,851	96.00 (90.30; 102.07)
	DRV/COBI FDC (G006) 800/150 mg	**DRV/COBI Single Agents 800/150 mg**	
TMC114IFD1003	**(Fed)**	**(Fed)**	
N	40	38	
C_{max}, ng/mL	6,650	6,873	96.76 (93.06; 100.60)
AUC_{last}, ng.h/mL	74,744	76,499	97.71 (93.08; 102.57)
AUC_{∞}, ng.h/mL	74,302	75,962	97.81 (92.85; 103.05)

N=maximum number of subjects with data.
Source: Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-3; Module 5.3.1.1/TMC114IFD1001-CSR/Table 8, Table 9, and Supporting Data Display PK10; Module 5.3.1.2/TMC114IFD1003-CSR/Table 13, and Table 17

3.1.2. Effect of Concomitant Food Intake

The effect of food on the oral bioavailability of DRV when administered as the DRV/COBI G006 FDC tablet was investigated in study TMC114IFD1003 (Section 2.2.1). Exposure to DRV following single-dose administration of DRV/COBI 800/150 mg as the G006 FDC tablet was higher with a high-fat breakfast relative to fasted conditions; the C_{max}, AUC_{last}, and AUC_{∞} values for DRV were 2.27-, 1.63-, and 1.70-fold higher, respectively (Table 19). Therefore, it is recommended that DRV/COBI FDC tablet be taken with food.

This effect of concomitant food intake on DRV exposure when administered as the DRV/COBI FDC tablet is consistent with the effect of food on DRV exposure when DRV was coadministered with rtv as a single agent. The effect of different meal types on the oral bioavailability of DRV when coadministered with rtv was investigated in study TMC114-C143

(Section 2.3.1). Exposure (C_{max} and AUC_{last}) of DRV was decreased by approximately 30% when administered under fasted conditions compared with a standard breakfast (Table 19). For all 4 meal types (standard breakfast, high-fat breakfast, nutritional protein-rich drink, and croissant and coffee) the exposure of DRV was comparable.

Based on these results, DRV/rtv is recommended to be taken with food, and the type of meal does not affect exposure to DRV. While COBI can be administered without regard to meals (Section 3.2.2), because a food effect is observed for DRV, it is recommended that the DRV/COBI FDC tablet be taken with food.

Table 19: Pairwise Comparison of DRV in Assessment of Food Effect (Studies TMC114IFD1003 and TMC114-C143)

Parameter	Test Geometric Mean	Reference Geometric Mean	Test/Reference Least Square Means Ratio, % (90% CI)
TMC114IFD1003	**DRV/COBI FDC (G006) 800/150 mg (Fasted)**	**DRV/COBI FDC (G006) 800/150 mg (Fed, High-Fat Breakfast)**	
N	18	18	
C_{max}, ng/mL	3,073	6,978	227.09 (205.75; 250.63)
AUC_{last}, ng.h/mL	44,487	72,597	163.18 (144.90; 183.78)
AUC_{∞}, ng.h/mL	43,549	74,119	170.20 (148.50; 195.06)
TMC114-C143	**DRV/rtv 400 mg sd/100 mg bid (Fasted)**	**DRV/rtv 400 mg sd/100 mg bid (Standard Breakfast)**	
N	12	23	
C_{max}, ng/mL	3,586	5,170	69.37 (62.4; 77.1)
AUC_{last}, ng.h/mL	48,025	68,227	70.39 (62.6; 79.2)
TMC114-C143	**DRV/rtv 400 mg sd/100 mg bid (High-Fat Breakfast)**	**DRV/rtv 400 mg sd/100 mg bid (Standard Breakfast)**	
N	12	23	
C_{max}, ng/mL	5,710	5,183	110.2 (97.9; 124)
AUC_{last}, ng.h/mL	71,406	68,385	104.4 (96.0; 114)
TMC114-C143	**DRV/rtv 400 mg sd/100 mg bid (Protein-Rich Drink)**	**DRV/rtv 400 mg sd/100 mg bid (Standard Breakfast)**	
N	10	23	
C_{max}, ng/mL	5,125	5,182	98.89 (86.0; 114)
AUC_{last}, ng.h/mL	68,482	68,593	99.84 (88.4; 113)
TMC114-C143	**DRV/rtv 400 mg sd/100 mg bid (Croissant With Coffee)**	**DRV/rtv 400 mg sd/100 mg bid (Standard Breakfast)**	
N	11	23	
C_{max}, ng/mL	5,139	5,198	98.86 (87.7; 111)
AUC_{last}, ng.h/mL	67,289	68,750	97.88 (86.7; 110)

N=maximum number of subjects with data; bid=twice daily; sd=single dose.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 21; Module 5.3.1.1/TMC114-C143/Table 8, Table 9, Table 10, Table 11, and Table 12

3.2. Relative Bioavailability of COBI

3.2.1. Impact of Formulation Changes

The exposure of COBI when coadministered with DRV in 2 candidate FDC tablet formulations (G003 and G004) at a dose of DRV/COBI 800/150 mg once daily was assessed in study TMC114IFD1001 (see Section 2.1.2). The exposure (C_{max} and AUC_{24h}) of COBI was comparable for both FDC tablet formulations. The median t_{max} was 4.0 hours for both formulations.

In the bioequivalence study TMC114IFD1003, the exposure of COBI was compared following single-dose administration of the DRV/COBI 800/150-mg G006 FDC tablet and DRV/COBI 800/150 mg coadministered as single agent tablets (Section 2.2.1). The DRV/COBI G006 FDC tablet was bioequivalent to DRV/COBI coadministered as single agents under both fasted and fed (standardized breakfast) conditions. For COBI C_{max}, AUC_{last}, and AUC_{∞}, the 90% CIs were within the 80.00% to 125.00% bounds (Table 20). No relevant differences were observed for the median t_{max} of COBI between the DRV/COBI G006 FDC tablet and the single agent COBI tablet.

Table 20: Pairwise Comparison of COBI Formulations (Fasted or Fed Conditions) (Study TMC114IFD1003)

Parameter	Test Geometric Mean	Reference Geometric Mean	Test/Reference Least Square Means Ratio, % (90% CI)
TMC114IFD1003	**DRV/COBI 800/150 mg FDC (G006) (Fasted)**	**DRV/COBI Single Agents 800/150 mg (Fasted)**	
N	73	72	
C_{max}, ng/mL	591	572	103.40 (94.25; 113.44)
AUC_{last}, ng.h/mL	4,226	4,175	101.20 (91.77; 111.61)
AUC_{∞}, ng.h/mL	4,580	4,390	104.33 (94.85; 114.77)
TMC114IFD1003	**DRV/COBI 800/150 mg FDC (G006) (Fed)**	**DRV/COBI Single Agents 800/150 mg (Fed)**	
N	40	38	
C_{max}, ng/mL	789	808	97.65 (93.77; 101.70)
AUC_{last}, ng.h/mL	5,751	5,879	97.82 (94.65; 101.10)
AUC_{∞}, ng.h/mL	5,842	5,975	97.77 (94.60; 101.05)

N=maximum number of subjects with data.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 15 and Table 19

3.2.2. Effect of Concomitant Food Intake

The effect of food on the oral bioavailability of COBI when administered as the DRV/COBI G006 FDC tablet was investigated in studies TMC114IFD1003 (Section 2.2.1) and GS-US-236-0105 (Section 2.3.2). In study TMC114IFD1003, exposure to COBI following single-dose administration of DRV/COBI 800/150 mg as the G006 FDC tablet was comparable when it was administered with a high-fat breakfast and under fasted conditions; the 90% CIs were within the 80.00% to 125.00% bounds (Table 21). Similarly, when COBI was administered as part of the EVG/COBI/FTC/TDF 150/150/200/300 mg FDC, no effect of a light meal or fasted conditions

on COBI exposure was observed (Section 2.3.2.3.1). Relative to a light meal or fasted conditions, slight decreases (17% to 27%) in COBI exposure parameters (C_{max}, AUC_{last}, and AUC_{∞}) were observed following a high-calorie/high-fat meal, although these decreases were not considered clinically relevant and did not alter the exposure of COBI-boosted EVG.

Although COBI can be administered without regard to meals, due to the food effect observed for DRV (see Section 3.1.2), it is recommended that the DRV/COBI FDC tablet be taken with food.

Table 21: Pairwise Comparison of COBI in Assessment of Food Effect (Study TMC114IFD1003)

Parameter	Test Geometric Mean	Reference Geometric Mean	Test/Reference Least Square Means Ratio, % (90% CI)
	DRV/COBI FDC (G006) 800/150 mg (Fasted)	DRV/COBI FDC (G006) 800/150 mg (Fed, High-Fat Breakfast)	
N	18	18	
C_{max}, ng/mL	708	751	106.02 (98.34; 114.29)
AUC_{last}, ng.h/mL	5,117	5,313	103.83 (96.32; 111.93)
AUC_{∞}, ng.h/mL	5,189	5,413	104.31 (96.45; 112.82)

N=maximum number of subjects with data.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 23

REFERENCES

The following reference list is also provided in Module 2.7.5, and linked from that location to Module 5.4 or Module 1, where applicable.

1. Committee for Medicinal Products for Human Use (CHMP). Guideline on the investigation of bioequivalence. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
2. EMA Guideline on Bioanalytical Method Validation. July 20113. Available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC500109686.pdf

APPENDIX

Appendix 1: In Vitro Dissolution Data for Formulations Used in Biopharmaceutic Studies

Dosage Form	Batch / Formulation Number	Dissolution Apparatus	Media Temperature Units	Collection Times (min), Mean % Dissolved (SD)								Study ID
				5	10	15	20	30	45	60	90	
[redacted]												

Appendix 1: In Vitro Dissolution Data for Formulations Used in Biopharmaceutic Studies

Dosage Form	Batch / Formulation Number	Dissolution Apparatus	Media Temperature Units	Collection Times (min), Mean % Dissolved (SD)								Study ID
				5	10	15	20	30	45	60	90	
[redacted]												
[redacted]												
[redacted]												

Appendix 2: Clinical Biopharmaceutic Studies

Study ID	Objective(s)	Subjects	DRV/COBI Dose	Route	Formulation	Included in Pop PK	Pivotal[a]	Section in Module 2.7.1	Location of Report
GS-US-216-0115	Relative bioavailability	Healthy	800/150 mg once daily	oral	F030 DRV single agent	-	-	2.1.1	Module 5.3.1.2
TMC114IFD1001	Relative bioavailability	Healthy	800/150 mg once daily	oral	G003 (DRV/COBI FDC) G004 (DRV/COBI FDC) F030 (DRV single agent)	-	-	2.1.2	Module 5.3.1.1
TMC114IFD1003	Bioequivalence, food effect	Healthy	800/150 mg single dose	oral	G006 (DRV/COBI FDC) F030 (DRV single agent)	-	X	2.2.1	Module 5.3.1.2
TMC114-C143	Food effect	Healthy	DRV/rtv: 400 mg/ 100 mg bid	oral	F014 DRV single agent	-	-	2.3.1	Module 5.3.1.1
GS-US-236-0105	Food effect	Healthy	EVG/COBI/ FTC/TDF 150/150/ 200/300 mg single dose	oral	FDC	-	-	2.3.2	Module 5.3.1.1

[a] PK and/or PK/pharmacodynamic results described in proposed product labeling.

Source: Module 5.3.1.2/GS-US-216-0115-CSR; Module 5.3.1.1/TMC114IFD1001-CSR; Module 5.3.1.2/TMC114IFD1003-CSR; Module 5.3.1.1/TMC114-C143-CRR; ; Module 5.3.1.1/GS-US-236-0105

Appendix 3: Bioanalytical Methods: Validation Parameters

Method	**LC-MS/MS**	**LC-MS/MS**	**LC-MS/MS**
Study Location	Module 5.3.1.4/TMC114-BA10396	Module 5.3.1.4/TMC114-BA1119	Module 5.3.1.4/TMC114-BA10243
	BA10396, Full Validation	**BA1119, Partial Validation**	**BA10243, Partial Validation**
Analyte	DRV	DRV	DRV
Matrix	Plasma	Plasma	Plasma
Validated concentration range	5 to 10,000 ng/mL	5 to 10,000 ng/mL	5 to 10,000 ng/mL
Inter-run accuracy (%RE)	-4.0 to 0.4	-7.4 to 1.3	-6.5 to -2.1
Inter-run precision (%CV)	0.0 to 2.5	4.0 to 5.6	6.3 to 7.4
Intra-run accuracy (%)	-5.4 to 4.3	-9.6 to 5.5	-13.7 to 11.3
Intra-run precision (%CV)	3.0 to 7.3	1.9 to 7.8	-
Intra-run accuracy (dilution) (%)	0.8 (10× dilution)	-5.3 (10× dilution)	-6.0 (10× dilution)
Intra-run precision (dilution) (%CV)	3.3 (10× dilution)	4.2 (10× dilution)	1.3 (10× dilution)
Incurred sample reproducibility	Study TMC114IFD1003: 305/308 samples within 20%	Study GS-US-216-0115: 47/48 samples within 20%	Study GS-US-216-0130: 168/171 samples within 20%
Selectivity	No relevant interferences	No relevant interferences	No relevant interferences
Stability in blood	2 hours at 0°C and room temperature	-	2 hours at 0°C and room temperature
Stability in plasma	4 freeze-thaw cycles 26 hours at room temperature	3 freeze-thaw cycles 72 hours at room temperature (BA502)	4 freeze-thaw cycles 27 hours at room temperature
Processed sample stability	119 hours at 10°C	96 hours at room temperature	118 hours at 10°C
Stability in frozen matrix	232 days at -20°C and -70°C 1,597 days at -20°C (BA502)	1,597 days at -20°C (BA502)	155 days at -20°C and -70°C 1,597 days at -20°C (BA502)

Appendix 3: Bioanalytical Methods: Validation Parameters

Method	**LC-MS/MS**
Study Location	Module 5.3.1.4/[redacted], **Full Validation**
Analyte	COBI
Matrix	Plasma
Validated concentration range	5 to 2,500 ng/ml
Inter-run accuracy (%RE)	-0.3 to 9.7
Inter-run precision (%CV)	3.9 to 8.3
Intra-run accuracy (%)	-6.6 to 11.8
Intra-run precision (%CV)	2.5 to 7.2
Intra-run accuracy (dilution) (%)	-0.7 (10× dilution)
Intra-run precision (dilution) (%CV)	2.7 (10× dilution)
Incurred sample reproducibility	Study TMC114IFD1003: 292/303 samples within 20%
Selectivity	No relevant interferences
Stability in blood	-
Stability in plasma	6 freeze-thaw cycles 20 hours at room temperature
Processed sample stability	124 hours at 4°C
Stability in frozen matrix	121 days at -10°C to -30°C 365 days at -60°C to -80°C

CV=coefficient of variation; LC-MS/MS=liquid chromatography coupled to tandem mass spectrometry; RE=relative error.

Appendix 4: Bioanalytical Methods Used for Clinical Studies With PK Measurements

Study ID (Location)	Matrix	Analyte	Concentration Range (LLOQ is lower end of the concentration range)	Method	Method Validation Report (Location)	Bioanalytical Study Number
TMC114IFD1001	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA1119	BC-00056
(Module 5.3.1.1)		COBI	5 to 2,500 ng/mL	LC-MS/MS	[redacted]	
TMC114IFD1003	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10396	BC-00153,
(Module 5.3.1.2)		COBI	5 to 2,500 ng/mL	LC-MS/MS	[redacted]	BC-00154
GS-US-215-0115	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA1119	-
(Module 5.3.1.1)		COBI	5 to 1,000 ng/mL	LC-MS/MS	[redacted]	
GS-US-216-0130	Plasma	DRV	5 to 10,000 ng/mL	LC-MS/MS	BA10243	-
(Module 5 3.5.2)		COBI	5 to 2,500 ng/mL	LC-MS/MS	[redacted]	
GS-US-236-0105	Plasma	COBI	5 to 2,500 ng/mL	LC-MS/MS	[redacted]	-
(Module 5.3.1.1)						

LC-MS/MS=liquid chromatography coupled to tandem mass spectrometry; LLOQ=lower limit of quantification.

Appendix 5: Bioanalytical Methods Used in Historical Studies With DRV/rtv: Validation Parameters of DRV

Method	LC-MS/MS ABL1982	LC-MS/MS ABL1983	LC-MS/MS ABL3021	LC-MS/MS ABL5150
Studies for which method was used	TMC114-C101, TMC114-C104, TMC114-C110	TMC114-C101, TMC114-C104, TMC114-C124	TMC114-C107, TMC114-C109, TMC114-C111, TMC114-C119, TMC114-C120, TMC114-C121, TMC114-C122, TMC114-C124, TMC114-C125, TMC114-C128, TMC114-C129, TMC114-C133, TMC114-C141, TMC114-C143, TMC114-C202, TMC114-C213, TMC125-C176	TMC114-C107, TMC114-C122, TMC114-C143, TMC114-C202, TMC114-C213
Analyte	DRV	DRV	DRV	DRV
Matrix	Plasma	Urine	Plasma	Plasma
Validated concentration range	2.01 to 2,008 ng/mL	20.0 to 20,000 ng/mL	10.0 to 10,000 ng/mL	10.0 to 10,000 ng/mL
Overall accuracy (%Bias)	8.00 ng/mL: ≤|20|% 50.0 ng/mL: ≤|15|% 1,500 ng/mL: ≤|15|%	80.0 ng/mL: ≤|20|% 500 ng/mL: ≤|15|% 15,000 ng/mL: ≤|15|%	10.0 ng/mL: ≤|20|%[a] 40.0 ng/mL: ≤|15|%[a] 400 ng/mL: ≤|15|%[a] 8,000 ng/mL: ≤|15|%[a] 20,000 ng/mL: ≤|15|%[a]	10.0 ng/mL: ≤|20|%[a] 30.0 ng/mL: ≤|15|%[a] 400 ng/mL: ≤|15|%[a] 8,000 ng/mL: ≤|15|%[a] 20,000 ng/mL: ≤|15|%[a]
Total precision (%CV)	8.00 ng/mL: ≤20% 50.0 ng/mL: ≤15% 1,500 ng/mL: ≤15%	80.0 ng/mL: ≤20% 500 ng/mL: ≤15% 15,000 ng/mL: ≤15%	10.0 ng/mL: ≤20%[b] 40.0 ng/mL: ≤15%[b] 400 ng/mL: ≤15% [b] 8,000 ng/mL: ≤15%[b] 20,000 ng/mL: ≤15%[b]	10.0 ng/mL: ≤20%[b] 30.0 ng/mL: ≤15%[b] 400 ng/mL: ≤15%[b] 8,000 ng/mL: ≤15%[b] 20,000 ng/mL: ≤15%[b]
Intra-run precision (%CV)	8.00 ng/mL: ≤20% 50.0 ng/mL: ≤15% 1,500 ng/mL: ≤15%	80.0 ng/mL: ≤20% 500 ng/mL: ≤15% 15,000 ng/mL: ≤15%[b]	10.0 ng/mL: ≤20%[b] 40.0 ng/mL: ≤15%[b] 400 ng/mL: ≤15%[b] 8,000 ng/mL: ≤15%[b] 20,000 ng/mL: ≤15%[b]	10.0 ng/mL: ≤20%[b] 30.0 ng/mL: ≤15%[b] 400 ng/mL: ≤15%[b] 8,000 ng/mL: ≤15%[b] 20,000 ng/mL: ≤15%[b]
Dilution, accuracy (%Bias)	≤|20|% (10× dilution)	≤|20|% (10× dilution)	Met criteria up to 10× dilution	Met criteria up to 10× dilution
Specificity	No interfering peaks	No interfering peaks	No interfering peaks	Only small interfering peaks, criteria met
Stability in plasma	3 freeze-thaw cycles 24 hours in refrigerator 24 hours at room temperature -	-	3 freeze-thaw cycles 24 hours in refrigerator 24 hours at room temperature -	-
Stability in urine		3 freeze-thaw cycles 24 hours in refrigerator 24 hours at room temperature	-	-

Processed sample stability	24 hours at room temperature	24 hours at room temperature	24 hours at room temperature	-
Method	**LC-MS/MS PBR040553 (PBRL-RD-642)**	**Centrifugal Filtration ABL3173**	**LC-MS/MS BA819**	**LC-MS/MS BA502**
Studies for which method was used	TMC114-C142, TMC114-C150, TMC114-C153	TMC114-C119, TMC114-C129	TMC114-C123, TMC114-C163, TMC114-C171, TMC114-C172, TMC114-C211	TMC114-C127, TMC114-C134, TMC278-C112
Analyte	DRV	free DRV (ie, not protein bound)	DRV	DRV
Matrix	Human Heparin Plasma	Plasma	Human Heparin Plasma	Human Heparin Plasma
Validated concentration range	10.0 to 10,000 ng/mL	Free DRV in filtrate: 2.00 to 2,000 ng/mL DRV in unfiltered plasma: 2.00 to 8,000 ng/mL	5 to 10,000 ng/mL	5 to 10,000 ng/mL
Overall accuracy (%Bias)	10.0 ng/mL: ≤|20|% 30.0 ng/mL: ≤|15|% 500 ng/mL: ≤|15|% 8,000 ng/mL: ≤|15|%	-	5 ng/mL: ≤|20|% 13.6 ng/mL: ≤|15|% 258 ng/mL: ≤|15|% 7,580 ng/mL: ≤|15|%	5.00 ng/mL ≤|20|% 13.3 ng/mL: ≤|15|% 266 ng/mL: ≤|15|% 7,600 ng/mL: ≤|15|%
Total precision (%CV)	10.0 ng/mL: ≤20% 30.0 ng/mL: ≤15% 500 ng/mL: ≤15% 8,000 ng/mL: ≤15%	6.74 ng/mL: ≤20% 35.8 ng/mL: ≤20% 174 ng/mL: ≤20% 466 ng/mL: ≤20%	5 ng/mL: ≤20% 13.6 ng/mL: ≤15% 258 ng/mL: ≤15% 7,580 ng/mL: ≤15%	5.00 ng/mL ≤20% 13.3 ng/mL: ≤15% 266 ng/mL: ≤15% 7,600 ng/mL: ≤15%
Intra-run precision (%CV)	-	6.74 ng/mL: ≤20% 35.8 ng/mL: ≤20% 174 ng/mL: ≤20% 466 ng/mL: ≤20%	-	-
Dilution, accuracy (%Bias)	Met criteria up to 10× dilution	≤|20|% (10× dilution)	≤|15|% (10× dilution)	Met criteria up to 10× dilution
Dilution, precision (%CV)	Met criteria up to 10× dilution	≤20% (10× dilution)	-	Met criteria up to 10× dilution
Specificity	No interfering peaks	-	No interfering peaks	No interfering peaks
Stability in blood	2 hours at 0°C and room temperature	-	24 hours in a refrigerator[a] 24 hours at room temperature[a] 2 hours at 37°C[a]	24 hours in a refrigerator[a] 24 hours at room temperature[a] 2 hours at 37°C[a]
Stability in plasma	3 freeze-thaw cycles 24 hours at room temperature 30 min at 56°C	-	3 freeze thaw cycles[b] 1,597 days in a freezer[b] 72 hours at room temperature[b]	3 freeze thaw cycles[b] 1,597 days in a freezer[b] 72 hours at room temperature[b]
Processed sample stability	71 hours at 10°C	-	5 days at room temperature	5 days at room temperature
Stability in frozen matrix	Short-term at –20°C: 10 days Long-term at –20°C: 100 days	-	-	
Stock stability	25 hours at room temperature 187 days at 4°C	-	6 months in a freezer 1 month in a refrigerator 3 days at room temperature	6 months in a freezer 1 month in a refrigerator 3 days at room temperature

Stability in filtrate	-	3 freeze-thaw cycles	-	-

Method	**LC-MS/MS BA1389**
Studies for which method was used	TMC114-C229
Analyte	DRV
Matrix	Plasma
Validated concentration range	5.00 to 5,000 ng/mL
Overall accuracy (%Bias)	5.00 ng/mL: ≤|20|% 15.0 ng/mL: ≤|15|% 250 ng/mL: ≤|15|% 4,000 ng/mL: ≤|15|%
Total precision (%CV)	5.00 ng/mL: ≤20% 15.0 ng/mL: ≤15% 250 ng/mL: ≤15% 4,000 ng/mL: ≤15%
Specificity	No interfering peaks
Processed sample stability	115 hours at 10°C
Stability in frozen matrix	401 days at -20°C

[a] Spiked human heparin blood.
[b] Spiked human heparin plasma.

Janssen Research & Development

Summary of Clinical Pharmacology Studies

Darunavir/Cobicistat 800/150-mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

Status:	Approved
Date:	11 September 2013
Prepared by:	Janssen Infectious Diseases - Diagnostics BVBA
EDMS no. and version:	EDMS-ERI-62793949, 1.0

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ABBREVIATIONS

AAG	alpha-1 acid glycoprotein
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
aGFR	actual glomerular filtration rate
AhR	aryl hydrocarbon receptor
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{last}	area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration
AUC_{th}	area under the plasma concentration-time curve over t hours
AUC_{∞}	area under the plasma concentration-time curve from time of intake until infinity
$AUC_{!}$	area under the plasma concentration-time curve over the dosing interval tau
BCRP	breast cancer resistance protein
C_{0h}	predose plasma concentration
$C_{!}$	plasma concentration at the end of the dosing interval tau
CI	confidence interval
CL/F	clearance
CL_p/F	intercompartmental clearance
CL_{ss}/F	apparent clearance at steady state
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
COBI	cobicistat
$C_{ss,av}$	average plasma concentration at steady-state
CV	coefficient of variability
CYP	cytochrome P450
DAIDS	Division of AIDS
ddI	didanosine
DHA	dihydroartemisinin
DRV	darunavir
DTG	dolutegravir
EC_{50}	median 50% effective concentration
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	estimated glomerular filtration rate calculated using the Cockcroft Gault equation
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed-dose combination
FTC	emtricitabine
GAM	generalized additive model
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
HMG-CoA	3-hydroxy-3-methylglutary coenzyme A
ICH	International Conference on Harmonisation
IC_{50}	50% inhibitory concentration
ISV	intersubject variability (synonymous with between subject variability)
LDL	low-density lipoprotein
LLOQ	lower limit of quantification
LPV	lopinavir
LS	least square

MATE1	multidrug and toxin extrusion protein 1
MATE2-K	multidrug and toxin extrusion protein 2-K
MDCK II	Madin Darby canine kidney cells
MRP	multidrug resistance-associated protein
NADPH	nicotinamide adenine dinucleotide phosphate
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OAT	organic anion transporter
OATP	organic anion transporter protein
OCT2	organic cation transporter 2
OCTN1	organic cation transporter novel 1
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	protease inhibitor
PK	pharmacokinetic(s)
PXR	pregnane X receptor
QTcF	QT interval corrected by Fridericia's formula
QTcM	QT interval corrected for heart rate using an individual-specific correction factor
RAM	resistance associated mutation
RNA	ribonucleic acid
RTV	ritonavir
rtv	low-dose ritonavir
SD	standard deviation
SE	standard error
SOC	system organ class
SSRI	selective serotonin reuptake inhibitor
STR	single-tablet regimen
$t_{1/2,term}$	terminal elimination half-life
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response
t_{max}	time to reach maximum plasma concentration
UGT	uridine diphosphate glucuronosyltransferase
V_c/F	central volume of distribution
V_p/F	peripheral volume of distribution

SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

The darunavir/cobicistat (DRV/COBI) fixed-dose combination (FDC) tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI). Cobicistat has recently been registered to be coadministered as a pharmacokinetic (PK) enhancer of DRV and atazanavir (ATV). The DRV/COBI 800/150-mg FDC tablet is dosed according to the same once-daily dosage regimen as the single agents.

The clinical program for DRV/COBI FDC is based on the comprehensive development programs of the 2 single agents and the PK bridging of DRV coadministered with COBI to DRV coadministered with low-dose ritonavir (rtv). The comparable PK (ie, area under the plasma concentration-time curve over 24 hours [AUC_{24h}] and maximum plasma concentration [C_{max}]) between DRV/rtv 800/100 mg and DRV/COBI 800/150 mg coadministered as single agents (study GS-US-216-0115) or as an FDC (study TMC114IFD1001) in healthy subjects allows the extrapolation of safety data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects. An extrapolation of the efficacy data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects can be made based on the comparable exposures to DRV (AUC_{24h}) achieved by both PK enhancers. Based on PK/pharmacodynamic (PD) analyses of the effect of DRV exposure on virologic response in the Phase 3 studies TMC114-C211 and TMC114-C229 with DRV/rtv, the modestly lower DRV plasma concentration at the end of the dosing interval (C_{τ}) observed with DRV/COBI relative to DRV/rtv is not expected to be clinically relevant. The PK bridging clinical program for DRV/COBI FDC further demonstrates the bioequivalence between DRV/COBI coadministered as single agents and the FDC (study TMC114IFD1003).

In this Summary of Clinical Pharmacology Studies, noncompartmental and population PK data as well as PK/PD comparisons from the Week-24 primary analysis of the Phase 3b study GS-US-216-0130, in which DRV and COBI were coadministered as single agents, are presented in support of the DRV/COBI 800/150-mg FDC tablet administered once daily for the treatment of antiretroviral therapy (ART)-naïve HIV-1 infected adults and ART-experienced HIV-1 infected adults with no DRV resistance associated mutations (RAMs). Additionally, supportive data with DRV administered either alone, with rtv, or with COBI, are presented. These include 2 Phase 2 and 2 Phase 3 studies in which a dosing regimen of DRV/rtv 800/100 mg once daily was administered to ART-naïve (TMC114-C211) or ART-experienced (TMC114-C202, TMC114-C213, and TMC114-C229) HIV-1 infected subjects for 24 or 48 weeks and a number of Phase 1 studies, mostly in healthy subjects, that assessed drug-drug interactions with DRV, DRV/rtv, or COBI; the impact of intrinsic factors (hepatic impairment and renal impairment) on DRV/rtv or COBI; and the effect of DRV/rtv and COBI on QT interval corrected for heart rate by Fridericia's formula (QTcF).

Key findings described in this Summary of Clinical Pharmacology are as follows:

Pharmacokinetics

Absorption and Distribution

- Darunavir and COBI are both orally available when coadministered as the FDC tablet. Darunavir has an absolute bioavailability of 82% when coadministered with rtv, and 37% when administered without rtv. The absolute bioavailability of DRV when administered as the DRV/COBI FDC is unknown.
- Darunavir exposure is enhanced by coadministration with COBI such that exposures (DRV AUC_{24h} and C_{max}) comparable to DRV coadministered with rtv are achieved.
- Darunavir/COBI administered as the FDC is bioequivalent to DRV/COBI administered as single agents under both fasted and fed conditions.
- Under fed conditions (ie, high-fat meal), with coadministration of COBI, the relative bioavailability of DRV was increased 1.6- to 2.3-fold relative to fasted conditions. The DRV/COBI FDC should therefore be taken with food. The type of food is not expected to affect the exposure to DRV.
- The mean DRV exposures following multiple-dose administration of DRV/COBI 800/150 mg once daily as FDC tablet formulations in healthy subjects were generally comparable to the exposure following administration of DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects.
- Darunavir is highly protein bound to alpha-1 acid glycoprotein (AAG).

Metabolism and Elimination

- Darunavir and COBI are primarily metabolized by cytochrome P450 (CYP) 3A. Cobicistat is an inhibitor of CYP3A and increases the exposure to DRV such that DRV exposures (AUC_{24h} and C_{max}) comparable to DRV coadministered with rtv are achieved. Darunavir is predominantly excreted in feces, with minimal renal excretion, when coadministered with COBI. The renal excretion of COBI is also low.

Specific Populations

- *Age:*
  - Age did not have a relevant effect on the exposure to DRV when administered as DRV/COBI 800/150 mg once daily (as single agents) in HIV-1-infected subjects, which was consistent with observations made when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in HIV-1-infected subjects.
  - The PK of COBI have not been fully evaluated in older patients (65 years of age and older).
- *Sex:*
  - Sex did not have a relevant effect on the exposure to DRV when administered as DRV/COBI 800/150 mg once daily (as single agents) in HIV-1-infected subjects. When DRV was administered as DRV/rtv 800/100 mg once daily (as single agents), the mean

DRV exposure was higher in women than men, but this difference was not clinically relevant.

- No clinically relevant PK differences due to sex have been identified for COBI.

- *Race:*
  - Race did not have a relevant effect on the exposure to DRV when administered as DRV/COBI 800/150 mg once daily (as single agents) in HIV-1-infected subjects, which was consistent with observations made when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in HIV-1-infected subjects.
  - No clinically relevant PK differences due to race or ethnicity have been identified for COBI.
- *Hepatic Impairment:*
  - Darunavir is primarily metabolized by the liver. The steady-state PK parameters of DRV were similar after multiple-dose administration of DRV/rtv 600/100 mg twice daily to non-HIV-1 infected subjects with normal hepatic function and non-HIV-1 infected subjects with mild or moderate hepatic impairment.
  - No clinically relevant differences in COBI PK were observed between non-HIV-1 infected subjects with normal hepatic function and non-HIV-1 infected subjects with moderate hepatic impairment.
  - Based on these results, no adjustment of the DRV/COBI dose is required in subjects with mild or moderate hepatic impairment.
  - The effect of severe hepatic impairment on the PK of DRV/(rtv), COBI, or DRV/COBI has not been evaluated.
- *Renal Impairment:*
  - A mass-balance study with ^{14}C-DRV/rtv showed that approximately 7.7% of the administered dose of DRV is excreted in the urine as unchanged drug. As DRV and rtv are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.
  - Creatinine clearance did not have a relevant effect on the exposure to DRV when administered as DRV/COBI 800/150 mg once daily (as single agents) in HIV-1-infected subjects.
  - Population PK analysis showed that the PK of DRV when administered as DRV/rtv 600/100 mg twice daily were not significantly affected in HIV-1-infected subjects with moderate renal impairment (creatinine clearance: 30 to 60 mL/min). There are no PK data available for DRV in HIV-1-infected patients with severe renal impairment or end stage renal disease.
  - No meaningful differences in the PK of COBI were observed between non-HIV infected subjects with normal renal function and non-HIV infected subjects with severe renal impairment (creatinine clearance below 30 mL/min), consistent with the low renal clearance of COBI.

- *ART Treatment Status:*
  - The PK of DRV (based on population PK estimates) are comparable in ART-naïve and ART-experienced HIV-1-infected subjects.

Drug Interactions

- Darunavir and COBI are both CYP3A inhibitors. Coadministration of the DRV/COBI FDC with drugs primarily metabolized by CYP3A may result in increased systemic exposure of those drugs. Coadministration of the DRV/COBI FDC with drugs that are primarily metabolized by CYP2D6 may also result in increased plasma concentrations of those drugs.
- Because DRV and COBI are metabolized by CYP3A, drugs that induce CYP3A activity are expected to increase the clearance of DRV and COBI, resulting in decreased plasma concentrations of DRV and COBI. Coadministration of the DRV/COBI FDC with other drugs that inhibit CYP3A may decrease the clearance of DRV and COBI and may result in increased plasma concentrations of DRV and COBI.

Pharmacodynamics

- There was no clinically relevant relationship between the exposure to DRV when coadministered with COBI and the decrease in viral load at Week 24 (from baseline) or virologic response (<50 HIV-1 ribonucleic acid [RNA] copies/mL) at Week 24 in ART-naïve HIV-1 infected subjects. In the same study, the small sample size for ART-experienced HIV-1 infected subjects limited the ability to draw conclusions on the relationship between DRV exposure and virologic response in this population.
- There was no apparent relationship between the exposure to DRV when coadministered with COBI and the occurrence of adverse events (AEs) or changes in laboratory parameters of interest.

1. BACKGROUND AND OVERVIEW

Darunavir (PREZISTA®, formerly known as TMC114) in combination with rtv is an HIV PI currently indicated for the treatment of HIV-1 infection in ART-naïve and ART-experienced adults and pediatric patients of 3 years of age and above. The dosing regimen of DRV/rtv 800/100 mg once daily (coadministered as single agents) is recommended in ART-naïve adults and ART-experienced adults with no DRV RAMs and with a viral load <100,000 HIV-1 RNA copies/mL and a CD4+ cell count of ≥100 cells/L at screening.

Cobicistat (COBI, formerly known as GS-9350) is a new chemical entity developed and registered by Gilead Sciences Inc. (Gilead) for use as a PK enhancer to increase systemic exposure of coadministered drugs metabolized by CYP3A, including the HIV-1 integrase strand transfer inhibitor elvitegravir (EVG), and the HIV PIs ATV and DRV. Cobicistat is a structural analog of rtv and a potent CYP3A inhibitor. Throughout its clinical development, COBI 150 mg once daily was generally safe and well tolerated, and boosted DRV, ATV, and EVG exposures to levels that were comparable to the boosting effect of coadministered rtv (refer to the Summary of Clinical Efficacy in Module 2.7.3).

An FDC tablet combining DRV 800 mg and COBI 150 mg in a single tablet for once daily administration has been developed for the treatment of HIV-1. This tablet is intended to be used in the same population for which DRV/rtv 800/100 mg once daily, coadministered as single agents, is recommended and registered, ie, ART-naïve HIV-1 infected adults and ART-experienced HIV-1 infected adults with no DRV RAMs. The availability of a DRV FDC tablet with a PK enhancer would simplify DRV-containing antiretroviral (ARV) regimens, which currently require coadministration of a separate rtv tablet as a PK enhancer.

The development program of the DRV/COBI FDC tablet has been built on the information accrued from the development program for DRV in combination with rtv from Janssen (formerly Tibotec) and on the development program for COBI from Gilead, as outlined in the sections below.

1.1. General Attributes of the Drug

1.1.1. Drug/Drug Product Information

Dosage form/strengths: Oral immediate-release FDC tablet containing a fixed ratio of 800 mg DRV, supplied as DRV ethanolate, and 150 mg COBI adsorbed on silicon dioxide.

Pharmacologic class: DRV is a PI registered for the treatment of HIV-1 infection when coadministered with rtv as a PK enhancer. Cobicistat has recently been registered to be coadministered as a PK enhancer used to increase systemic exposure of certain coadministered ARV drugs metabolized by CYP3A enzymes.

Chemical Name: DRV: [(1S,2R)-3-[[(4-aminophenyl) sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b] furan-3-yl ester ethanolate; COBI: 1,3-thiazol-5-ylmethyl (2R,5R)-(5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-

1,3-thiazol-4-yl]methyl}carbamoyl)amino]]-4-(morpholin-4-yl)butanamido}-1,6-diphenylhexan-2-yl)carbamate.

Physical Characteristics: Darunavir and COBI differ in their pKa and solubility profiles. Darunavir is very slightly soluble at a pH range of 1 to 12 (<1 mg/100 mL). The solubility of COBI varies from soluble to practically insoluble depending on pH, with high solubility at low pH (>40 mg/mL at a pH of 1.1) and low solubility at moderate pH (0.04 mg/mL at a pH of 7.5 and 8.2).

Formulation: DRV/COBI is supplied as a pink, oval shaped, film-coated tablet containing a fixed ratio of 800 mg DRV (as 867 mg of DRV ethanolate) and 150 mg COBI (adsorbed on silicon dioxide). The quantitative formula is provided in Module 3.2.P.1.

1.1.2. Proposed Mechanisms of Action and Indications

Darunavir is an inhibitor of the dimerization and of the catalytic activity of HIV-1 protease. It selectively inhibits the cleavage of HIV-encoded Gag Pol polyproteins in virus-infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir binds tightly to HIV-1 protease, with a dissociation constant of $4.5 \times 10^{\#12}$ M. It is not an inhibitor of any of 13 tested human cellular proteases (Summary of Virology in Module 2.7.2). Darunavir, in combination with rtv and other ARV agents, is currently indicated for the treatment of HIV-1 infection in ART-naïve and ART-experienced adults and pediatric patients 3 years of age and above.

Cobicistat is a structural analog of rtv that, in contrast to rtv, possesses no anti-HIV activity. Like rtv, it is a potent, selective, mechanism-based inhibitor of CYP3A. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure to CYP3A substrates, such as DRV, ATV, or EVG, where bioavailability is limited and elimination half-life is shortened by CYP3A-dependent metabolism. Cobicistat has been shown in clinical studies to provide DRV, ATV, and EVG exposures comparable to those obtained with rtv boosting. The clinical proof-of-concept study, GS-US-216-0115, showed that a 150-mg dose of COBI led to similar DRV exposures as a 100-mg dose of rtv, in each case when coadministered with DRV 800 mg (Module 2.7.1/Section 2.1.1).

The DRV/COBI FDC tablet combines DRV 800 mg and COBI 150 mg in a single oral tablet for once daily use. It is intended to be used in the same adult population for which DRV/rtv 800/100 mg once daily (coadministered as single agents) is recommended and registered.

1.1.3. Proposed Dosage and Route of Administration

The recommended dose of DRV/COBI is 800/150 mg once daily, orally, which must be taken with food.

1.2. Human Biomaterial Studies

The nonclinical pharmacology, PK, metabolism, and toxicology of DRV have been established in support of the marketing authorization of DRV (Nonclinical Overview in Module 2.4).

Pertinent information from human biomaterial studies conducted with DRV relating to the general absorption, distribution, metabolism, and excretion (ADME) characteristics of DRV is summarized in Section 1.2.1.

A comprehensive nonclinical program has been carried out by Gilead, documenting the primary pharmacology, safety pharmacology, nonclinical PK, and toxicology of COBI. Pertinent information from human biomaterial studies conducted with COBI relating to the general ADME characteristics of COBI is summarized in Section 1.2.2.

Nonclinical studies have not been conducted with DRV in combination with COBI, and none are planned. The overall nonclinical program conducted separately for each agent is considered adequate to support the safety of the FDC tablet of DRV and COBI. The DRV/COBI FDC is not expected to induce clinically relevant additive or synergistic effects.

1.2.1. Human Biomaterial Studies With DRV

An overview of the human biomaterial studies that provide supporting information on the clinical pharmacology of DRV is shown in Table 1.

Table 1: Human Biomaterial Studies With DRV

Study ID	Objective	Human Biomaterial	DRV Concentration [a]	Location
TMC114-NC113	Protein binding	Plasma	100; 1,000; 10,000 ng/mL (0.182; 1.82; 18.2 µM)	TMC114-NC113[32]
TMC114-NC215	Protein binding and blood distribution	Plasma, blood	52; 520; 1,875; 4,688; 18,750 ng/mL (0.095; 0.949; 3.42; 8.55; 34.2 µM)	Module 4.2.2.3/ TMC114-NC215
TMC114-NC112	Characterization of CYP enzymes involved in metabolism of DRV, metabolic profiling	Liver microsomes	(1,096; 2,740; 5,480; 10,960; 27,400 ng/mL) 2; 5; 10; 20; 50 µM	TMC114-NC112[31]
TMC114-NC154	Metabolism of ^{14}C-DRV	Hepatocytes, liver subcellular fractions	(2,740 ng/mL) 5 µM	Module 4.2.2.4/ TMC114-NC154
TMC114-NC202	Kinetics of DRV metabolism	Liver microsomes	(548; 1,644; 2,740; 5,480; 16,440; 27,400; 54,800 ng/mL) 1; 3; 5; 10; 30; 50; 100 µM	Module 4.2.2.4/ TMC114-NC202
TMC114-NC213	Metabolite profiling and identification of major metabolites	Urine, feces, plasma	C_{max} in plasma: 4,763 ng-eq/mL (without rtv), 6,812 ng-eq/mL (with rtv)	Module 4.2.2.4/ TMC114-NC213
TMC114-NC123	Inhibition of human CYP enzymes by DRV	CYP probe substrates, selective towards human CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A	(274; 27,400; 54,800 ng/mL) 0.5; 50; 100 µM	Module 4.2.2.6/ TMC114-NC123

TMC114-NC392	Inhibition of human CYP2C8 and UGT1A1	Pooled liver microsomes	(55; 219; 822; 3,288; 13,700; 137,000 ng/mL) 0.1; 0.4; 1.5; 6, 25; 100; 250 µM	Module 4.2.2.6/ TMC114-NC392
TMC114-NC134	Interaction of 6 anti-HIV compounds with the CYP-mediated metabolism of DRV	Pooled liver microsomes	(548; 1,096; 2,740; 5,480; 10,960; 16,440; 27,400 ng/mL) 1; 2; 5; 10; 20; 30; 50 µM	Module 4.2.2.6/ TMC114-NC134
TMC114-NC171	Potential of DRV to induce CYP mRNA	Cryopreserved human hepatocytes	(1,370; 5,480; 13,700; 27,400 ng/mL) 2.5; 10; 25; 50 µM	Module 4.2.2.4/ TMC114-NC171
TMC114-NC137	Transport characteristics of DRV in Caco-2 monolayers	Colon carcinoma-derived Caco-2 cells	(548; 1,644; 5,480; 16,440; 54,800 ng/mL) 1; 3; 10; 30; 100 µM	Module 4.2.2.2/ TMC114-NC137

Caco-2= human colonic adenocarcinoma cell line; mRNA=messenger RNA; UGT=uridine diphosphate glucuronosyltransferase.

[a] Concentrations in study reports were reported as either ng/mL or µM, and have been converted to ng/mL or µM assuming 1 ng/mL=0.0018248 µM and 1 µM=548 ng/mL. The conversions are the values listed in parentheses.

1.2.1.1. In Vitro Protein Binding of DRV

The binding of DRV to human plasma proteins was assessed in studies TMC114-NC113 (TMC114-NC113[32]) and TMC114-NC215 (Module 4.2.2.3/TMC114-NC215).

In study TMC114-NC113, the binding of DRV to human plasma proteins was assessed by equilibrium dialysis at concentrations of 100, 1,000, and 10,000 ng/mL (0.182, 1.82, 18.2 µM). The mean protein binding of DRV in human plasma was 92.3% to 96.1% across all concentrations, which covered the range of plasma concentrations that occur at therapeutic doses of DRV (see Section 3.1.1). However, liquid chromatography with tandem mass-spectrometry (LC-MS/MS) analysis of buffer quality control samples indicated that the observed concentrations of DRV were systematically lower than the nominal concentrations, which was most probably caused by adsorption to the polypropylene containers. As this adsorption may have also occurred in the buffer compartment of the equilibrium dialysis system, the concentration of DRV in this matrix, and thereby the free fraction of DRV as well, may have been underestimated. Therefore, these protein binding data have to be interpreted with caution.

In study TMC114-NC215, the binding of DRV to human plasma protein was studied by equilibrium dialysis of plasma samples from healthy male adults after fortification with ^{14}C-DRV. The distribution of DRV in blood was also studied. The mean plasma protein binding of DRV was 95.3% at a DRV concentration of 500 ng base-eq/mL in plasma. The percentage protein binding was independent of pH and apparently dependent on the plasma concentration of DRV (the concentration range of 52 to 18,750 ng base-eq/mL [0.095 to 34.2 µM] covered the range of plasma concentrations that occur at therapeutic doses of DRV), including concentrations above 5,000 ng/mL (Table 2).

Table 2: Mean Plasma Protein Binding at Different Concentrations of ^{14}C-DRV in Plasma of Healthy Males (Study TMC114-NC215)

DRV Concentration (ng base-eq/mL)	Percentage Bound (%)
52	93.86
520	93.23
1,875	91.47
4,688	92.64
18,750	75.46

Source: Module 4.2.2.3/TMC114-NC215

Darunavir was mostly bound to AAG and to a lesser extent to albumin.

At a concentration of 500 ng base-eq/mL, the mean blood-to-plasma concentration ratio of DRV was 0.64. The fraction of DRV distributed to plasma water was 3.79%, the fraction distributed to plasma proteins was 77.43%, and the fraction distributed to blood cells was 18.79%. In general, the results on the distribution of DRV in blood at a concentration of 5,000 ng base-eq/mL were similar to those at the concentration of 500 ng base-eq/mL. Therefore, measuring DRV concentrations in human plasma is relevant for clinical PK evaluation of DRV.

1.2.1.2. In Vitro Metabolism of DRV

An in vitro metabolism study was performed to characterize the CYP isozymes involved in the oxidative metabolism of DRV (TMC114-NC112[31]). The in vitro metabolism pathways of DRV were studied using human liver subcellular fractions and/or hepatocytes (Module 4.2.2.4/TMC114-NC154).

In study TMC114-NC112, CYP enzymes involved in the in vitro metabolism of DRV were identified, and the CYP-mediated metabolism in human liver microsomes was investigated. Darunavir was incubated at concentrations of 2, 5, 10, 20, and 50 µM (1,096, 2,740, 5,480, 10,960, 27,400 ng/mL) with a microsomal protein concentration of 0.2 mg/mL. Only ketoconazole (a CYP3A inhibitor) showed significant inhibition (55%) of DRV metabolism. In addition, DRV metabolism was inhibited to a minor extent (10%) by sulfaphenazole (a CYP2C inhibitor). Of the human CYP enzymes investigated, only CYP3A showed detectable metabolism of DRV. Incubations were also monitored for possible hydroxylated metabolites. In human liver microsomes, 2 different hydroxylated metabolites were formed, with the hydroxyl groups present in either the benzyl and/or in the amino-benzene sulfonyl group.

The in vitro metabolism of ^{14}C-DRV (5 µM, 2,740 ng/mL) was evaluated in human hepatocytes (suspensions and primary cultures) and liver subcellular fractions (12,000 x g supernatant fractions and microsomes) in study TMC114-NC154. Using co-chromatography, enzyme hydrolysis, and LC-MS/MS, a relatively large number of metabolites was detected. Major metabolic pathways of DRV were aliphatic, aromatic, and alicyclic hydroxylation occurring at different locations of the molecule, which led to the formation of several metabolites. Aliphatic hydroxylation was observed at the isobutyl function (M21) and, most probably, at the methylene bridge of the benzyl-2-hydroxy-propyl moiety (M23). Aromatic hydroxylation occurred at the aniline moiety (M24 and M29; in M29, at the ortho position with respect to the amine function),

whereas alicyclic hydroxylation was observed at the hexahydro-furo-[2,3-b]furan moiety (M12, M27, and M28). The hydroxylated metabolites were further metabolized by either hydroxylation with formation of a di-hydroxylated metabolite (M25, formed by either alicyclic hydroxylation of M24 or by aromatic hydroxylation of M12, M27, and M28), by aliphatic oxidation with formation of an acid metabolite (M8, formed by oxidation of M21) or by carbamate hydrolysis (M2, formed by carbamate hydrolysis of M21). Hydroxylation in combination with glucuronidation at the [(4-amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl moiety (M10, M17, and M22) was also observed.

A fourth major biotransformation pathway of DRV was carbamate hydrolysis (M19). M19 itself was further metabolized to different metabolites. Aliphatic hydroxylation at the isobutyl function led to the formation of M2. Aromatic hydroxylation of M19 occurred at the benzene moiety (M6) and at the aniline moiety (M15). M6 and M15 were further metabolized by glucuronidation with formation of M1 and M11, respectively. Hydroxylation of M19 in combination with glucuronidation resulted in the formation of M3.

A fifth metabolic pathway of DRV was glucuronidation, either at the aniline moiety (M18) or at the [(4-amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxy-propyl moiety (M20). Hydroxylation in combination with glucuronidation of DRV resulted in the formation of M17. A sixth metabolic pathway of DRV was oxidative *N*-dealkylation, leading to the formation of M14, and a seventh metabolic pathway of DRV was *N*-acetylation, leading to the formation of M30.

A number of metabolites (M4, M5, M7, M9, M13, M16, M26, M31, and M32) remained unidentified.

1.2.1.2.1. Kinetics of DRV Metabolism

The in vitro metabolism of ^{14}C-DRV was studied in human liver microsomes in study TMC114-NC202 (Module 4.2.2.4/TMC114-NC202). The in vivo metabolism of ^{14}C-DRV was studied in feces, urine, and plasma collected from healthy male subjects after a single dose of 400 mg DRV in the absence and presence of rtv in the mass-balance clinical study TMC114-C109 (Module 4.2.2.4/TMC114-NC213 and Section 2.1.1).

In study TMC114-NC202, human liver microsomes catalyzed the nicotinamide adenine dinucleotide phosphate (NADPH)-dependent metabolism of DRV to 3 primary DRV metabolites (M19 [resulted from carbamate hydrolysis of DRV], M23 [aliphatic hydroxylation on the ω-1 carbon of the isobutyl carbon of DRV], and M29 [hydroxylation of aniline moiety of DRV]) and 3 minor metabolites (M6 [product resulted from hydroxylation of M19] and M27 and M28 [both resulting from hydroxylation of hexahydro furo-furan ring]).

Incubations with DRV were conducted at varying concentrations (1, 3, 5, 10, 30, 50, 100 µM [548, 1,644, 2,740, 5,480, 16,440, 27,400, 54,800 ng/mL]), and the kinetics of DRV metabolism was investigated by Michaelis-Menten equation. The apparent formation rate constant and maximum velocity values for the metabolism of DRV in human liver microsomes were 3.82 µM and 328 pmol/mg/min, respectively.

Darunavir metabolism in human liver microsomes to M6, M19, M23, M27, M28, and M29 was markedly inhibited by CYP3A diagnostic inhibitors (ketoconazole, troleandomycin, rtv). The results of expressed CYP isoforms indicated that the metabolic reactions for the formation of the 6 metabolites were catalyzed by CYP3A isoforms. Additionally, it was observed that formation of M29 was also catalyzed to some extent by CYP2C19 and CYP2D6 isoforms along with CYP3A isoforms. Other CYP isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8/9, CYP2E1) yielded negligible or no metabolism of DRV. Although higher metabolism rates were observed with Supersomes, the results were in agreement with *Escherichia coli* systems. The metabolism rates of DRV and its metabolites were correlated with CYP-isoform specific activities of a panel of 10 batches of characterized human liver microsomes. For DRV metabolism and its metabolites, both pairwise correlation and Spearman's rank order correlation methods showed positive correlation coefficients >0.50 with CYP3A isoform activities.

The effect of ATV on DRV metabolism was also investigated in human liver microsomes. The 50% inhibitory concentration (IC_{50}) of ATV on the metabolism of DRV was 11 µM, suggesting moderate inhibition of DRV metabolism by ATV.

Overall, in study TMC114-NC202, it was found that DRV metabolism to 6 metabolites (M6, M19, M23, M27, M28, and M29) in human liver microsomes was mainly catalyzed by CYP3A enzymes and DRV metabolic profile in recombinant CYP3A isoforms was similar to the metabolic profile obtained with human liver microsomes in vitro.

The kinetics of DRV metabolism in plasma, urine, and feces of man was assessed in study TMC114-NC213 (Module 4.2.2.4/TMC114-NC213) using samples from the clinical mass-balance study TMC114-C109 (Section 2.1.1).

In the absence of rtv, biotransformation of DRV occurred through aliphatic and aromatic hydroxylation, carbamate hydrolysis, and glucuronidation. The predominant metabolic pathway was carbamate hydrolysis, accounting for 13.2% of the dose. Other major pathways included aliphatic hydroxylation at the isobutyl moiety towards the tertiary alcohol function (9.8%) and aromatic hydroxylation at the aniline moiety (4.5%). Aromatic hydroxylation at the benzylic moiety was a minor metabolic pathway when DRV was administered alone (1.6%) and the excretion of glucuronide metabolites could hardly be observed (0.12%). The excretion of DRV and its metabolites in urine and feces after administration of DRV alone is summarized in Table 3. Coadministration of rtv with DRV resulted in significant inhibition of the carbamate hydrolysis, isobutyl aliphatic hydroxylation, and aniline aromatic hydroxylation pathways, accounting for 0.67%, 2.26%, and 1.42% of the dose, respectively. The aromatic hydroxylation at the benzylic moiety was not inhibited by coadministration of rtv (1.7%), and the excretion of glucuronide metabolites (2.2%) was markedly higher in the presence of rtv than in the absence of rtv.

Table 3: Excretion of DRV and its Metabolites in Urine and Feces After Administration of a Single Dose of 400 mg ^{14}C-DRV, With and Without rtv (Study TMC114-NC213)

	Mean (%) of Dose			
	0-48h Urine (N=4)		0-48h Feces (N=4)	
Metabolite No.	**DRV Alone**	**DRV + rtv**	**DRV Alone**	**DRV + rtv**
M6	1.02	-	4.38	-
M11	0.45	-	-	-
M15	-	-	3.62	-
M15+M17+M18	0.98	-	-	-
M17+ M18+M19	-	1.57	-	-
M19	0.56	-	2.14	0.67
M20	0.12	0.66	-	-
M23	0.47	0.25	3.92	2.01
M29	0.28	0.42	4.17	1.00
M33	-	-	1.60	1.70
Unchanged drug (DRV)	1.15	7.65	6.83	41.16
Total	5.00	10.55	26.65	46.54

Source: Module 4.2.2.4/TMC114-NC213/Table 5-7 and Table 5-8

Unchanged drug accounted for the largest fraction of the radioactivity in plasma samples obtained after administration of DRV in the absence or presence of rtv, with a higher percentage of unchanged drug in the presence of rtv (Table 4).

None of the metabolites found in humans showed activity in the range of DRV activity against wild-type HIV (DRV median 50% effective concentration [EC_{50}]=0.016 µM [8.77 ng/mL] versus EC_{50} for M19, M29, and M33=32, 0.26, and 1.3 µM, respectively [17,536, 4.56, and 712 ng/mL, respectively]).

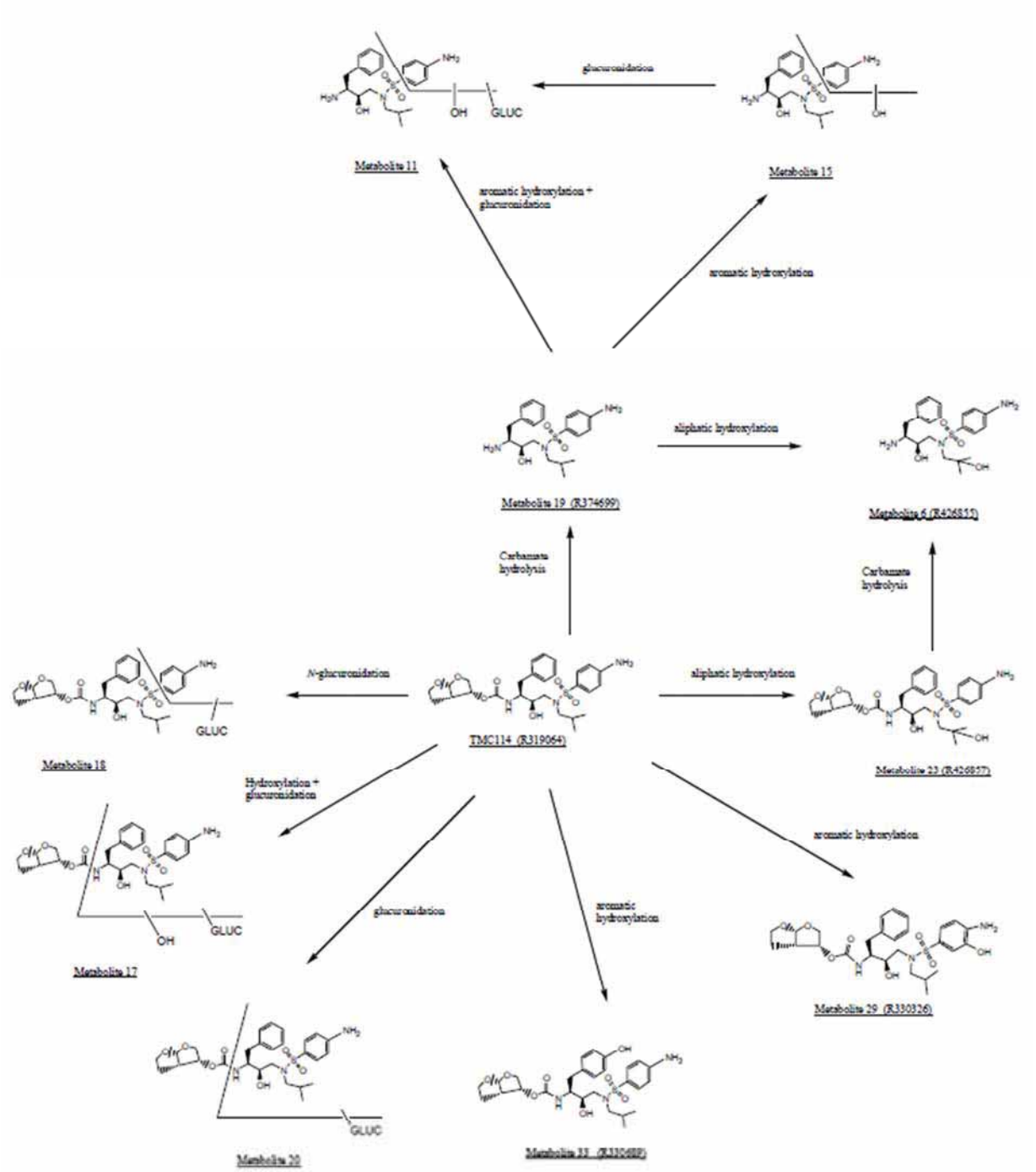
Table 4: Recovery of DRV and its Metabolites in Plasma After Administration of a Single Dose of 400 mg ^{14}C-DRV, With and Without rtv (Study TMC114-NC213)

	Mean (%) of Dose					
	Without rtv (N=4)			With rtv (N=4)		
Metabolite No.	**1 h**	**2 h**	**4 h**	**1 h**	**2 h**	**4 h**
M6	4.8	8.4	-	-	-	-
Unknown [a]	6.0	14.5	-	7.9	5.0	-
M23	7.7	9.2	-	-	-	-
M29	2.4	-	-	-	-	-
Unchanged Drug (DRV)	48.5	50.0	25.9	79.4	79.7	86.3
Total	69.4	82.1	25.9	87.3	84.7	86.3

[a] Metabolites eluting between 53 and 56 min.
Source: Module 4.2.2.4/TMC114-NC213/Table 5-9

The metabolic pathways for ^{14}C-DRV after single-dose oral administration of 400 mg ^{14}C-DRV in humans are shown in Figure 1.

Figure 1: Metabolic Pathways of ^{14}C-DRV in Humans After Single-Dose Oral Administration of 400 mg ^{14}C-DRV



Source: Module 4.2.2.4/TMC114-NC213/Figure 5-15

1.2.1.3. Potential for Drug-Drug Interactions With DRV

The interaction of DRV with human CYP isozymes was assessed in vitro with incubations with CYP probe substrates in study TMC114-NC123 (Module 4.2.2.6/TMC114-NC123), and the potential inhibition of CYP2C8 and uridine diphosphate glucuronosyltransferase (UGT) -1A1 enzymes by DRV was investigated in human liver microsomes in study TMC114-NC392

(Module 4.2.2.6/TMC114-NC392). The potential of DRV to induce CYP enzymes was determined in primary hepatocyte cultures from cryopreserved human hepatocytes (study TMC114-NC171) (Module 4.2.2.4/TMC114-NC171). The in vitro interaction of 6 HIV compounds with DRV in vitro was assessed in study TMC114-NC134 (Module 4.2.2.6/TMC114-NC134)

In study TMC114-NC123, incubations were performed with CYP probe substrates selective towards human CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A in the absence and presence of DRV. In preliminary experiments, a concentration-dependent inhibition was observed for CYP2C9, CYP2C19, CYP2D6, and CYP3A activities. CYP1A2 and CYP2B6 were only slightly inhibited at the highest DRV concentration (100 µM), while no inhibition of CYP2A6 and CYP2E1 could be detected. Because less than 20% inhibition was found for CYP1A2 at the highest DRV concentration, inhibition of CYP1A2 activity was not further investigated.

The selected DRV concentrations (0.5, 50, 100 µM [274, 27,400, 54,800 ng/mL]), type of inhibition, and calculated inhibition constant values are summarized in Table 5. When inhibitor concentration/inhibition constant ratios are >1, drug interactions can be considered likely. The results show that CYP3A is most potently inhibited by DRV. The inhibition constant values for the other CYP enzymes were all at least 60-fold higher than that of CYP3A, and the resultant concentration/inhibition constant ratios were all <1, indicating a much lower affinity for these CYP enzymes compared with CYP3A. Since the established inhibition constant for the inhibition of CYP3A is relatively low (<1 µM), inhibition of CYP3A by DRV could be clinically relevant.

Table 5: Summary of Inhibition of CYP Probe Substrates by DRV (Study TMC114-NC123)

CYP Enzyme	DRV Concentration (µM)	Type of Inhibition	Mean Inhibition Constant K_i (µM)	I/K_i Ratio		
				I=7.1 µM[a]	I=10.0 µM[b]	I=10.5 µM [c]
CYP2B6	100	Non-competitive	500	0.01	0.02	0.02
CYP2C9	100	Competitive	52	0.14	0.19	0.20
CYP2C19	50	Competitive	25	0.28	0.40	0.42
CYP2D6	50	Competitive	41	0.17	0.24	0.26
CYP3A	0.5	Competitive	0.40	17.8	25.0	26.3

I=inhibitor concentration (C_{max} at the recommended dose in µM); K_i=inhibition constant.
[a] I=7.1 µM (3,913 ng/mL) for DRV/rtv 400/100 mg twice daily (study TMC114-C137[10]).
[b] I=10.0 µM (5,460 ng/mL) for DRV/rtv 600/100 mg twice daily (study TMC125-C139[13]).
[c] I=10.5 µM (5,736 ng/mL) for DRV/rtv 800/100 mg twice daily (study TMC114-C137[10]).
Source: Module 4.2.2.6/TMC114-NC123 and C_{max} values from clinical research reports.

In study TMC114-NC392, the potential inhibition of CYP2C8-mediated paclitaxel 6-α-hydroxylation and UGT1A1-mediated bilirubin glucuronidation by DRV was investigated in human liver microsomes. The inhibition constant was 56.1 µM for CYP2C8 and 201 µM for UGT1A1. Therefore, the potential for DRV to cause drug-drug interactions via these enzyme pathways is clinically unlikely.

The potential of DRV to induce CYP enzymes was determined in primary hepatocyte cultures originating from 3 different human donors in study TMC114-NC171. Omeprazole, rifampicin, phenobarbital, or rtv were used as positive controls. In general, treatment of the hepatocytes with DRV did not result in significant cytotoxic effects, as determined by the measurement of the intracellular ATP content of the cells, while incubation with 50 µM rifampicin or 10 µM rtv elicited an approximate 25% decrease of the cellular ATP content as compared with the vehicle control-treated cells. In contrast, treatment with different concentrations of DRV resulted in a consistent increase of the intracellular ATP content.

Cells from the different donors responded well to treatment with positive control compounds. Treatment of the cells with different concentrations of DRV resulted in a minor, statistically non-significant mean 2.2-fold increase of CYP1A2 messenger RNA (mRNA) expression at the highest DRV concentration (50 µM). In comparison, treatment of the cells with 25 µM omeprazole elicited an approximate 22-fold increase of CYP1A2 mRNA. However, across the 3 batches of hepatocytes, treatment of the cells with 50 µM DRV resulted in a statistically significant mean 5.9-, 5.4-, 3.0-, 2.4-, 2.6-, and 5.5-fold increase of the CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, and CYP3A mRNA expression, respectively. It should be noted, however, that 50 µM is approximately 5-times the in vivo C_{max} value of 10.5 µM (5,736 ng/mL) obtained for DRV in plasma after administration of DRV/rtv 800/100 mg twice daily in the dose-escalation study TMC114-C137 (TMC114-C137[10]).

The rank order of induction potential of DRV and the positive controls for these CYPs was rifampicin > rtv ≅ DRV > phenobarbital.

The interaction of 6 anti-HIV compounds (delavirdine, saquinavir, rtv, indinavir, nelfinavir, and amprenavir) with the CYP-mediated metabolism of DRV was investigated in vitro in pooled human liver microsomes in study TMC114-NC134. The anti-HIV compounds were selected because of their known capacity to inhibit CYP3A metabolism in humans. Darunavir was incubated at concentrations of 1, 2, 5, 10, 20, 30, and 50 µM (548, 1,096, 2,740, 5,480, 10,960, 16,440, 27,400 ng/mL) using a microsomal protein concentration of 0.25 mg/mL. Formation rate constant and maximum velocity values of DRV metabolism were between 1.5 and 2.5 µM, and between 489 and 632 pmol/min/mg microsomal protein, respectively. All 6 anti-HIV compounds inhibited DRV metabolism (Table 6).

Table 6: Summary of Inhibition of DRV Metabolism by Anti-HIV Compounds (Study TMC114-NC134)

Inhibitor	Inhibitor Concentration (µM)	Type of Inhibition	Mean Inhibition Constant (µM)
Delavirdine	10	Non-competitive	2.5
Saquinavir	5	Competitive	1.6
Ritonavir	0.1	Competitive	0.014
Indinavir	0.2	Competitive	0.28
Nelfinavir	1	Competitive	0.18
Amprenavir	2	Competitive	2.0

Source: Module 4.2.2.6/TMC114-NC134

To predict the in vivo inhibition of DRV metabolism by the anti-HIV compounds, the average plasma concentrations of DRV and the anti-HIV compounds were used. For DRV,

2 concentrations from a clinical study were used for the calculations: the average minimum plasma concentration (C_{min}) (250 ng/mL) and C_{max} (6,000 ng/mL). Delavirdine, indinavir, and nelfinavir were predicted to strongly inhibit DRV metabolism in vivo. For rtv, complete inhibition of DRV metabolism was predicted. Saquinavir and amprenavir were predicted to be minor to moderate inhibitors of metabolism, depending on the DRV concentration.

1.2.1.4. In Vitro Transport Characteristics of DRV

Human colon-carcinoma derived Caco-2 cells were used as an in vitro model to investigate the bi-directional transepithelial transport characteristics of ^{14}C-DRV in study TMC114-NC137 (Module 4.2.2.2/TMC114-NC137). In addition, possible inhibition of human P-glycoprotein (P-gp) by DRV was also studied.

Comparison of the transepithelial permeation rates of DRV with those obtained for the reference compounds alniditan, levocabastine, and theophylline indicated that DRV can be classified as a compound with intermediate to high absorptive permeability in Caco-2 monolayers. Darunavir permeation across Caco-2 monolayers at early timepoints (0 to 15 minutes) was highly polarized with efflux ratio (secretory/absorptive permeation) values of up to approximately 17. At later timepoints (45 to 60 minutes), DRV transport was still moderately polarized (efflux ratio up to approximately 6). Both transport polarity and bi-directional transport rates were concentration-dependent (3 to 300 µM), supporting the involvement of an efflux transporter.

Co-incubation with the P-gp inhibitor verapamil reduced the efflux ratio of DRV at 30 µM from 5.4 to 3.1, whereas a more pronounced effect on initial efflux ratio was obtained with rtv (efflux ratio: 2.1). Passive transcellular diffusion is proposed as the predominant mechanism for transepithelial DRV permeation. One or more efflux transporters (of the ATP Binding Cassette family) are modulating DRV permeation, but the impact of these efflux mechanism(s) is limited at higher DRV concentrations (>100 µM, ie, >10-times the in vivo C_{max} value of approximately 10.5 µM (5,736 ng/mL) obtained for DRV in plasma after administration of DRV/rtv 800/100 mg twice daily in study TMC114-C137)[10].

Bi-directional transport experiments with the P-gp substrate paclitaxel demonstrated that DRV has P-gp inhibitory properties with an apparent IC_{50} value of 32.9 µM (ie, approximately 3-times greater than the in vivo C_{max} value of approximately 10.5 µM (5,736 ng/mL). Given the fact that DRV solubility and dissolution rate in the gastrointestinal environment are not limiting factors at the therapeutic dose, it was concluded that DRV would exhibit sufficient membrane permeability to obtain adequate intestinal absorption. Inhibition of transepithelial permeation of P-gp substrates by DRV cannot be excluded, but for most drugs, a possible effect is unlikely to be clinically significant with regard to intestinal absorption.

A clinical study investigating the interaction between digoxin (a P-gp substrate) and DRV indicated that DRV/rtv 600/100 mg twice daily results in inhibition of P-gp (see Section 2.1.7.2.2).

1.2.2. Human Biomaterial Studies with COBI

An overview of the human biomaterial studies that provide supporting information on the clinical pharmacology of COBI is shown in Table 7.

Table 7: Human Biomaterial Studies Conducted With COBI

Study ID	Objective	Human Biomaterial	Location
AD-216-2023	Bidirectional permeability and transport characteristics	Colon carcinoma-derived Caco-2 cells	Module 4.2.2.2/AD-216-2023
AD-216-2024	In vitro metabolism	Human hepatocytes and hepatic subcellular fractions	Module 4.2.2.4/AD-216-2024
AD-216-2026	Protein binding	Plasma	Module 4.2.2.3/AD-216-2026
AD-216-2027	Potential for COBI to induce human drug metabolizing enzymes and transporters	Human hepatoma cell lines	Module 4.2.2.4/AD-216-2027
AD-216-2028	Inhibition of CYPA3A	Human microsomal fractions	Module 4.2.2.4/AD-216-2028
AD-216-2029	CYP inhibition other than CYP3A	Pooled human hepatic microsomal fractions	Module 4.2.2.4/AD-216-2029
AD-216-2030	Potential of COBI to inhibit transporters	MDCK II cells expressing human P-gp, MRP1, and MRP2	Module 4.2.2.6/AD-216-2030
AD-216-2038	Identification of COBI metabolites	Primary Hepatocytes	Module 4.2.2.4/AD-216-2038
AD-216-2070	CYP inhibition other than CYP3A	Pooled human hepatic microsomal fractions	Module 4.2.2.4/AD-216-2070
AD-216-2071	Potential for COBI to induce human drug metabolizing enzymes and transporters	Primary cultures of human hepatocytes	Module 4.2.2.4/AD-216-2071
AD-216-2072	Potential for COBI to inhibit P-gp and BCRP	Caco-2 cell monolayers	Module 4.2.2.6/AD-216-2072
AD-216-2074	In vitro metabolism	Human liver microsomes	AD-216-2074[30]
AD-216-2075	Inhibition of human UGT1A1	Hepatic microsomal fractions	Module 4.2.2.4/AD-216-2075
AD-216-2093	Potential of COBI to inhibit transporters	CHO cells expressing human OCT2	Module 4.2.2.6/AD-216-2093
AD-216-2094	Potential of COBI to inhibit transporters	HEK293 cells expressing human MATE1 and MATE2-K	Module 4.2.2.6/AD-216-2094
AD-216-2098	Potential of COBI to inhibit transporters	S_2 cells expressing human OCTN1	Module 4.2.2.6/AD-216-2098
AD-216-2099	Potential of COBI to inhibit transporters	MDCK II cells expressing human BCRP	Module 4.2.2.6/AD-216-2099
AD-216-2100	Potential of COBI to inhibit transporters	CHO cells expressing human OATP1B1 and OATP1B3	Module 4.2.2.6/AD-216-2100
AD-216-2103	Potential of COBI to be a substrate of P-gp or BCRP	MDCK II cells expressing human P-gp and BCRP	Module 4.2.2.6/AD-216-2103
AD-216-2104	Potential for COBI to inhibit P-gp and BCRP	Caco-2 cell monolayers	Module 4.2.2.6/AD-216-2104
AD-216-2105	Potential of COBI to inhibit transporters	LLC-PK1, CHO, or HEK93 cells expressing MRP4, OAT1, and OAT3	Module 4.2.2.6/AD-216-2105

AhR=aryl hydrocarbon receptor; BCRP=breast cancer resistance protein; CHO=Chinese hamster ovary cell line; HEK293=human embryonic kidney 293 cells; MATE1=multidrug and toxin extrusion protein 1; MATE2-K=multidrug and toxin extrusion protein 2-K; LLC-PK1=porcine kidney cell line; MDCK II=Madin Darby canine kidney cells; MRP=multidrug resistance protein; OATP=organic anion transporter protein; OCT2=organic cation transporter 2; OCTN1=organic cation transporter novel 1; PXR=pregnane X receptor.

1.2.2.1. Absorption of COBI

Monolayers of Caco-2 cells were used as an in vitro model to investigate the bidirectional permeability and polarized transport characteristics of COBI in study AD-216-2023 (Module 4.2.2.2/AD-216-2023). Cobicistat displayed high forward permeability (7.61 x $10^{\#6}$ cm/s), with little evidence for efflux (efflux ratio: 1.1).

The potential for COBI to be a substrate for human P-gp or breast cancer resistance protein (BCRP) was evaluated using Madin Darby canine kidney cells (MDCK II) expressing these transporters in study AD-216-2103 (Module 4.2.2.6/AD-216-2103). The efflux ratio in P-gp-transfected cells and BCRP-transfected cells was higher (16-fold and 1.9-fold, respectively) than in the corresponding wild-type cells, suggesting that COBI can act as a substrate for these transporters.

1.2.2.2. Distribution of COBI

The binding of COBI to human plasma proteins was determined by equilibrium dialysis in study AD-216-2026 (Module 4.2.2.3/AD-216-2026). The blood-to-plasma ratios of ^{14}C radioactivity after a single oral dose of 150 mg ^{14}C-COBI were investigated in a mass-balance study (Section 2.1.2).

Based on equilibrium dialysis studies (in vitro and plasma samples from healthy subjects from clinical studies, including subjects with renal or hepatic impairment), COBI was, on average, 97% to 98% bound to human plasma proteins and binding was independent of concentration. The plasma protein binding of COBI across all species (mouse, rat, dog, monkey, human) ranged from 90.9% to 97.7% (study AD-216-2076 [Module 4.2.2.3/AD-216-2076] for mouse; study AD-216-2026 for all other species).

1.2.2.3. Metabolism and Excretion of COBI

The in vitro metabolism of COBI was studied in human hepatocytes and hepatic microsomal fractions in studies AD-216-2074[30] and AD-216-2024 (Module 4.2.2.4/AD-216-2024). In all species apart from dog, COBI metabolism could be accounted for by the generation of 3 metabolites: M21 (also called E1), M31 (E3), and M26 (E5). The in vivo metabolism of ^{14}C-COBI was studied in a mass-balance study based on sampling in feces, urine, and plasma collected from healthy subjects after a single oral dose of 150 mg ^{14}C-COBI (Section 2.1.2).

1.2.2.4. Potential for Drug-Drug Interactions With COBI

1.2.2.4.1. Potential for COBI to Inhibit CYP and UGT Enzymes

The ability of COBI to inhibit CYP3A enzyme activity was evaluated using human hepatic microsomal fractions in study AD-216-2028 (Module 4.2.2.4/AD-216-2028). Assessment of CYP3A inhibitions in human hepatic microsomal fractions, using rtv as a comparator, demonstrated that COBI is a potent mechanism-based inhibitor of human CYP3A based on all the human hepatic microsomal activities tested. Studies with midazolam 1%-hydroxylase and testosterone 6&-hydroxylase showed that the apparent inhibitory potency could be increased in a

preincubation time-dependent and NADPH cofactor-dependent manner, suggesting that COBI is a mechanism-based inhibitor of human CYP3A enzymes.

Detailed enzyme inactivation kinetic studies were performed with COBI and ritonavir (RTV). Cobicistat was found to be an efficient inactivator of human hepatic microsomal CYP3A activity, with kinetic parameters (k_{inact}=0.47 min^{-1}, K_I=1.1 μM) similar to those of RTV (k_{inact}=0.23 min^{-1}, K_I=0.26 μM), but with a higher theoretical maximal inactivation rate and a lower affinity (Table 8).

Table 8: Effect of COBI or RTV on Activities Catalyzed by Human Hepatic Microsomal CYP3A Enzymes (Study AD-216-2028)

	Calculated IC_{50} (μM)	
CYP Enzyme	**COBI**	**RTV**
Midazolam 1′-hydroxylase	0.15	0.11
Testosterone 6β-hydroxylase	0.15	0.12
Terfenadine *t*-butyl-hydroxylase	0.29	0.28
EVG hydroxylase (to metabolite M1)	0.03	0.03
ATV oxidation	0.04	0.04

Source: Module 4.2.2.4/AD-216-2028.

The potential for COBI to inhibit CYPs other than CYP3A was evaluated using pooled human hepatic microsomal fractions and enzyme specific activities in studies AD-216-2029 (Module 4.2.2.4/AD-216-2029) and AD-216-2070 (Module 4.2.2.4/AD-216-2070). At concentrations of up to 25 μM, COBI did not inhibit CYP1A2, CYP2C8, CYP2C9, or CYP2C19 activities (Table 9). Although COBI displayed mild inhibition of CYP2D6 and relatively stronger inhibition of CYP2B6, the IC_{50} was above the expected human plasma C_{max} value for COBI. At clinically relevant plasma concentrations, drug interactions with CYP2D6 (C_{max}/IC_{50}=0.16) or CYP2B6 (C_{max}/IC_{50}=0.53) are either unlikely or expected to be modest and brief. These results are consistent with the clinical probe drug interaction study, GS-US-216-0112 (Section 2.1.8.1).

Table 9: Inhibition of Human CYP Enzymes by COBI, RTV, or Positive Control Inhibitors

		Mean Calculated IC_{50} (μM) (N=6)		
CYP Enzyme	**Activity**	**Control Inhibitor[a]**	**COBI**	**RTV**
CYP1A2	Ethoxyresorufin O-deethylase	0.03	>25	>25
CYP2B6	Bupropion 4-hydroxylase	2.8	2.8	2.9
CYP2C8	Paclitaxel 6α-hydroxylase	0.06	30.1	5.5
CYP2C9	Tolbutamide hydroxylase	1.6	>25	3.9
CYP2C19	(S)-Mephenytoin 4'-hydroxylase	10.8	>25	>25
CYP2D6	Dextromethorphan O-demethylase	0.04	9.2	3.4
CYP3A	Midazolam 1'-hydroxylase	0.07	0.15	0.10
	Testosterone 6β-hydroxylase	0.09	0.15	0.11

[a] Control Inhibitors: CYP1A2, α-Naphthoflavone (0-100 μM); CYP2B6, Triethylenethiophosphoramide (0–30 μM); CYP2C8 Montelukast (0–30 μM); CYP2C9, Sulfaphenazole (0-10 μM); CYP2C19, Tranylcypromine (0-100 μM); CYP2D6, Quinidine (0-10 μM); CYP3A, Ketoconazole (0-10 μM).

Source: Module 4.2.2.4/AD-216-2029 and Module 4.2.2.4/AD-216-2070.

The potential for COBI to inhibit the catalytic activity of human UGT1A1 was evaluated using hepatic microsomal fractions in study AD-216-2075 (Module 4.2.2.4/AD-216-2075). Based on an assessment of β-estradiol metabolism in hepatic microsomal fractions, it was found that COBI does not inhibit UGT1A1.

1.2.2.4.2. Potential for COBI to Inhibit Transporters

The potential for COBI to inhibit human transporters was evaluated using cell lines or vesicles expressing individual recombinant proteins in studies AD-216-2030, AD-216-2105, AD-216-2099, AD-216-2093, AD-216-2094, AD-216-2098, and AD-216-2100 (Module 4.2.2.6/AD-216-2030; Module 4.2.2.6/AD-216-2105; Module 4.2.2.6/AD-216-2099; Module 4.2.2.6/AD-216-2093; Module 4.2.2.6/AD-216-2094; Module 4.2.2.6/AD-216-2098; Module 4.2.2.6/AD-216-2100). Cobicistat was a moderate inhibitor of the uptake transporters, organic anion transporter protein -1B1 and -1B3 (OATP1B1 and OATP1B3, respectively), and a mild inhibitor of organic cation transporter 2 (OCT2) (Table 10). Cobicistat also inhibited the renal efflux transporters organic cation transporter novel, type 1 (OCTN1) and multidrug and toxin extrusion protein 1 (MATE1). Cobicistat showed mild or undetectable inhibition of multidrug resistance-associated proteins -1, -2, and -4 (MRP1, MRP2, and MRP4, respectively), as well as BCRP, multidrug and toxin extrusion protein 2-K (MATE2-K), and the renal uptake transporters, organic anion transporter- 1 and -3 (OAT1 and OAT3, respectively), although systemic concentrations of COBI would be insufficient to inhibit their activity. Inhibition of OATP transporters is consistent with the clinical drug-drug interaction study GS-US-216-0123 (Section 2.1.8.5) in which, after dosing with EVG/COBI 150/150 mg, there was a modest increase (1.38-fold) in exposure of coadministered rosuvastatin.

Table 10: Summary of the Effect of COBI on the Activity of Human Transporters

Transporter	Cell Line	Substrate	Substrate Concentration (µM)	COBI IC_{50} (µM)
P-gp	MDCK II	Calcein AM	10	22.5-45.0[a]
MRP1	MDCK II	Calcein AM	10	45.0-90.0[a]
MRP2	MDCK II	Calcein[b]	-	45.0-90.0[a]
MRP4	LLC-PK1[c]	DHEAS	0.02	20.7
BCRP	MDCK II	Hoechst 33342	10	59.0
OAT1	CHO	p-Aminohippurate	5	)100[d]
OAT3	HEK293	Estrone 3-sulfate	0.2	)100[d]
OCT2	CHO	Metformin	2	8.24
OCTN1	S_2	Tetraethylammonium	5	2.49
MATE1	HEK293	Tetraethylammonium	5	1.87
MATE2-K	HEK293	Tetraethylammonium	5	33.5
OATP1B1	CHO	Fluo 3	2	3.50
OATP1B3	CHO	Fluo 3	2	1.88

[a] Range of tested concentrations bracketing 50% inhibition (IC_{50} not calculated).
[b] Generated from 10 µM calcein AM.
[c] Study performed with vesicles derived from the cell line.
[d] Maximum concentration tested.

Source: Module 4.2.2.6/AD-216-2030; Module 4.2.2.6/AD-216-2105; Module 4.2.2.6/AD-216-2099; Module 4.2.2.6/AD-216-2093; Module4.2.2.6/AD 216-2094; Module 4.2.2.6/AD-216-2098; and Module 4.2.2.6/AD-216-2100

The potential for COBI to inhibit intestinal P-gp or BCRP was evaluated by determining its effects on the bidirectional transport of the selective substrates, digoxin (P-gp substrate) and prazosin (BCRP substrate), using Caco-2 cell monolayers in studies AD-216-2072 (Module 4.2.2.6/AD-216-2072) and AD-216-2104 (Module 4.2.2.6/AD-216-2104). At very high concentrations (90 μM), such as those present in the intestinal lumen during drug absorption, COBI reduced the polarized transport of P-gp and BCRP substrates. However, based on the data in Table 10, COBI is a mild inhibitor of these transporters, with no effects expected at concentrations achieved systemically. The result for P-gp is consistent with the clinical drug-drug interaction study GS-US-216-0112 (Section 2.1.8.1) in which COBI was found to increase the C_{max} of digoxin (a P-gp substrate) by 1.41-fold, but to have a notably lesser effect on the area under the plasma concentration-time curve (AUC) (1.08-fold increase), suggesting that the effect was limited to transient inhibition of intestinal P-gp activity.

1.2.2.4.3. Potential for COBI to Induce Drug-Metabolizing Enzymes

The potential for COBI to induce human drug metabolizing enzymes and transporters through the activation of aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) was evaluated using human hepatoma cell lines transfected with expression vectors for these receptors in study AD-216-2027 (Module 4.2.2.4/AD-216-2027) and using primary cultures of human hepatocytes in study AD-216-2071 (Module 4.2.2.4/AD-216-2071). COBI showed no significant induction of AhR and mild inhibition of human PXR. Accordingly, induction assays using primary cultures of human hepatocytes indicated no relevant increases in CYP1A2 or CYP2B6 activities over a wide COBI concentration range (1 to 30 μM). Mild activity was observed for CYP3A at higher concentrations (27% of positive control at 10 μM). At plasma concentrations found in humans, COBI would be expected to have no effect on the expression of secondary targets of PXR such as CYP2C9, CYP2C19, UGT1A1, and P-gp, and would have very little effect on the expression of CYP3A4 mRNA. Any effect on CYP3A enzyme activity would be masked by mechanism-based inhibition.

1.3. Clinical Pharmacology Studies

1.3.1. Overview

The PK data for DRV with the proposed DRV/COBI 800/150 mg FDC tablet were bridged with the existing data for DRV/rtv coadministered as single agents by conducting 2 relative oral bioavailability studies:

- Study GS-US-216-0115 compared DRV/rtv 800/100 mg coadministered as single agents with DRV/COBI 800/150 mg coadministered as single agents following repeated once daily dosing under fed conditions (summarized in Module 2.7.1/Section 2.1.1).
- Study TMC114IFD1001 compared 2 candidate DRV/COBI 800/150-mg FDC tablet formulations versus DRV/rtv 800/100 mg coadministered as single agents in healthy subjects following repeated once daily dosing under fed conditions (summarized in Module 2.7.1/Section 2.1.2).

Based on the results obtained from study TMC114IFD1001, 1 of the candidate DRV/COBI FDC tablet formulations was selected for registration, but with use of a different color coating for the intended commercial tablet (G006 formulation).

In addition, an ongoing Phase 3b, open-label, single-arm study in 313 ART-naïve and ART-experienced HIV-1 infected adults without DRV RAMs is being performed by Gilead in collaboration with Janssen (study GS-US-216-0130, summarized in Section 2.2.5). This study was designed to assess the safety and virologic outcome of the combined use of DRV and COBI. Analysis of the primary safety endpoint occurred at Week 24 and is reported in the current submission. Analyses of the population PK of DRV and exposure-response relationships (PK/PD) were conducted on the basis of samples obtained from all participating subjects. In addition, the noncompartmental PK of DRV and COBI were assessed on the basis of rich sampling between Week 2 and Week 8 in a substudy of these subjects. Study GS-US-216-0130 was conducted with DRV (two 400-mg commercial tablets) and COBI (one 150-mg commercial tablet) administered as single agents.

Additionally, a bioequivalence study (TMC114IFD1003, summarized in Module 2.7.1/Section 2.2.1) comparing the DRV/COBI 800/150-mg FDC tablet formulation (G006, selected on the basis of study TMC114IFD1001) with DRV 800 mg coadministered with COBI 150 mg as single agents was conducted to support the extrapolation of data from study GS-US-216-0130 to the intended DRV/COBI FDC commercial tablet.

In addition to the studies conducted with coadministration of DRV/COBI, supportive studies conducted with DRV alone, DRV coadministered with rtv, or with COBI alone were conducted. For DRV, these included a mass-balance study, a hepatic impairment study, 24 drug-drug interaction studies, a thorough QT/QTc study, 2 Phase 3 studies with DRV/rtv administered in ART-naïve (Section 2.2.5.2) and ART-experienced (Section 2.2.5.3) subjects, and an integrated analysis of 2 Phase 2b studies in ART-experienced subjects (Section 2.2.5.4). Additionally, to determine the effect of different types of food on the PK of DRV, a study in which DRV/rtv was given with 4 different types of food or under fasted conditions was conducted (Module 2.7.1/Section 2.3.1).

For COBI, additional supportive studies conducted with COBI in the absence of DRV and summarized in this document include 2 Phase 1 dose-escalation studies in healthy subjects, 1 mass-balance study, 1 hepatic impairment study, 2 renal impairment studies, 6 drug-drug interaction studies, and 1 thorough QT/QTc study.

In the 36 studies with DRV included in the current submission, the PK and/or PD properties of DRV were studied in 2,979 subjects in 31 Phase 1 studies, 2 Phase 2 studies (presented together as 1 integrated analysis), and 3 Phase 3 studies (Table 11). In the 18 studies in which COBI was administered (with or without DRV), the PK and/or PD properties of COBI were studied in 952 subjects in 17 Phase 1 studies and 1 Phase 3 study (Table 12).

More details are given in the tabular listing of all clinical studies (Module 5.2), in the synopses (Module 2.7.6), in the study reports (Module 5.3), and in Appendix 1. As applicable, data from

the biopharmaceutic studies have been included in the comparisons of data across studies in Section 3.1 of this Summary of Clinical Pharmacology Studies.

Table 11: Number of Studies and Subjects for Which DRV was Administered (in the Presence or Absence of COBI)

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1:			
Single dose PK	2 (TMC114IFD1003, TMC114-C143)	Healthy subjects	157 (133 + 24)
Multiple dose PK	2 (TMC114IFD1001, GS-US-216-0115)	Healthy subjects	69 (36 + 33)
Mass-balance	1 (TMC114-C109)	Healthy subjects	8
Hepatic impairment	1 (TMC114-C134)	Healthy subjects and subjects with hepatic-impairment	32
Drug-drug interaction	24 (TMC114-C123, TMC114-C124, TMC114-C111, TMC114-C119, TMC125-C176, TMC278-C112, TMC114-MK0518, TMC114-A4001052, TMC114-C122, TMC114-C150, TMC114-C142, TMC114-C172, TMC114-C121, TMC114-C129, TMC125VIR1001, TMC114-C107, TMC114-C163, TMC114-C131, VX950-C124 TMC114-C133, TMC114-C120, TMC114-C171, TMC114-C127, TMC114-C128)	Healthy subjects, HIV-negative subjects on stable methadone therapy (C127), HIV-negative subjects on buprenorphine/naloxone maintenance therapy (C171), HIV-1 infected subjects on stable nevirapine (C119)	485 (18+ 13 + 12 + 19 + 32 + 16 + 18 +16 + 18 + 17 + 18 + 32 + 36 + 26 + 33 + 16 + 27 + 19 + 20 + 16 + 14 + 17 + 16+ 16)
QT/QTc	1 TMC114-C153	Healthy subjects	40
Phase 2:			
Integrated PK Analysis (2 studies)	2 (TMC114-C926 [TMC114-C202 + TMC114-C213])	ART-experienced HIV-1 infected subjects	596 (278 + 318)
Phase 3:			
Efficacy	2 (TMC114-C211, TMC114-C229)	ART-naïve and ART-experienced HIV-1 infected subjects	1,279 (689 + 590)
Safety	1 (GS-US-216-0130)	HIV-1 infected subjects	313
Total	36		2,979

Number of subjects includes all subjects that were treated in studies.
Source: Clinical Study Reports

Table 12: Number of Studies and Subjects for Which COBI was Administered (in the Presence or Absence of DRV)

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1:			
Single dose PK	2 (TMC114IFD1003, GS-US-236-0105)	Healthy subjects	157 (133 + 24)
Multiple dose PK	4 (TMC114IFD1001, GS-US-216-0115, GS-US-216-0101, GS-US-216-0113)	Healthy subjects	153 (36 + 33 + 60 + 24)
Mass-balance	1 (GS-US-216-0111)	Healthy subjects	8
Renal impairment	2 (GS-US-216-0121, GS-US-216-0124)	Healthy subjects and subjects with renal-impairment	78 (54 + 24)
Hepatic impairment	1 (GS-US-183-0133)	Healthy subjects and subjects with hepatic-impairment	20
Drug-drug interaction	6 (GS-US-216-0112, GS-US-201-0104, GS-US-216-0120, GS-US-216-0122, GS-US-216-0123, GS-US-236-0106)	Healthy subjects	175 (53 +18 + 33 + 16 + 34 + 21)
QT/QTc	1 (GS-US-216-0107)	Healthy subjects	48
Phase 3:			
Safety	1 (GS-US-216-0130)	HIV-1 infected subjects	313
Total	18		952

Number of subjects includes all subjects that were treated in studies.
Source: Clinical Study Reports

Information on the dosage form, formulation number, and dose of DRV or COBI together with the dosage form of any coadministered drugs for all studies summarized in this document is provided in Table 13 and Table 14, respectively.

Table 13: Clinical Pharmacology Studies With DRV Summarized in the Current Document, Including Information on DRV Dosage Form and Formulation Number and Dosage Form of Coadministered Drugs

	DRV			
Clinical Study Number	**Dosage Form**	**Dose**	**Formulation Number**	**Dosage Form of Coadministered Drugs**
Phase 1 - Mass-Balance				
TMC114-C109 Section 2.1.1	20-mg/mL Vit E-TPGS/PEG400 oral solution (^{14}C-labeled)	400 mg sd	FK4811	rtv: 100-mg capsule
Phase 1 - Effect of Hepatic Impairment				
TMC114-C134 Section 2.1.6.1	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule
Phase 1 - Drug-Drug Interaction				
TMC114-C123 Section 2.1.7.1.1	300-mg tablet	600 mg bid	F016	Didanosine (ddI): 400-mg enteric-coated capsule rtv: 100-mg capsule
TMC114-C124 Section 2.1.7.1.2	20-mg/mL Vit E-TPGS/PEG400 oral solution	300 mg bid	TF019	rtv: 100-mg capsule Tenofovir disoproxil fumarate (TDF): 300-mg tablet

TMC114-C111 Section 2.1.7.1.3	20-mg/mL Vit E-TPGS/PEG400 oral solution	300 mg bid	TF019	rtv: 100-mg capsule Efavirenz: 200-mg capsule
TMC114-C119 Section 2.1.7.1.4	20-mg/mL Vit E-TPGS/PEG400 oral solution 400-mg tablet	300 mg bid	TF019 F001	rtv: 100-mg capsule Nevirapine (NVP): 200-mg tablet
TMC125-C176 Section 2.1.7.1.5	400-mg tablet 200-mg tablet	600 mg bid	F001 F002	rtv: 100-mg capsule Etravirine: 100-mg tablet
TMC278-C112 Section 2.1.7.1.6	400-mg tablet	800 mg qd	F021	Rilpivirine: 50- and 100-mg tablets rtv: 100-mg capsule
TMC114-MK0518 Section 2.1.7.1.7	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Raltegravir: 400-mg tablet
TMC114-A4001052 Section 2.1.7.1.8	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Maraviroc: 150-mg tablet
TMC114-C122 Section 2.1.7.2.1	400-mg tablet	400 mg bid	F001	rtv: 100-mg capsule Ranitidine: 150-mg tablet Omeprazole: 20-mg capsule
TMC114-C150 Section 2.1.7.2.2	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Digoxin: 0.2-mg capsule
TMC114-C142 Section 2.1.7.2.3	400-mg tablet	400 mg bid	F001	rtv: 100-mg capsule Clarithromycin: 500-mg tablet
TMC114-C172 Section 2.1.7.2.4	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Carbamazepine: 200-mg tablet
TMC114-C121 Section 2.1.7.2.5	400-mg tablet	400 mg bid	F001	rtv: 100-mg capsule Paroxetine: 20-mg tablet Sertraline: 50-mg tablet
TMC114-C129 Section 2.1.7.2.6	200-mg tablet	400 mg bid	F002	rtv: 100-mg capsule Ketoconazole: 200-mg tablet
TMC125VIR1001 Section 2.1.7.2.7	600-mg tablet	600 mg bid	F032	rtv: 100-mg film-coated tablet Artemether/lumefantrine: 20/120-mg FDC tablet

TMC114-C107 Section 2.1.7.2.8	400-mg tablet	400 mg bid	F001	rtv: 100-mg capsule Rifabutin: 150-mg capsule
TMC114-C163 Section 2.1.7.2.9	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Rifabutin: 150-mg capsule
TMC114-C131 Section 2.1.7.2.10	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Ethinyl estradiol/norethindrone 35 µg/1-mg tablet
VX950-C124 Section 2.1.7.2.11	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Telaprevir: 375-mg tablet
TMC114-C133 Section 2.1.7.2.12	20-mg/mL Vit E-TPGS/PEG400 oral solution	300 mg bid	TF019	rtv: 100-mg capsule Atorvastatin: 10-mg tablet
TMC114-C120 Section 2.1.7.2.13	20-mg/mL Vit E-TPGS/PEG400 oral solution	600 mg bid	TF019	rtv: 100-mg capsule Pravastatin: 40-mg tablet
TMC114-C171 Section 2.1.7.2.14	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Buprenorphine/naloxone: 24/6-mg tablet
TMC114-C127 Section 2.1.7.2.15	300-mg tablet	600 mg bid	F016	rtv: 100-mg capsule Methadone: 5-mg tablet
TMC114-C128 Section 2.1.7.2.16	400-mg tablet	400 mg bid	F001	rtv: 100-mg capsule Sildenafil: 25- or 100-mg tablets
Phase 1 - Effect on Electrocardiogram (ECG)				
TMC114-C153 Section 2.2.3	400-mg tablet	1,600 mg qd 800 mg bid	F001	rtv: 100-mg capsule
Phase 2				
TMC114-C926 (TMC114-C202 + TMC114-C213) Section 2.2.5.4	400-mg tablet 200-mg tablet	400, 800 mg qd 400, 600 mg bid	F001 F002	rtv: 100-mg capsule
Phase 3				
TMC114-C211 Section 2.2.5.2	400-mg tablet	800 mg qd	F021 [e]	rtv: 100-mg capsule
TMC114-C229 Section 2.2.5.3	400-mg tablet (commercial) 600-mg tablet (commercial)	800 mg qd 600 mg bid	F030 F032	rtv: 100-mg capsule
GS-US-216-0130 (Section 2.2.5.1)	400-mg tablet	800 mg qd	F030 (DRV)	COBI 150-mg tablet + 2 fully active NRTIs

bid=twice daily; qd=once daily; sd=single dose.

Table 14: Clinical Pharmacology Studies With COBI Summarized in the Current Document, Including Information on COBI Dosage Form and Formulation Number and Dosage Form of Coadministered Drugs

	COBI		
Clinical Study Number	**Dosage Form**	**Dose**	**Dosage Form of Coadministered Drugs**
Phase 1 - Mass-Balance			
GS-US-216-0111 Section 2.1.2	150-mg tablet 150-mg capsule with 148.5 mg nonradiolabeled COBI and 100 µCi [1.5 mg] ^{14}C-COBI	150 mg qd	-
Phase 1 - Healthy Subject PK			
GS-US-216-0101 Section 2.1.4.1	25-mg tablet 100-mg tablet	50, 100, 200 mg qd	rtv: 100-mg soft gelatin capsule
GS-US-216-0113 Section 2.1.4.2	100-mg tablet	300, 400 mg qd	-
Phase 1 - Renal Impairment			
GS-US-216-0121 Section 2.1.5.1	150-mg tablet	150 mg qd	Iohexol: 1500 mg as IV bolus
GS-US-216-0124 Section 2.1.5.2	150-mg tablet	150 mg qd	EVG: 150-mg tablet
Phase 1 - Hepatic Impairment			
GS-US-183-0133 Section 2.1.6.2	150-mg tablet	150 mg qd	EVG: 150-mg tablet
Phase 1 - Drug-Drug Interaction			
GS-US-216-0112 Section 2.1.8.1	150-mg tablet	150 mg qd	Desipramine: 50-mg tablet Digoxin: 0.25-mg tablet EFV: 600-mg tablet
GS-US-201-0104 Section 2.1.8.2	150-mg tablet	150 mg qd	EVG: 150-mg tablet GS-8374: 150-mg tablet DRV: 400-mg tablet
GS-US-216-0120 Section 2.1.8.3	150-mg tablet	150 mg qd	EVG: 150-mg tablet Famotidine: 40-mg tablet Omeprazole: 20-mg capsule
GS-US-216-0122 Section 2.1.8.4	150-mg tablet	150 mg qd	EVG: 150-mg tablet Famotidine: 40-mg tablet
GS-US-216-0123 Section 2.1.8.5	150-mg tablet	150 mg qd	EVG: 85- and 150-mg tablets Rosuvastatin: 10-mg tablet ATV: 300-mg capsule Rifabutin: 150-mg capsule

GS-US-236-0106 Section 2.1.8.6	STR tablet containing COBI 150-mg	150 mg qd	EVG/COBI/FTC/TDF: 50/150/200/300 mg Norgestimate [NGM]/ Ethinyl estradiol [EE]: 0.180-, 0.215-, or 0.250- mg/ 0.025 mg tablets
Phase 1 - Effect on Electrocardiogram (ECG)			
GS-US-216-0107 Section 2.2.4	100-mg tablet 150-mg tablet	250, 400 mg sd	-
Phase 3			
GS-US-216-0130 (Section 2.2.5.1)	150-mg tablet	150 mg qd	DRV: 400-mg tablet 2 fully active NRTIs

bid=twice daily; qd=once daily; sd=single dose; STR=single-tablet regimen.

The following sections provide a summary of the information obtained in the clinical pharmacology studies that were conducted to support development of the intended commercial DRV/COBI FDC tablet. Throughout this document, references to plasma concentrations refer to total concentrations (bound and unbound) and references to drug exposure refer to the AUC, unless stated otherwise.

1.3.2. Noncompartmental PK

The noncompartmental PK of DRV and COBI when DRV was coadministered with COBI as an 800/150-mg FDC tablet were evaluated in healthy subjects in a bioavailability study (TMC114IFD1001; multiple doses) and a bioequivalence study (TMC114IFD1003; single doses), which are described in Module 2.7.1/Section 2. Pharmacokinetic data for DRV coadministered with COBI as the 800/150-mg FDC tablet were compared with data following single- and multiple-dose administration of DRV/rtv 800/100 mg or DRV/COBI 800/150 mg coadministered as single agents in Section 3.1.3.1 and Section 3.1.3.2 (for single- and multiple-dose DRV PK, respectively). Pharmacokinetic data for COBI when coadministered with DRV as the DRV/COBI 800/150-mg FDC tablet were compared with single- and multiple- dose administration of COBI 150 mg when administered with DRV as single agents in Section 3.1.4.1 and Section 3.1.4.2.

In HIV-1 infected subjects, the noncompartmental PK of DRV and COBI when coadministered as single agents (DRV/COBI 800/150 mg once daily) were assessed in a substudy of the Phase 3b study GS-US-216-0130 (Section 2.2.5.1). These data were compared with data obtained following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve HIV-1 infected subjects (study TMC114-C211) and ART-experienced HIV-1 infected subjects (studies TMC114-C202 and TMC114-C213 [presented together as an integrated analysis]) (Section 3.1.3.3).

1.3.3. Population PK Analysis

Based on an update of a previously developed population PK model for DRV, a population PK analysis of DRV 800 mg once daily when coadministered with COBI 150 mg once daily (as single agents) was conducted in the Phase 3b study GS-US-216-0130 (Section 2.2.6.1). The

DRV population PK estimates from this study in ART-naïve HIV-1 infected subjects and ART-experienced HIV-1 infected subjects with no DRV RAMs were compared with data obtained following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve HIV-1 infected subjects (study TMC114-C211) and ART-experienced HIV-1 infected subjects (studies TMC114-C229, TMC114-C202, and TMC114-C213) (Section 3.1.4.3).

1.3.4. Drug-Drug Interactions

No drug-drug interaction studies have been performed using DRV/COBI FDC tablet formulations, or using DRV coadministered with COBI as separate agents. The drug-drug interaction potential of the FDC of DRV/COBI has been evaluated on the basis of interactions observed with each of the single agents, in the case of DRV, when coadministered with rtv. The drug-drug interaction potential of DRV/COBI is discussed in Section 3.3.2.

1.3.5. Selection of Response Endpoints and Biomarkers

The PD parameters for antiviral activity that were used in PK/PD analyses of DRV/COBI coadministered as single agents in HIV-1 infected subjects included virologic outcome (ie, virologic success [plasma viral load of <50 HIV-1 RNA copies/mL], virologic failure [plasma viral load of ≥50 HIV-1 RNA copies/mL], or no virologic data in the Week 24 window) and change in viral load from baseline at Week 24 (Section 2.2.5.1.3.3). These are standard measures of virologic response in studies in HIV-1 infected subjects, and were also employed in studies TMC114-C211 and TMC114-C229, which are used in the current submission for making historical comparisons with DRV/rtv 800/100 mg once daily (both regimens coadministered as single agents).

The PD parameters for safety included the occurrence of certain prespecified AEs (rash, diarrhea, vomiting, nausea) and the worst laboratory abnormality for selected laboratory parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], total cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL], triglycerides, glucose, amylase, or lipase). These are standard measures of safety in studies in HIV-1 infected subjects, and were also evaluated in the historical studies of DRV/rtv 800/100 mg once daily coadministered as single agents.

1.3.6. PD and PK/PD Analyses

The exposure-response relationships between DRV exposure and virologic response were assessed by comparing DRV exposure in HIV-1 infected subjects with changes in viral load or with virologic outcome (success, failure, or no data in the Week-24 window) in study GS-US-216-0130 (Section 2.2.7.1). A generalized additive model (GAM) for virologic success by DRV exposure was also performed (Section 2.2.7.1).

The exposure-response relationships between DRV exposure and safety measures were assessed in study GS-US-216-0130 using descriptive statistics per subgroup, defined as whether or not a subject experienced an AE of rash, diarrhea, vomiting, and nausea; whether or not a subject experienced an AE leading to permanent discontinuation of study medication; and by worst

laboratory abnormality (according to the Division of Acquired Immunodeficiency Syndrome [DAIDS] grading scale) for selected laboratory parameters (Section 1.3.5).

These exposure-response relationships for virologic response and safety parameters were compared with data obtained following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve HIV-1 infected subjects (study TMC114-C211) and ART-experienced HIV-1 infected subjects with no DRV RAMs (study TMC114-C229) (Sections 3.4.1.1 and 3.4.1.2).

1.4. Critical Aspects of Methods Used

1.4.1. Bioanalytical Methods

An overview of bioanalytical methods used in clinical pharmacology studies in which DRV and COBI were coadministered is provided in Module 2.7.1/Section 1.3. An overview of the validation parameters for each method is provided in Module 2.7.1/Appendix 3, and a tabulated listing of the bioanalytical methods that were used for each clinical study is provided in Module 2.7.1/Appendix 4.

1.4.2. Study Design

The PK and PD for DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects were investigated in the Phase 3b study GS-US-216-0130. This is an ongoing, open-label, single-arm, multicenter study performed in ART-naïve HIV-1 infected subjects and ART-experienced HIV-1 infected subjects with no DRV RAMs to evaluate the safety and antiviral activity of DRV/COBI 800/150 mg once daily coadministered as single agents and with 2 fully active nucleotide reverse transcriptase inhibitors (NRTIs). A primary analysis was conducted at Week 24, and a final analysis will be conducted when all subjects have either completed the ongoing extension phase or discontinued. The primary objective of the study was to assess safety and tolerability of DRV/COBI 800/150 mg once daily, given together with 2 NRTIs, after 24 weeks; assessments of safety and tolerability at Week 48, antiviral activity (virologic outcome at Weeks 24 and 48), and change from baseline in CD4+ count (Weeks 24 and 48) were secondary objectives.

The PK and PD for DRV/rtv 800/100 mg once daily coadministered as single agents was assessed in 2 Phase 2b studies and 2 Phase 3 studies in either ART-naïve HIV-1 infected subjects study TMC114-C211) or ART-experienced HIV-1 infected subjects (studies TMC114-C202 and TMC114-C213) for 24 weeks (studies TMC114-C202 and TMC114-C213) or 48 weeks (studies TMC114-C211 and TMC114-C229). The primary objective of the Phase 2b studies was to evaluate the dose-response relationship of efficacy among different DRV/rtv treatment groups; the primary objective of study TMC114-C211 was to demonstrate the noninferiority in virologic response with DRV/rtv versus lopinavir (LPV)/rtv across 48 weeks; and the primary objective of TMC114-C229 was to demonstrate the noninferiority in virologic response with DRV/rtv 800/100 mg once daily versus DRV/rtv 600/100 mg twice daily in early ART-experienced subjects.

All Phase 1 clinical pharmacology studies with DRV were conducted as open-label studies. Additionally, most drug-drug interaction studies were conducted with a randomized, crossover design.

The majority of Phase 1 clinical pharmacology studies conducted with COBI without DRV coadministration were conducted as open-label studies, with the exception of 3 blinded studies: 2 healthy subject PK studies with COBI (GS-US-216-0101, GS-US-216-0113) and 1 study assessing the effect of COBI versus rtv on renal impairment (GS-US-216-0121). In general, clinical pharmacology studies entailed multiple dosing in order to assess the effects of intrinsic and extrinsic factors at clinically relevant steady-state exposures of COBI. Mechanistic PD studies entailed single and/or multiple dosing to evaluate the effects of COBI at appropriate doses/exposures.

1.4.3. Choice of Dose Levels for Clinical Pharmacology Studies

A dose regimen of DRV/COBI 800/150 mg once daily coadministered as single agents was used for the Phase 3b study GS-US-216-0130. The doses of COBI and DRV were chosen based on evaluation of the PK of DRV 800 mg once daily coadministered with COBI 150 mg once daily or rtv 100 mg once daily (as single agents) in a clinical relative bioavailability study conducted by Gilead (study GS-US-216-0115) (Module 5.3.1.2/GS-US-216-0115 and Module 5.3.5.2/GS-US-216-0130-W24/Section 7.4.4). In study GS-US-216-0115, the DRV/rtv 800/100 mg once daily dosing regimen was selected as the reference treatment because this is registered for ART-naïve and ART-experienced adults with no DRV RAMs based on 2 prior Phase 3b studies conducted by Janssen (TMC114-C211 and TMC114-C229 [Section 2.2.5.2 and Section 2.2.5.3, respectively]). In study GS-US-216-0115, COBI 150 mg enhanced DRV exposure to a similar extent as rtv 100 mg (Module 2.7.1/Section 2.1.1). The DRV AUC_{24h} and C_{max} were bioequivalent for DRV/COBI 800/150 mg once daily and DRV/rtv 800/100 mg once daily (both regimens coadministered as single agents). Therefore, DRV/COBI 800/150 mg once daily was selected as the dosing regimen for the Phase 3b study GS-US-216-0130. The NRTI (emtricitabine/tenofovir disoproxil fumarate [FTC/TDF]) doses used as the background regimen in this study were the registered doses for the treatment of HIV infection in adults.

1.4.4. Study Populations

Study GS-US-216-0130 was conducted in ART-naïve HIV-1 infected adults and ART-experienced HIV-1 infected adults with no DRV RAMs (Section 2.2.5.1). All Phase 1 studies with DRV were conducted in healthy subjects except for TMC114-C127 (HIV-negative subjects on stable methadone therapy), TMC114-C171 (HIV-negative subjects on buprenorphine/naloxone maintenance therapy), TMC114-C119 (HIV-1 infected subjects on stable therapy with nevirapine [NVP]), and TMC114-C134 (healthy subjects and subjects with hepatic impairment) (Section 2.1). The Phase 2b studies with DRV/rtv (TMC114-C202 and TMC114-C213) were conducted in ART-experienced subjects (Section 2.2.5.4), and the Phase 3 studies with DRV/rtv, TMC114-C211 and TMC114-C229, were conducted in ART-naïve subjects (Section 2.2.5.2) and ART-experienced subjects with no DRV RAMs (Section 2.2.5.3), respectively.

All Phase 1 studies with COBI (in the absence of DRV) were conducted in healthy subjects with the exception of 2 studies conducted in subjects with renal impairment (alone or compared with healthy subjects) (GS-US-216-0121 and GS-US-216-0124; Section 2.1.5) and 1 study conducted in subjects with hepatic impairment (versus healthy subjects) (Section 2.1.6.2).

1.4.5. PK Analysis Methods

For studies with DRV/COBI, DRV/rtv, or DRV alone, all DRV and COBI noncompartmental PK parameters in the Phase 1 studies, Phase 2b substudies, the substudy of TMC114-C211, and the substudy of GS-US-216-0130 were calculated using conventional noncompartmental methods using actual times of blood sampling, unless otherwise stated in the clinical study report. The population PK analyses for DRV coadministered with COBI in the Phase 3b study GS-US-216-0130 used a nonlinear mixed-effects approach to generate the PK parameters, as did the Phase 2b studies with DRV/rtv (TMC114-C202 and TMC114-C213) and Phase 3 studies with DRV/rtv (TMC114-C211 and TMC114-C229) with DRV/rtv (Section 2.2.6). For the Phase 1 studies conducted with COBI in the absence of DRV, intensive PK sampling was performed in all healthy subject and special population studies.

1.4.6. Measurement and Analysis Methods for Response Endpoints and Biomarkers

1.4.6.1. Change in Viral Load From Baseline and Virologic Outcome

In the Phase 3b study with DRV/COBI (study GS-US-216-0130), plasma HIV-1 RNA was measured at baseline and Weeks 2, 4, 8, 12, 16, and 24. Virologic outcome at Week 24 was defined according to 3 categories: (1) virologic success defined as subjects whose last available HIV-1 RNA value was <50 copies/mL in the Week 24 window; (2) virologic failure defined as subjects whose last available HIV-1 RNA value was ≥50 copies/mL in the Week 24 window; and (3) no virologic data—subjects who did not have on-treatment HIV-1 RNA data in the Week 24 window (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 7). The proportion of subjects with virologic success was analyzed using the Food and Drug Administration (FDA)-defined snapshot analysis algorithm. For the PK/PD analysis, change in viral load from baseline and virologic success were analyzed by relating the DRV PK variables (AUC_{24h} and predose plasma concentrations [C_{0h}]) on the observed virologic response data with the quartiles calculated from all subjects (ART-naïve and ART-experienced) with PK data. A GAM analysis for Week 24 virologic success by DRV AUC_{24h} or C_{0h}, fitted as a smoothed spline with 2 degrees of freedom, was also conducted.

In the Phase 3 studies with DRV/rtv (TMC114-C211 and TMC114-C229), relationships were evaluated between the DRV PK parameters AUC_{24h} and C_{0h} and the efficacy parameters (1) change in $\log_{10}$ viral load at Week 48, and (2) virologic response defined as viral load <50 copies/mL at Week 48. For the PK/PD analysis, $\log_{10}$ viral load and virologic response were both analyzed by DRV exposure quartiles. A univariate GAM analysis exploring the relationship between Week-48 virologic response and DRV C_{0h} was also performed.

In the Phase 2b studies with DRV/rtv (TMC114-C202 and TMC114-C213), the primary efficacy variable measured was the confirmed virologic response at Week 24, which was defined as a decrease in viral load (HIV-1 RNA copies/mL) of at least 1.0 $\log_{10}$ versus baseline (Module 5.3.4.2/TMC114-C926-CPKPD/Section 3.2.2); PK/PD relationships were determined using graphic and statistical methods.

1.4.6.2. Safety Endpoints

In the Phase 3b study with DRV/COBI, the PK/PD relationship between DRV exposure (AUC_{24h} or C_{0h}) and safety was evaluated by means of descriptive statistics per subgroup defined as whether or not a subject experienced an AE of rash, diarrhea, vomiting, and nausea; whether or not a subject experienced an AE leading to permanent stop of study medication; and by worst laboratory abnormality (according to the DAIDS grading scale) for selected laboratory parameters (AST, ALT, ALP, total cholesterol, LDL, HDL, triglycerides, glucose, amylase, or lipase).

In the Phase 3 studies with DRV/rtv (TMC114-C211 and TMC114-C229), the PK/PD relationship between DRV exposure and safety was evaluated using descriptive statistics of exposure for subjects who did or did not present with the following AEs of interest: rash-related cardiac-related, gastrointestinal-related, liver-related, lipid-related, and glucose-related; and AEs from the system organ classes (SOCs) psychiatric disorders and nervous system disorders. In the Phase 2b studies with DRV/rtv (TMC114-C202 and TMC114-C213), the PK/PD relationship between DRV exposure and safety was evaluated using descriptive statistics of exposure for subjects who did or did not present with the following AEs of interest: rash-related cardiac-related, liver-related, lipid-related, and glucose-related; and AEs from the SOCs psychiatric disorders, nervous system disorders, gastrointestinal disorders, and cardiac disorders.

1.4.7. Statistical Methods

Values presented in the tables in this module represent geometric or arithmetic mean values with standard deviation (SD) (studies with DRV) or coefficient of variability (%CV) (studies with COBI in the absence of DRV) for the individual treatments, unless otherwise noted; time to reach maximum plasma concentration (t_{max}) and terminal elimination half-life ($t_{1/2,term}$) values are presented as median (range) for studies with DRV and median (interquartile range) for studies with COBI in the absence of DRV unless otherwise noted. Population PK parameter estimates are presented as mean (SD) and median (range). For values presented in boxplots, the solid line in the box is the median. The boundaries of the box represent the first and third quartiles. The whiskers represent maximum and minimum values.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

The clinical pharmacology studies that support the requested marketing authorization are summarized in this section and listed in Appendix 1. Supplementary information about these studies is provided in the tabular listing of all clinical studies (Module 5.2), in the synopses (Module 2.7.6), and in the study reports (Module 5.3).

2.1. Human PK Studies

2.1.1. Mass-Balance of DRV in Healthy Subjects

TMC-114-C109

Module 5.3.3.1/TMC114-C109-CRR

2.1.1.1. Objective

To characterize the excretion and overall metabolic profile of DRV in humans, with and without coadministration of rtv.

2.1.1.2. Subjects and Methods

This was a Phase 1, open-label, single-dose, mass-balance study in 8 healthy male subjects. One group of 4 subjects received a single 400 mg dose of DRV alone, formulated as an oral solution (FK4811) containing both ^{14}C-labeled and unlabeled DRV at a concentration of 20 mg base-eq/mL. The other group of 4 subjects received a single 400 mg dose of the ^{14}C-labeled and unlabeled oral solution of DRV, while rtv 100 mg twice daily was administered from 2 days before until 6 days after DRV administration. Darunavir was taken under fasted conditions and, except when taken together with DRV, rtv was taken under fed conditions.

Plasma, urine, and feces samples were collected up to at least 168 hours after DRV administration. Unchanged DRV and rtv were determined in plasma. Total radioactivity was determined in whole blood, plasma, urine, and feces. Metabolic profiles were determined in selected plasma, urine, and feces samples, and structures of major metabolites were characterized, whenever possible. The mass-balance was calculated.

2.1.1.3. Results

2.1.1.3.1. DRV PK

The single-dose PK of (unchanged) DRV, with and without coadministration of rtv, are summarized in Table 15. For both treatments, DRV was rapidly absorbed without a lag-time. When DRV was coadministered with rtv, the mean C_{max} of unchanged DRV was increased by approximately 2-fold and the mean area under the plasma concentration-time curve from time of intake until the last measurable or measured concentration (AUC_{last}) and area under the plasma concentration-time curve from time of intake until infinity (AUC_{∞}) values were increased by approximately 11-fold.

Table 15: PK Parameters of DRV Given as ^{14}C-DRV With and Without Coadministration of rtv (Study TMC114-C109)

	Mean (SD); t_{max}: Median (Range)	
Parameter	**DRV 400 mg (FK4811)**	**DRV/rtv 400/100 mg (FK4811)**
N	4	4
t_{max}, h	0.5 (0.5-1.0)	0.75 (0.5 - 1.5)
C_{max}, ng/mL	2,730 (648)	5,125 (906)
AUC_{last}, ng.h/mL	4,291 (1,956)	50,389 (15,631)
AUC_{∞}, ng.h/mL	4,746[a] (1,647)	50,760 (15,600)
$t_{1/2,term}$, h	29.4[a] (45.3)	13.5 (1.83)

N=maximum number of subjects with data.
[a] Accurate determination not possible.
Source: Module 5.3.3.1/TMC114-C109-CRR/Table 6

2.1.1.3.2. Mass-Balance of DRV, and Metabolite Profiling and Identification

The administered radioactivity was predominantly excreted in feces, amounting on average to 81.7% and 79.5% of the dose at 168 hours after dosing in the absence and presence of rtv, respectively. An average of 12.2% and 13.9% of the administered radioactivity was recovered in urine in the absence and presence of rtv, respectively. At 168 hours after dosing, approximately 93% of the dose had been recovered irrespective of whether rtv was coadministered or not.

Orally administered ^{14}C-DRV was extensively metabolized in the absence of rtv: only about 8% of the dose was excreted unchanged in feces and urine. Coadministration of rtv markedly reduced metabolism: 48.8% of the dose was excreted unchanged in feces and urine in the presence of rtv. Unchanged DRV was mainly excreted via the feces in the absence (6.8%) or presence (41.2%) of rtv; the mean excretion of unchanged DRV in urine was 1.2% and 7.7%, respectively.

Unchanged drug accounted for the largest fraction of the radioactivity in plasma samples obtained after administration of DRV in the absence or presence of rtv, with a higher percentage in the presence of rtv (eg, 48.5% and 79.4% at 1 hour after administration, in the absence and presence of rtv, respectively).

Details of the metabolic profiles in urine, feces, and plasma are available in Section 3.1.1.3.

2.1.2. Mass-Balance of COBI in Healthy Subjects

GS-US-216-0111

Module 5.3.3.1/GS-US-216-0111-CSR

2.1.2.1. Objective

To determine the mass balance of COBI at steady-state.

2.1.2.2. Subjects and Methods

This was a Phase 1 open-label, mass-balance study in 8 healthy male subjects to evaluate the steady-state PK, metabolism, and excretion of COBI (150-mg tablet and 150-mg capsule with 148.5 mg nonradiolabeled COBI and 100 µCi [1.5 mg] ^{14}C-COBI) after administration of

multiple oral doses of COBI 150 mg once daily for 6 days followed by a single oral dose of ^{14}C-COBI 150 mg on the morning of Day 7. All treatments were administered under fed conditions within 5 minutes after a meal.

2.1.2.3. Results

2.1.2.3.1. Mass-Balance of COBI

Cobicistat was extensively metabolized; the total combined mean (SD) recovery of ^{14}C-radioactivity in feces and urine was 94.4% (3.75%), with most of the radioactive dose recovered in feces (86.2% [3.95%]). The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total ^{14}C-radioactivity over 24 hours. There were no quantifiable metabolites in the plasma. In most subjects, plasma radioactivity was undetectable beyond 32 hours postdose. Cobicistat was the major species in the feces (27%), followed by known oxidative metabolites, M31 (E3) (14%), which results from hydroxylation of isopropyl thiazole, and M21 (E1) (5.5%), which results from carbamate cleavage. All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the administered radioactive dose. The whole blood-to-plasma concentration ratio of COBI was approximately 0.5, indicating that COBI was excluded from erythrocytes. As expected, renal excretion of COBI was a minor pathway for elimination (+10% of the administered dose was present in urine as parent drug plus metabolites).

2.1.3. Healthy Subject PK for DRV

Data from a relative bioavailability study comparing DRV/COBI 800/150 mg coadministered as single agents with DRV/rtv 800/100 mg coadministered as single agents, a relative bioavailability study comparing 2 candidate DRV/COBI 800/150-mg FDC tablet formulations with DRV/rtv 800/100 mg coadministered as single agents, and a bioequivalence study comparing the intended DRV/COBI 800/150-mg FDC commercial tablet formulation with DRV/COBI 800/150 mg coadministered as single agents are summarized in Module 2.7.1/Section 2. As applicable, data from these studies are included in the comparisons of data across studies in Section 3.1 of this Summary of Clinical Pharmacology Studies.

2.1.4. Healthy Subject PK for COBI

Data from a relative bioavailability study comparing DRV/COBI 800/150 mg coadministered as single agents with DRV/rtv 800/100 mg coadministered as single agents, a relative bioavailability study comparing 2 candidate DRV/COBI 800/150-mg FDC tablet formulations with DRV/rtv 800/100 mg coadministered as single agents, and a bioequivalence study comparing the intended DRV/COBI 800/150-mg FDC commercial tablet formulation with DRV/COBI 800/150 mg coadministered as single agents are summarized in Module 2.7.1/Section 2. Additional studies that assessed the PK of COBI in the absence of DRV are presented in this section.

2.1.4.1. Single- and Multiple-Dose Escalation Study to Evaluate Safety, Tolerability, PK, and PD of COBI

GS-US-216-0101

Module 5.3.4.1/GS-US-216-0101-CSR

2.1.4.1.1. Objective

To investigate the safety and tolerability of escalating single and multiple oral doses of COBI and to characterize the single-dose PK and steady-state PK and PD (anti-CYP3A activity) of COBI.

2.1.4.1.2. Subjects and Methods

This was a Phase 1, double-blind, randomized, placebo- and active-controlled, single- and multiple-dose escalation study to investigate the PK, PD, safety, and tolerability of COBI (25- and 100-mg tablets) in 60 healthy adult subjects. In each of 3 staggered dose-escalation cohorts, subjects were randomized in a 4:1:1 ratio to receive COBI (50, 100, or 200 mg), rtv 100 mg, or placebo as follows:

Part A:

- Cohort 1: Period 1: COBI 50 mg, rtv 100 mg, or matching placebo(s), administered orally as a single dose;

  Period 2: COBI 50 mg, rtv 100 mg, or matching placebo(s), administered orally once daily for 14 consecutive days;
- Cohort 2: Period 1: COBI 100 mg, rtv 100 mg, or matching placebo(s), administered orally as a single dose;

  Period 2: COBI 100 mg, rtv 100 mg, or matching placebo(s), administered orally once daily for 14 consecutive days.

Part B:

- Cohort 3: Period 1: COBI 200 mg, rtv 100 mg, or matching placebo(s), administered orally once daily for 14 consecutive days.

In Part A, midazolam 5 mg (2.5 mL of a 2 mg/mL oral syrup) was administered orally as a PD probe substrate the day before dosing began in Period 1 (ie, Day 0) for each cohort, and on the final day of dosing in Period 2 (ie, Day 14) for each cohort. In Part B, midazolam was given the day before dosing began (ie, Day 0), and on the final day of dosing (ie, Day 14).

All treatments were administered under fed conditions within 5 minutes after a meal.

2.1.4.1.3. Results

2.1.4.1.3.1. COBI PK

Cobicistat exhibited nonlinear PK with respect to dose and time (Table 16). Single-dose escalation from COBI 50 mg to 100 mg and from COBI 100 mg to 200 mg resulted in dramatic decreases in COBI apparent clearance (CL/F); the least square (LS) means ratio of CL/F for COBI 100 mg versus 50 mg was 23.6% and for COBI 200 mg versus 100 mg, the ratio was 38.4%. Similarly, the CL/F of COBI at steady state (CL_{ss}/F) following multiple-dose administration of COBI decreased with increasing dose; the LS means ratio of CL_{ss}/F for COBI 100 mg versus 50 mg was 33.5% and for COBI 200 mg versus 100 mg was 42.5%.

When CL/F was compared following single versus multiple doses, lower values were observed following multiple doses of COBI at all dose levels versus single doses; the LS means ratios of single versus multiple doses were 312%, 219%, and 199% for 50, 100, and 200 mg, respectively. At steady-state, systemic exposure of COBI 100 mg was 60% lower than that of rtv 100 mg.

Table 16: PK Parameters of COBI After Single- and Multiple-Dose Administration of COBI at 50 to 200 mg Under Fed Conditions in Healthy Subjects (Study GS-US-216-0101)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)		
	COBI 50 mg	COBI 100 mg	COBI 200 mg
Single Dose			
N	12	15	15
t_{max}, h	3.26 (2.53; 4.25)	4.00 (3.50; 4.50)	4.00 (3.50; 4.50)
C_{max}, ng/mL	61.6 (57.2)	343 (34.6)	1,200 (30.1)
AUC_{last}, ng.h/mL	229 (71.8)	1,611 (49.0)	8,111 (40.0)
AUC_{∞}, ng.h/mL	243 (69.5)	1,651 (48.3)	8,422 (41.4)
$t_{1/2,term}$, h	1.4 (1.0; 1.8)	2.7 (2.3; 3.0)	4.2 (3.3; 5.1)
CL/F, mL/h	435,292.1 (92.0)	77,125.2 (58.9)	29,097.6 (53.3)
Multiple Dose			
N	12	11	12
t_{max}, h	4.50 (3.50; 4.50)	4.50 (4.50; 4.53)	4.50 (4.50; 4.50)
C_{max}, ng/mL	170 (70.1)	563 (30.7)	1,855 (28.0)
AUC_{24h}, ng.h/mL[a]	827 (81.6)	3,436 (34.3)	16,108 (34.3)
$t_{1/2,term}$, h	2.2 (1.3; 2.5)	3.1 (2.6; 3.4)	5.2 (4.1; 6.1)
CL_{ss}/F, mL/h	154,288.3 (106.9)	33,190.3 (43.6)	13,952.5 (38.4)

Q=quartile.
[a] Reported as AUC_{τ}.
Source: Module 5.3.4.1/GS-US-216-0101-CSR/Table 5.1

2.1.4.1.3.2. Midazolam PK

Relative to midazolam alone, exposure (AUC_{∞}) to midazolam following coadministration of COBI 200 mg and rtv 100 mg increased 19.2- and 22.5-fold, respectively. Cobicistat 200 mg and rtv 100 mg inhibited MDZ CL/F to a similar extent (#94.8% and –95.6%, respectively), while COBI 100 mg inhibited MDZ CL/F to a slightly lesser extent (#92.7%) (Table 17). Cobicistat effectively inhibited CYP3A metabolism at low doses (, 100 mg) with low systemic drug exposure.

Table 17: PK Parameters of Midazolam After a Single Dose of Midazolam 5 mg Alone, With COBI, or With rtv in Healthy Subjects (Study GS-US-216-0101)

	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)				
Parameter	**MDZ 5 mg**	**MDZ + COBI 50 mg**	**MDZ + COBI 100 mg**	**MDZ + COBI 200 mg**	**MDZ + rtv 100 mg**
N	60	12	11	12	9
t_{max}, h	1.00 (1.00; 2.00)	1.75 (1.27; 3.75)	4.00 (2.50; 4.52)	2.25 (1.75; 4.25)	3.00 (2.00; 4.00)
C_{max}, ng/mL	14.5 (28.5)	45.3 (26.6)	55.0 (17.5)	56.0 (20.7)	58.5 (16.4)
AUC_{last}, ng.h/mL	58.0 (29.2)	493.2 (34.1)	665.3 (17.8)	690.1 (16.2)	729.4 (22.9)
AUC_{∞}, ng.h/mL	64.1 (33.3)	626.0 (49.9)	855.7 (18.2)	1219.6 (26.6)[a]	1526.3 (42.8)
$t_{1/2,term}$, h	5.2 (3.9; 6.9)	8.9 (6.4; 10.9)	11.2 (8.2; 12.9)	19.4 (11.3; 28.2)[a]	25.8 (16.4; 35.1)
CL/F, mL/h	87,336 (35.4)	9,661 (41.8)	6,020 (17.9)	4,351 (24.3)[a]	3,936 (45.4)

MDZ=midazolam; Q=quartile.
Source: Module 5.3.4.1/GS-US-216-0101-CSR/Table 5.3

2.1.4.1.4. Conclusion

Cobicistat exhibited nonlinear PK with respect to dose and time, which was expected for a mechanism-based inhibitor of CYP3A. At steady-state, systemic exposure of COBI 100 mg was 60% lower than rtv 100 mg. Cobicistat effectively inhibited CYP3A metabolism at doses ≤100 mg, with low systemic drug exposure.

2.1.4.2. PK, Safety, and Tolerability of COBI in Healthy Subjects

GS-US-216-0113

Module 5.3.3.1/GS-US-216-0113

2.1.4.2.1. Objective

To investigate the PK of COBI following single- and multiple-dose administration.

2.1.4.2.2. Subjects and Methods

This was a Phase 1, open-label, single- and multiple-dose, staggered dose escalation study to investigate the PK, safety, and tolerability of COBI (100-mg tablet) in 24 healthy adult subjects. Subjects were enrolled into 1 of 2 sequential cohorts, and received the following treatments:

- Cohort 1: COBI 300 mg (3 COBI 100-mg tablets), administered orally once daily in the morning for 7 consecutive days.
- Cohort 2: COBI 400 mg (4 COBI 100-mg tablets), administered orally as a single dose in the morning.

All treatments were administered under fed conditions within 5 minutes after a meal.

2.1.4.2.3. Results

2.1.4.2.3.1. COBI PK

Cobicistat exhibited nonlinear PK with respect to time and dose (Table 18). Single-dose escalation from 300 to 400 mg resulted in statistically significant decreases in COBI CL/F and corresponding increases in AUC and C_{max} without changes in $t_{1/2,term}$, consistent with higher

COBI bioavailability. Comparison of single-dose administration of 300 mg COBI with multiple-dose administration of 300 mg COBI revealed a large decrease in CL/F and increases in $t_{1/2,term}$, AUC, and C_{max}.

Table 18: PK Parameters of COBI After Single- and Multiple-Dose Administration of COBI at 300 and 400 mg Under Fed Conditions in Healthy Subjects (Study GS-US-216-0113)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)			
	Cohort 1 COBI 300 mg (qd)			Cohort 2 COBI 400 mg (qd)
	Day 1	Day 4	Day 7	Day 1
N	12	12	12	12
t_{max}, h	3.75 (3.50; 4.50)	4.50 (3.75; 4.50)	4.00 (3.25; 4.50)	4.25 (3.75; 4.50)
C_{max}, ng/mL	2,339 (16.9)	3,510 (18.9)	3,837 (16.7)	4,113 (17.2)
AUC, ng.h/mL[a]	20,773 (27.7)	35,799 (26.8)	39,125 (27.6)	39,899 (26.2)
$t_{1/2,term}$, h	5.2 (4.3; 5.8)	6.3 (5.4; 8.4)	8.1 (5.9; 9.0)	4.8 (4.1; 4.9)
CL/F, mL/h	15,526 (28.8)	9,007 (28.7)	8,282 (29.9)	10,592 (23.2)

Q=quartile; qd=once daily.
[a] AUC=AUC_{∞} for Day 1 and AUC_{τ} for Days 4 and 7.
Source: Module 5.3.3.1/GS-US-216-0113-CSR/Table 4

2.1.4.2.4. Conclusion

Cobicistat exhibited nonlinear PK with respect to dose and time, which was expected for a mechanism-based inhibitor of CYP3A. Single-dose escalation from 300 to 400 mg resulted in statistically significant decreases in COBI CL/F and corresponding increases in AUC and C_{max} without changes in $t_{1/2,term}$ consistent with higher COBI bioavailability. Relative to a single dose of COBI 300 mg there was a large decrease in CL/F as well as increases in $t_{1/2,term}$, AUC, and C_{max} following multiple doses of COBI 300 mg, indicative of changes in COBI bioavailability, systemic clearance, or both with time.

2.1.5. Intrinsic Factor PK: Effect of Renal Impairment on COBI

2.1.5.1. Effect of COBI and rtv on Renal Function as Assessed by Markers of Glomerular Filtration Rate

GS-US-216-0121

Module 5.3.3.3/GS-US-216-0121-CSR

2.1.5.1.1. Objective

This study had 2 subject cohorts. For Cohort 1, the primary objective was to assess renal function before, during, and after completion of COBI or rtv administration in healthy subjects. For Cohort 2, the primary objective was to assess renal function in subjects with stable mild to moderate renal impairment before, during, and after completion of COBI administration.

2.1.5.1.2. Subjects and Methods

This was a Phase 1 study in 54 subjects that sequentially evaluated 2 subject cohorts. Cohort 1 was a randomized, double-blinded, placebo-controlled, parallel-group cohort to investigate renal function and renal creatinine handling before, during, and after completion of administration of

COBI (150-mg tablet) or rtv in 36 healthy subjects. Cohort 2 was a single-treatment, open-label, multiple-dose cohort to evaluate renal function and renal creatinine handling in 18 subjects with stable mild to moderate renal impairment (estimated glomerular filtration rate [eGFR] 50 to 79 mL/min) before, during, and after completion of COBI administration, and to assess the PK and safety of COBI in subjects with stable mild to moderate renal impairment

Subjects in Cohort 1 were randomized evenly (1:1:1) to receive 1 of the following 3 treatments for 7 consecutive days:

- Treatment 1: COBI 150 mg once daily and rtv placebo 100 mg once daily.
- Treatment 2: rtv 100 mg once daily and COBI placebo 150 mg once daily.
- Treatment 3: COBI placebo 150 mg once daily and rtv placebo 100 mg once daily.

All treatments were administered immediately after subjects had completed a meal.

In Cohort 2, subjects received COBI 150 mg once daily for 7 days.

Subjects in both cohorts received the intravenous probe drug iohexol to determine actual GFR (aGFR) at Days 0, 7, and 14.

2.1.5.1.3. Results

2.1.5.1.3.1. COBI PK

Pharmacokinetic parameters of COBI on Day 7 following once daily dosing in subjects with normal renal function (eGFR ≥80 mL/min) in Cohort 1 and subjects with mild to moderate renal impairment (eGFR 50 to 79 mL/min) in Cohort 2 are presented in Table 19. Higher COBI exposures were observed in Cohort 2 than in Cohort 1.

Table 19: PK Parameters of COBI Following Administration of COBI 150 mg Once Daily for 7 Days in Healthy Subjects and Subjects With Mild to Moderate Renal Impairment (Study GS-US-216-0121)

Parameter	Mean (%CV)	
	Cohort 1 Healthy ($eGFR_{CG}$ ≥80 mL/min)	**Cohort 2 Mild to Moderate Renal Impairment ($eGFR_{CG}$ 50 to 79 mL/min)**
N	12	18
C_{24h}, h[a]	99.8 (59.2)	303 (70.6)
C_{max}, ng/mL	1,719 (19.8)	2,029 (31.6)
AUC_{24h} ng.h/mL[b]	14,545 (28.2)	20,820 (38.5)

$eGFR_{CG}$=eGFR calculated using the Cockcroft-Gault equation.
[a] Reported as C_τ.
[b] Reported as AUC_τ.
Source: Module 5.3.3.3/GS-US-216-0121-CSR/Table 13.1.1

2.1.5.1.3.2. COBI PD

Mean (SD) values for eGFR calculated using the Cockcroft-Gault equation ($eGFR_{CG}$) within each treatment group in Cohorts 1 and 2, and mean (SD) changes from baseline (Day 0) for these

values at Day 7 and Day 14 are shown in Table 20. Serum creatinine-based GFR estimations demonstrated statistically significant (p +0.05) decreases on Day 7 in both cohorts in subjects receiving COBI. These decreases had reversed on Day 14. No statistically significant changes in eGFR relative to Day 0 were observed on Day 7 in subjects who had received rtv or placebo or on Day 14 in subjects who had received placebo; a statistically significant increase in eGFR was observed on Day 14 in subjects who had received rtv. Similar results were also obtained for both eGFR calculated using the modification of diet in renal disease equation and measured GFR determined using 24-hour urinary output and serum creatinine concentration.

Table 20: Estimated GFR_{CG} by Visit and Change from Baseline at Days 7 and 14 (Study GS-US-216-0121)

	Mean (SD)		
Parameter	**Day 0**	**Day 7**	**Day 14**
Placebo - Healthy			
N	12	12	12
$eGFR_{CG}$ (mL/min)	114 (26.7)	116 (24.0)	137 (59.0)
Change from Day 0 (mL/min)	-	2.2 (9.10) (p=0.42)	22.8 (59.9) (p=0.21)
COBI - Healthy			
N	12	12	12
$eGFR_{CG}$ (mL/min)	121 (22.9)	111.4 (26.6)	123 (28.0)
Change from Day 0 (mL/min)	-	#9.9 (13.1) (p=0.024)	1.4 (11.5) (p=0.69)
COBI - Mild to Moderate Renal Impairment			
N	18	18	18
$eGFR_{CG}$ (mL/min)	68.7 (9.67)	56.8 (10.98)	66.5 (10.6)
Change from Day 0 (mL/min)	-	#11.9 (6.97) (p<0.001)	#2.2 (5.61) (p=0.12)
rtv - Healthy			
N	12	12	12
$eGFR_{CG}$ (mL/min)	117 (17.5)	117.9 (18.46)	123 (21.2)
Change from Day 0 (mL/min)	-	1.0 (8.62) (p=0.70)	5.7 (8.21) (p=0.035)

Source: Module 5.3.3.3/GS-US-216-0121-CSR/Table 4.2.1

In contrast to eGFR, aGFR, determined using the probe drug iohexol, was unchanged from baseline (Day 0) in the presence of COBI, rtv, or placebo on both Day 7 and Day 14 (p)0.05). Consistent with these results, there were also no statistically significant changes from baseline on Day 7 or Day 14 in cystatin C-derived GFR (calculated using clearance of the endogenous serum protein cystatin C).

2.1.5.1.4. Conclusion

Higher COBI exposure was observed in subjects with mild to moderate renal impairment relative to subjects with normal renal function. On Day 7, decreases from baseline in $eGFR_{CG}$ were observed in subjects with normal or mild to moderately impaired renal function who received COBI. These decreases had reversed on Day 14. In contrast to eGFR, aGFR was unchanged, indicating that COBI inhibits tubular secretion of creatinine and does not alter true GFR.

Information on dosing recommendations in subjects with renal impairment is available in Section 3.2.5.

2.1.5.2. PK of COBI-Boosted EVG in Subjects With Severe Renal Impairment

GS-US-216-0124

Module 5.3.3.3/GS-US-216-0124

2.1.5.2.1. Objective

To investigate whether the PK of EVG and COBI are altered in subjects with severe renal impairment (but not on dialysis) compared with healthy control subjects.

2.1.5.2.2. Subjects and Methods

This was a Phase 1, open-label, parallel-group study to investigate the PK of EVG and COBI when coadministered in subjects with severe renal impairment compared with matched healthy subjects. The study population included 24 subjects: 13 subjects with severe renal impairment ($eGFR_{CG}$ <30. mL/min) of which 12 received all planned doses and 11 healthy control subjects ($eGFR_{CG}$ ≥90 mL/min) (it was not possible to find a healthy control subject for 1 of the renally impaired subjects). Subjects were matched for age (±10 years), sex, and BMI (±15%, 18≤ BMI ≤34 kg/m^2). Elvitegravir 150 mg and COBI 150 mg (COBI 150-mg tablet) were coadministered once daily, in the morning immediately after a standard meal, for 7 days followed by a 7-day follow-up period.

2.1.5.2.3. Results

2.1.5.2.3.1. COBI and EVG PK

The LS means ratios for C_{24h}, C_{max}, and AUC_{24h} of COBI when EVG/COBI 150/150 mg once daily was administered to subjects with severe renal impairment relative to matched healthy control subjects were 113%, 122%, and 125%, respectively (Table 21). The LS means ratios for C_{24h}, C_{max}, and AUC_{24h} of EVG when EVG/COBI 150/150 mg was administered to subjects with severe renal impairment relative to healthy control subjects were 69%, 67%, and 76%, respectively. Notably, EVG exposure on Day 7 among subjects with normal renal function was substantially higher than that observed in previous clinical studies with EVG/COBI (GS-US-216-0123, Section 2.1.8.5; and GS-US-183-0133, Section 2.1.6.2).

For both EVG and COBI, the mean (SD) % free fraction (plasma unbound concentration) was determined in the subjects with severe renal impairment and the matched healthy control subjects on Day 7. For EVG, the mean (SD) % free fraction was 1.42 (0.17) in the renally impaired subjects and 1.16 (0.16) in the healthy control subjects. For COBI, the mean (SD) % free fraction was 2.47 (0.62) in the renally impaired subjects and 2.49 (0.29) in the healthy control subjects.

Table 21: PK Parameters of COBI and EVG Following Coadministration of COBI 150 mg and EVG 150 mg Once Daily in Healthy Subjects and Subjects With Severe Renal Impairment (Study GS-US-216-0124)

Parameter	Mean (%CV) Test	Mean (%CV) Reference	Test/Reference Least Square Means Ratio, % (90% CI)
	Severe Renal Impairment ($eGFR_{CG}$ <30 mL/min) EVG/COBI 150/150 mg qd	**Healthy Subjects ($eGFR_{CG}$ ≥90 mL/min) EVG/COBI 150/150 mg qd**	
N	12	11	
C_{24h}, ng/mL	166 (128.2)	97.0 (61.0)	112.85 (56.75; 224.40)
C_{max}, ng/mL	2,149 (35.0)	1,709 (22.4)	122.42 (99.82; 150.13)
AUC_{24h} ng.h/mL	18,553 (36.8)	14,212 (24.4)	125.48 (98.57; 159.73)
	Severe Renal Impairment ($eGFR_{CG}$ <30 mL/min) EVG/COBI 150/150 mg qd	**Healthy Subjects ($eGFR_{CG}$ ≥90 mL/min) EVG/COBI 150/150 mg qd**	
N	12	11	
C_{24h}, ng/mL	531 (42.3)	761 (38.9)	69.07 (51.82; 92.06)
C_{max}, ng/mL	2,224 (26.7)	3,349 (33.9)	67.30 (54.78; 82.68)
AUC_{24h} ng.h/mL	26,045 (24.3)	34,597 (26.9)	75.50 (62.82; 90.75)

qd=once daily.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.3.3/GS-US-216-0124-CSR/Table 3.3 and Table 3.4

2.1.5.2.3.2. COBI and EVG PD

Following dosing with EVG/COBI once daily for 7 days, $eGFR_{CG}$ was 10.5% lower on Day 7 than at baseline among subjects with severe renal impairment, and 8.4% lower on Day 7 than at baseline among subjects with normal renal function. Similar results were obtained using eGFR calculated using the modification of diet in renal disease equation. The observed decreases in eGFR were reversible, with values returning to baseline levels by Day 14. The decrease in eGFR is attributed to inhibition by COBI of the proximal tubular secretion of creatinine.

2.1.5.2.4. Conclusion

No clinically relevant changes in EVG or COBI PK were observed in subjects with severe renal impairment (not on dialysis) compared with matched healthy control subjects with normal renal function.

Estimated GFR_{CG} values were slightly lower at Day 7 than at baseline in both subjects with severe renal impairment and matched healthy control subjects with normal renal function. The decreases were reversible, and had returned to baseline by Day 14. These PD findings are consistent with those of study GS-US-216-0121 (Section 2.1.5.1), which compared subjects with normal renal function with subjects with mild to moderate renal impairment.

Information on dosing recommendations in subjects with renal impairment is available in Section 3.2.5.

2.1.6. Intrinsic Factor PK: Hepatic Impairment

2.1.6.1. Effect of Hepatic Impairment on DRV

TMC114-C134

Module 5.3.3.3/TMC114-C134-CRR

2.1.6.1.1. Objective

To investigate the single-dose and steady-state PK of DRV in subjects with mild or moderate hepatic impairment compared with healthy control subjects.

2.1.6.1.2. Subjects and Methods

This was a Phase 1, open-label, parallel-group, controlled study to investigate the steady-state PK of DRV, administered as the 300-mg tablet formulation F016, together with rtv in non-HIV-1 infected subjects with mild to moderate hepatic impairment compared with matched healthy subjects with normal hepatic function. The study population included 32 subjects divided into 2 panels: 8 subjects with mild hepatic impairment and 8 healthy matched control subjects in Panel A, and 8 subjects with moderate hepatic impairment and 8 healthy matched control subjects in Panel B. Panels A and B were conducted sequentially. Subjects in both panels received DRV/rtv at a dose of 600/100 mg twice daily for 6 days and on the morning of Day 7; subjects also received rtv on the evening of Day 7 and in the morning and evening of Days 8 and 9. Darunavir/rtv was administered under fed conditions within 10 minutes after a meal.

In addition to the measurement of PK parameters of DRV and rtv on Days 1 and 7, the plasma concentrations of AAG and the percentage of unbound DRV in plasma were measured on Day 1.

2.1.6.1.3. Results

2.1.6.1.3.1. DRV PK

The mean PK parameters for DRV on Days 1 and 7 in healthy subjects and subjects with mild or moderate hepatic impairment are shown in Table 22 and Table 23, respectively. On Days 1 and 7, relative to the healthy matched control subjects, the mean exposure to DRV (C_{max}, AUC_{12h}, and C_{min}) was lower in subjects with mild hepatic impairment and higher in subjects with moderate hepatic impairment.

On Day 1, the LS mean ratios for C_{max} and AUC_{12h} of DRV were 80% and 86%, respectively, in subjects with mild hepatic impairment relative to healthy control subjects, and were 102% and 110%, respectively, in subjects with moderate hepatic impairment relative t healthy control subjects. For all comparisons, the 90% confidence intervals (CIs) of the LS means ratios were outside of the 80.00% to 125.00% bounds.

On Day 7, the LS mean ratios for C_{max} and AUC_{12h} of DRV were 88% and 94%, respectively, in subjects with mild hepatic impairment relative to healthy control subjects, and were 122% and 120%, respectively, in subjects with moderate hepatic impairment relative to healthy control

subjects. For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds.

Table 22: PK Parameters of DRV Following Administration of DRV/rtv in Healthy Subjects and Subjects With Mild Hepatic Impairment (Study TMC114-C134)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Panel A Mild Hepatic Impairment DRV/rtv 600/100 mg bid	Panel A Healthy Subjects DRV/rtv 600/100 mg bid	
Day 1			
N	8	8	
t_{max}, h	5.0 (2.0-9.0)	5.0 (2.0-6.0)	-
C_{max}, ng/mL	4,099 (854)	5,376 (2,167)	80.29 (60.08; 107.3)
AUC_{12h} ng.h/mL	28,660 (6,709)	34,980 (13,750)	85.98 (63.24;116.9)
Day 7			
N	8	8	
t_{max}, h	4.0 (3.0-5.0)	3.0 (1.0-5.0)	-
C_{0h}, ng/mL	2,661 (677)	3,748 (1,226)	-
C_{min}, ng/mL	2,346 (664)	2,840 (926)	83.37 (63.46; 109.5)
C_{max}, ng/mL	5,583 (992)	6,401 (1,673)	88.49 (73.21; 107.0)
AUC_{12h}, ng.h/mL	47,920 (9,908)	52,310 (15,900)	93.54 (74.54; 117.4)
$C_{ss,av}$, ng/mL	3,994 (826)	4,359 (1,325)	-
$t_{1/2,term}$, h	18.7 (11.8)	17.4 (9.4)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.3/TMC114-C134-CRR/Table 7, Table 8, and Table 9

Table 23: PK Parameters of DRV Following Administration of DRV/rtv in Healthy Subjects and Subjects With Moderate Hepatic Impairment (Study TMC114-C134)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Panel B Moderate Hepatic Impairment DRV/rtv 600/100 mg bid	Panel B Healthy Subjects DRV/rtv 600/100 mg bid	
Day 1			
N	8	8	-
t_{max}, h	5.0 (4.0-5.0)	4.5 (2.0-5.0)	-
C_{max}, ng/mL	4,799 (2,008)	4,494 (815)	101.9 (80.05; 129.8)
AUC_{12h} ng.h/mL	34,780 (18,980)	29,290 (5,654)	110.1 (83.49; 145.3)
Day 7			
N	8	8	
t_{max}, h	5.0 (0.0-5.0)	3.0 (1.0-5.0)	-
C_{0h}, ng/mL	3,681 (1,555)	2,740 (1,090)	-
C_{min}, ng/mL	2,610 (1,480)	2,054 (1,096)	126.7 (86.89;184.6)
C_{max}, ng/mL	5,768 (1,806)	4,715 (1,333)	121.6 (94.89; 155.8)
$C_{ss,av}$, ng/mL	3,789 (1,520)	3,157 (1,152)	-
AUC_{12h}, ng.h/mL	45,470 (18,240)	37,880 (13,820)	119.7 (89.63; 159.9)
$t_{1/2,term}$, h	12.1 (5.6)	16.11 (6.3)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.3/TMC114-C134-CRR/Table 7, Table 10, and Table 11

2.1.6.1.3.2. Plasma Protein Binding of DRV and AAG Concentrations

On Day 1, the percentage of unbound DRV in plasma was relatively stable throughout the initial 12-hour dosing period for all subjects (Module 5.3.3.3/TMC114-C134-CRR/Section 4.2.5). At 12 hours after dosing, the mean percentage of unbound DRV was higher in subjects with mild (11.7%) or moderate (16.4%) hepatic impairment compared with the corresponding healthy subjects in each panel (7.6% and 7.7%, respectively) (Table 24).

On Day 1, the plasma concentrations of AAG were also relatively stable throughout the initial 12-hour dosing period for all subjects (Module 5.3.3.3/TMC114-C134/Section 4.2.5). At 12 hours after dosing, the mean concentration of AAG was lower in subjects with mild (52.2 mg/100 mL) or moderate (39.4 mg/100 mL) hepatic impairment compared with healthy matched control subjects in each panel (76.9 and 75.1 mg/100 mL, respectively), with a lower mean concentration in subjects with moderate hepatic impairment compared with subjects with mild hepatic impairment (Table 24).

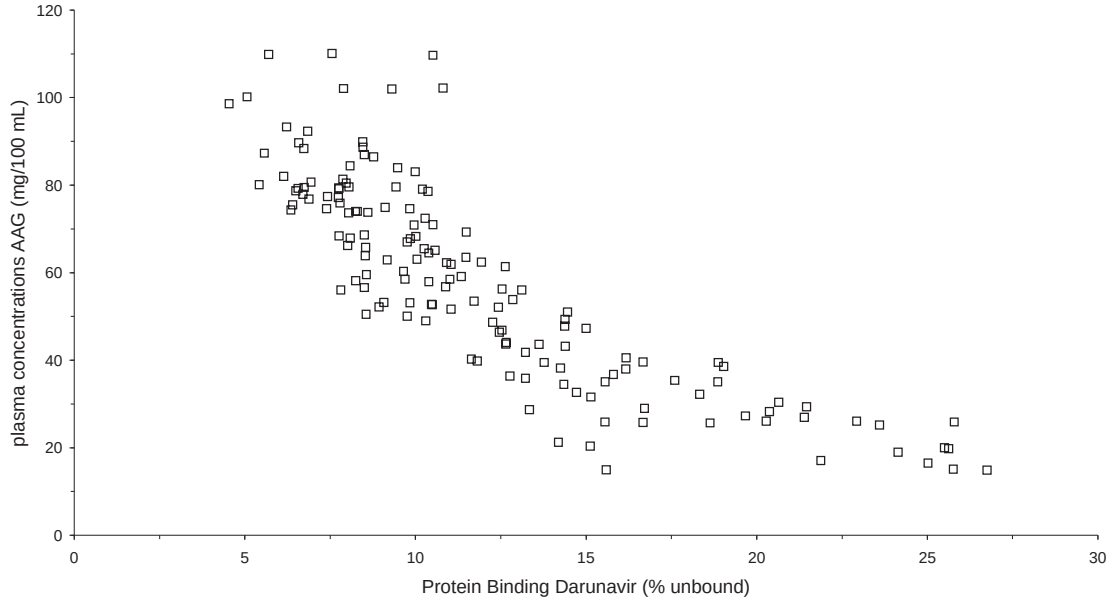
There was an inverse relationship between plasma concentrations of AAG and percentages of unbound DRV in plasma (Figure 2).

Table 24: Percentage Unbound DRV in Plasma and Plasma Concentrations of AAG After Administration of DRV/rtv (600/100 mg twice daily) in Healthy Subjects and Subjects With Mild or Moderate Hepatic Impairment (Day 1, 12 hours) (Study TMC114-C134)

	Mean (SD)			
	Panel A		Panel B	
Parameter	Healthy Subjects (Reference)	Mild Hepatic Impairment (Test)	Healthy Subjects (Reference)	Moderate Hepatic Impairment (Test)
N	8	8	7	8
Unbound DRV (%)	7.57 (1.13)	11.67 (2.27)_	7.70 (1.28)	16.41 (4.75)
AAG (mg/100 mL)	76.9 (16.9)	52.2 (14.5)	75.1 (12.1)	39.4 (32.0)

N=maximum number of subjects with data.
Source: Module 5.3.3.3/TMC114-C134-CRR/Table 12 and Table 13

Figure 2: Plasma Concentrations of AAG Versus Percent Unbound DRV in Plasma (all Values From Panels A and B Combined) (Study TMC114-C134)



Source: Module 5.3.3.3/TMC114-C134-CRR/Figure 12

2.1.6.1.3.3. RTV PK

On Days 1 and 7, the mean exposure to rtv (C_{max} and AUC_{12h}), coadministered with DRV, was comparable between healthy subjects and subjects with mild hepatic impairment, but was higher in subjects with moderate hepatic impairment (Table 25). Mild or moderate hepatic impairment had no relevant effect on the median t_{max} of rtv.

Table 25: PK Parameters of rtv Following Administration of DRV/rtv in Healthy Subjects and Subjects With Mild or Moderate Hepatic Impairment (Study TMC114-C134)

	Mean (SD); t_{max}: Median (Range)			
	Panel A		Panel B	
Parameter	Healthy Subjects DRV/rtv 600/100 mg bid (Reference)	Mild Hepatic Impairment DRV/rtv 600/100 mg bid (Test)	Healthy Subjects DRV/rtv 600/100 mg bid (Reference)	Moderate Hepatic Impairment DRV/rtv 600/100 mg bid (Test)
Day 1				
N	8	8	8	8
t_{max}, h	5.0 (3.0-5.0)	4.5 (2.0-6.0)	5.0 (1.5-5.0)	5.0 (1.0-5.0)
C_{max}, ng/mL	413 (209)	402 (156)	340 (135)	858 (497)
AUC_{12h}, ng.h/mL	2,400 (1,050)	2,370 (991)	2,018 (664)	4,626 (2,258)
Day 7				
N	8	8	8	8
t_{max}, h	4.0 (1.5-6.0)	5.0 (4.0-6.0)	4.5 (1.0-5.0)	5.0 (3.0-5.0)
C_{0h}, ng/mL	308 (242)	319 (114)	221 (71.9)	601 (216)
C_{min}, ng/mL	182 (62.9)	215 (76.8)	140 (42.1)	291 (90.0)
C_{max}, ng/mL	1,004 (499)	963 (202)	830 (330)	1,173 (486)
$C_{ss,av}$, ng/mL	499 (194)	492 (109)	388 (134)	594 (197)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.3/TMC114-C134-CRR/Table 14

2.1.6.1.4. Conclusion

After administration of DRV/rtv 600/100 mg twice daily, compared to healthy matched control subjects, the mean exposure (C_{max} and AUC_{12h}) to DRV was slightly lower in subjects with mild hepatic impairment and slightly higher in subjects with moderate hepatic impairment. The exposure to rtv was comparable in healthy subjects and subjects with mild hepatic impairment, but approximately 1.5-fold higher in subjects with moderate hepatic impairment. Higher percentages of unbound DRV in plasma and lower AAG plasma concentrations were observed in subjects with hepatic impairment compared with healthy subjects, with an inverse relationship between plasma concentrations of AAG and percentages of unbound DRV.

Information on dosing recommendations in subjects with hepatic impairment is available in Section 3.2.4.

2.1.6.2. Effect of Hepatic Impairment on COBI

GS-US-183-0133

Module 5.3.3.3/GS-US-183-0133-CSR

2.1.6.2.1. Objective

To investigate the PK and safety of COBI and EVG following coadministration of EVG/COBI in subjects with moderate hepatic impairment (Child-Pugh-Turcotte Classification B) compared with subjects with normal hepatic function.

2.1.6.2.2. Subjects and Methods

This was a Phase 1, open-label, parallel-group study to investigate the steady-state PK of EVG and COBI when coadministered in non HIV-1 infected subjects with normal and impaired hepatic function. A total of 20 subjects (10 healthy subjects and 10 subjects with moderate hepatic impairment) received a single 150 mg EVG tablet and a single 150 mg COBI tablet once daily for 10 days. Elvitegravir and COBI were coadministered in the morning immediately after consuming a standard meal. Each subject in the moderate hepatic impairment group was matched for age (±5 years), sex, and BMI (±15%) with a subject in the healthy control group.

2.1.6.2.3. Results

2.1.6.2.3.1. COBI and EVG PK

The AUC_{24h} and C_{max} of COBI were comparable in subjects with moderate hepatic impairment relative to healthy control subjects (Table 26). The C_{24h} of COBI was increased (LS means ratio of 208%), although this was not considered to be clinically relevant.

Elvitegravir exposure was modestly increased in subjects with moderate hepatic impairment relative to healthy control subjects. However, the observed increases were well below the protocol-defined clinically significant increase of 100% in EVG AUC_{24h} or C_{max} for subjects with moderate hepatic impairment compared to healthy matched control subjects, and were not considered to be clinically relevant.

Table 26: PK Parameters of COBI and EVG Following Administration of EVG/COBI in Healthy Subjects and Subjects With Moderate Hepatic Impairment (Study GS-US-183-0133)

Parameter	LS Means		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Moderate Hepatic Impairment EVG/COBI 150/150 mg qd	**Healthy Subjects EVG/COBI 150/150 mg qd**	
N	10	10	-
C_{24h}, ng/mL[a]	69.2	33.3	207.70 (117.13; 368.31)
C_{max}, ng/mL	1,077	1,250	86.10 (65.35; 113.43)
AUC_{24h} ng.h/mL[b]	9,335	9,359	99.74 (76.01; 130.89)
	Moderate Hepatic Impairment EVG/COBI 150/150 mg qd	**Healthy Subjects EVG/COBI 150/150 mg qd**	
N	10	10	
C_{24h}, ng/mL[a]	602	335	179.63 (111.03; 290.60)
C_{max}, ng/mL	2,657	1,881	141.28 (108.80; 183.45)
AUC_{24h} ng.h/mL[b]	27,722	20,537	134.99 (103.09; 176.75)

qd=once daily.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.3.3/GS-US-183-0133-CSR/Table 5.1

2.1.6.2.3.2. PK/PD Analyses

Exploratory analyses indicated no clinically relevant correlations between the EVG or COBI exposure and Child-Pugh-Turcotte score or its individual laboratory components (ie, albumin,

total bilirubin, prothrombin time, and international normalized ratio) for subjects with moderate hepatic impairment.

The mean (SD) % free fraction (unbound concentration) for EVG in the healthy control subjects and subjects with moderate hepatic impairment was 1.15 (0.14) and 1.22 (0.23), respectively. These findings indicate the lack of effect of hepatic impairment on EVG protein binding. Similar results were observed for COBI; corresponding values were 2.71 [0.56] and 3.23 [0.63], respectively.

2.1.6.2.4. Conclusion

No clinically relevant changes in COBI or EVG exposure were observed in subjects with moderate hepatic impairment relative to healthy control subjects following once daily administration of EVG/COBI 150/150 mg. No clinically relevant correlations between EVG or COBI exposure and Child-Pugh-Turcotte score or individual liver function laboratory parameters were observed.

Information on dosing recommendations in subjects with hepatic impairment is available in Section 3.2.4.

2.1.7. Extrinsic Factor PK: Concomitant Administration of DRV With Other Drugs

2.1.7.1. Antiretrovirals Coadministered With DRV

2.1.7.1.1. Didanosine

TMC114-C123

Module 5.3.3.4/TMC114-C123-CRR

2.1.7.1.1.1. Objective

To investigate the PK interaction between steady-state concentrations of didanosine (ddI) and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.1.1.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-period crossover study in 18 healthy subjects to investigate the PK interaction between DRV, administered as the 300-mg tablet formulation F016, together with rtv, and ddI (an NRTI often used in combination with DRV/rtv) at steady-state. In 3 sessions, the following treatments were administered, with a washout period of at least 7 days between sessions:

- Treatment A (reference): DRV/rtv 600/100 mg twice daily for 6 days, with an additional morning dose on Day 7.
- Treatment B (test): ddI 400 mg once daily for 7 days.

- Treatment C (test): DRV/rtv 600/100 mg twice daily and ddI 400 mg once daily for 7 days.

Coadministration of DRV/rtv and ddI in the morning was as follows: ddI was administered under fasted conditions, a breakfast was taken 1.5 hours after ddI intake, and DRV/rtv was administered under fed conditions within 10 minutes after completion of the breakfast. The evening dose of DRV/rtv was administered under fed conditions.

2.1.7.1.1.3. Results

2.1.7.1.1.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with ddI relative to administration of DRV/rtv alone were 93% and 101%, respectively (Table 27). For all comparisons, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds. There was no change in the median t_{max} of DRV.

Table 27: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of ddI (Study TMC114-C123)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 600/100 mg bid + ddI 400 mg qd	DRV/rtv 600/100 mg bid	
N	17	17	
t_{max}, h	3.0 (1.5-5.0)	3.0 (2.0-5.0)	-
C_{0h}, ng/mL	2,800 (699)	2,742 (625)	101.6 (93.96; 109.9)
C_{min}, ng/mL	2,483 (694)	2,353 (744)	107.3 (94.80; 121.4)
C_{max}, ng/mL	5,591 (1,309)	5,908 (917)	92.57 (85.76; 99.91)
AUC_{12h} ng.h/mL	46,010 (10,310)	44,750 (7,773)	101.0 (95.28; 107.1)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
[a] Accurate determination not possible.
Source: Module 5.3.3.4/TMC114-C123-CRR/Table 6 and Table 7

2.1.7.1.1.3.2. Didanosine PK

Because the predose concentrations of ddI and the concentrations at 24 hours after dosing were below the lower limit of quantification (LLOQ) in all cases but 1, the C_{min} and C_{0h} of ddI were not quantifiable. The LS mean ratios for C_{max} and AUC_{24h} of ddI when ddI was coadministered with DRV/rtv relative to administration of ddI alone were 84% and 91%, respectively (Table 28). For both comparisons, the lower limit of the 90% CIs of the LS means ratios was below 80.00%. There was no change in the median t_{max} of ddI.

Table 28: PK Parameters of ddI Following Administration of ddI in the Absence and Presence of DRV/rtv (Study TMC114-C123)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	ddI 400 mg qd + DRV/rtv 600/100 mg bid	ddI 400 mg qd	
N	17	17	
t_{max}, h	2.0 (1.0-3.0)	2.0 (1.0-6.0)	-
C_{max}, ng/mL	1,312 (678)	1,737 (1,002)	84.02 (58.98; 119.7)
AUC_{24h} ng.h/mL	3,365 (1,334)	3,903 (1,589)	90.91 (75.02; 110.2)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C123-CRR/Table 10 and Table 11

2.1.7.1.1.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with ddI relative to administration of DRV/rtv alone were 79% and 86%, respectively (Table 29). For all comparisons, with the exception of C_{min}, the 90% CIs of the LS means ratios were outside the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of rtv.

Table 29: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of ddI (Study TMC114-C123)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 600/100 mg bid + ddI 400 mg qd	DRV/rtv 600/100 mg bid	
N	17	16	
t_{max}, h	5.0 (1.5-9.0)	4.0 (1.0-5.0)	-
C_{0h}, ng/mL	308 (137)	235 (124)	131.6 (118.0; 146.8)
C_{min}, ng/mL	169 (72.7)	162 (78.9)	105.2 (96.38; 114.7)
C_{max}, ng/mL	830 (351)	1,063 (488)	78.76 (65.72; 94.40)
AUC_{12h} ng.h/mL	4,941 (1,842)	5,787 (2,427)	85.99 (76.19; 97.05)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C123-CRR/Table 8 and Table 9

2.1.7.1.1.4. Conclusion

The mean exposure (AUC_{12h}) to DRV, coadministered with rtv, was comparable in the absence and presence of ddI. The mean exposure to ddI (AUC_{24h}) was decreased by 9% in the presence of DRV/rtv; this decrease was not considered to be clinically relevant.

Information on dosing recommendations is available in Section 3.3.2.1.1.

2.1.7.1.2. Tenofovir Disoproxil Fumarate

TMC114-C124

Module 5.3.3.4/TMC114-C124-CRR

2.1.7.1.2.1. Objective

To investigate the PK interaction between steady-state concentrations of TDF and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.1.2.2. Subjects and Methods

This was a Phase 1, open-label, 1-sequence, crossover study in 13 healthy subjects to investigate the PK interaction between DRV, administered as the oral solution TF019, together with rtv, and TDF (an NRTI that is not a CYP3A substrate[54]). Subjects were randomized into 2 groups. In Session 1, both groups received DRV/rtv 300/100 mg twice daily for 6 days, with an additional morning dose on Day 7. In Session 2, both groups received 300 mg TDF (the prodrug of tenofovir) once daily for 14 days. In addition to TDF, Group 1 received DRV/rtv 300/100 mg twice daily from Day 8 through Day 14, and Group 2 received DRV/rtv 300/100 mg twice daily from Day 1 through Day 7. Subsequent sessions were separated by a washout period of at least 6 days. All treatments were administered under fed conditions.

2.1.7.1.2.3. Results

2.1.7.1.2.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with TDF relative to administration of DRV/rtv alone were 116% and 121%, respectively (Table 30). For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125%. There was no change in the median t_{max} of DRV.

Table 30: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Tenofovir (Study TMC114-C124)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 300/100 mg bid + TDF 300 mg qd	DRV/rtv 300/100 mg bid	
N	12	12	
t_{max}, h	0.5 (0.5-0.5)	0.5 (0.5-4.0)	-
C_{min}, ng/mL	2,220 (1,051)	1,845 (842)	123.6 (90.4; 169)
C_{max}, ng/mL	4,448 (1,008)	3,971 (1,385)	115.5 (94.1; 142)
AUC_{12h} ng.h/mL	35,755 (12,582)	29,837 (10,345)	120.8 (95.1; 154)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C124-CRR/Table 7 and Table 8

2.1.7.1.2.3.2. Tenofovir PK

The LS mean ratios for C_{max} and AUC_{24h} of tenofovir when TDF was coadministered with DRV/rtv relative to administration of TDF alone were 124% and 122%, respectively (Table 31). For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125.00%. There was no relevant change in the median t_{max} of tenofovir when TDF was coadministered with DRV/rtv.

Table 31: PK Parameters of Tenofovir Following Administration of TDF in the Absence and Presence of DRV/rtv (Study TMC114-C124)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	TDF 300 mg qd + DRV/rtv 300/100 mg bid	TDF 300 mg qd	
N	12	12	
t_{max}, h	1.0 (1.0-4.0)	1.5 (0.5-2.5)	-
C_{min}, ng/mL	86.8 (15.7)	65.6 (13.4)	136.6 (119; 157)
C_{max}, ng/mL	528 (106)	423 (75.2)	123.9 (108; 142)
AUC_{24h} ng.h/mL	4,633 (735)	3,789 (499)	121.8 (110; 135)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C124-CRR/Table 10 and Table 11

2.1.7.1.2.3.3. RTV PK

There was no change in the median t_{max} of rtv when rtv was administered in the presence or absence of tenofovir (Table 32). In the presence of tenofovir, individual ratios for AUC_{12h} ranged from 70% to 133%, and individual ratios for C_{max} ranged from 57% to 153%. However, mean values indicated that the exposure to rtv was not affected by the presence of tenofovir.

Table 32: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Tenofovir (Study TMC114-C124)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Test	Reference
	DRV/rtv 300/100 mg bid + TDF 300 mg qd	DRV/rtv 300/100 mg bid
N	12	12
t_{max}, h	4.0 (1.0-6.0)	4.0 (2.0-6.0)
C_{min}, ng/mL	169 (99.1)	174 (84.6)
C_{max}, ng/mL	916 (356)	1,030 (343)
AUC_{12h} ng.h/mL	5,488 (1,738)	5,811 (1,960)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C124-CRR/Table 9

2.1.7.1.2.4. Conclusion

The mean exposure (AUC_{12h}) to DRV, coadministered with rtv, was increased in the presence of tenofovir (administered as the prodrug TDF), and the mean exposure to tenofovir (AUC_{24h}) was increased in the presence of DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.1.2.

2.1.7.1.3. Efavirenz

TMC114-C111

Module 5.3.3.4/TMC114-C111-CRR

2.1.7.1.3.1. Objective

To investigate the PK interaction between steady-state concentrations of efavirenz (EFV) and repeated doses of DRV/rtv.

2.1.7.1.3.2. Subjects and Methods

This was a Phase 1, open-label, crossover study in 12 healthy subjects to investigate the PK interaction between DRV, administered as the oral solution TF019, together with rtv, and EFV (a non-nucleoside reverse transcriptase inhibitor [NNRTI] and a CYP3A and CYP2B6 inducer and substrate[48]). In Session 1, subjects received DRV/rtv 300/100 mg twice daily for 6 days, with an additional morning dose on Day 7. In Session 2, EFV 600 mg once daily was administered for 18 days. From Day 11 through Day 16, DRV/rtv 300/100 mg twice daily was coadministered with EFV. On Day 17 a single dose of DRV/rtv 300/100 mg was administered. Subsequent sessions were separated by a washout period of at least 7 days. All treatments were administered under fed conditions.

2.1.7.1.3.3. Results

2.1.7.1.3.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with EFV relative to administration of DRV/rtv alone were 85% and 87%, respectively (Table 33). For all comparisons, the lower limit of the 90% CIs of the LS means ratios was below 80.00%. There was no relevant change in the median t_{max} of DRV.

Table 33: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of EFV (Study TMC114-C111)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 300/100 mg bid + EFV 600 mg qd	DRV/rtv 300/100 mg bid	
N	12	12	
t_{max}, h	0.5 (0.5-3.0)	0.75 (0.0-2.0)	-
C_{min}, ng/mL	1,250 (511)	1,772 (708)	68.72 (54.2; 87.2)
C_{max}, ng/mL	2,998 (938)	3,460 (943)	84.59 (71.8; 99.6)
AUC_{12h} ng.h/mL	25,483 (7,844)	28,865 (8,360)	86.57 (74.5; 101)
$t_{1/2,term}$, h	5.0 (1.1)	12.5 (4.8)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C111-CRR/Table 5 and Table 6

2.1.7.1.3.3.2. Efavirenz PK

The LS mean ratios for C_{max} and AUC_{24h} of EFV when EFV was coadministered with DRV/rtv relative to administration of EFV alone were 115% and 121%, respectively (Table 34). For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125%. There was no change in the median t_{max} of EFV.

Table 34: PK Parameters of EFV Following Administration of EFV in the Absence and Presence of DRV/rtv (Study TMC114-C111)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	EFV 600 mg qd + DRV/rtv 300/100 mg bid	EFV 600 mg qd	
N	12	12	
t_{max}, h	4.0 (3.0-5.0)	4.0 (2.0-5.0)	-
C_{min}, ng/mL	1,989 (1,621)	1,647 (1,078)	117.0 (101; 136)
C_{max}, ng/mL	5,297 (1,889)	4,595 (1,480)	114.7 (97.3; 135)
AUC_{24h} ng.h/mL	76,429 (45,527)	61,800 (30,350)	121.0 (108; 136)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C111-CRR/Table 9 and Table 10

2.1.7.1.3.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with EFV relative to administration of DRV/rtv alone were 68% and 72%, respectively (Table 35). There was no relevant change in the median t_{max} of rtv.

Table 35: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of EFV (Study TMC114-C111)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 300/100 mg bid + EFV 600 mg qd	DRV/rtv 300/100 mg bid	
N	12	12	
t_{max}, h	5.0 (1.0-9.0)	4.0 (0.5-6.0)	-
C_{min}, ng/mL	164 (154)	211 (142)	60.07 (46.7; 77.3)
C_{max}, ng/mL	707 (858)	861 (624)	68.29 (57.8; 80.6)
AUC_{12h} ng.h/mL	4,820 (4,788)	5,733 (3,499)	71.79 (61.3; 84.0)
$t_{1/2,term}$, h	4.7 (0.8)	8.6 (4.6)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C111-CRR/Table 7 and Table 8

2.1.7.1.3.4. Conclusion

Based on the PK/PD relationships and dose-response relationships observed in studies TMC114-C202 and TMC114-C213 in HIV-1 infected subjects (see Section 2.2.7.4), the 13% decrease in DRV exposure in the presence of EFV is not considered clinically relevant.

Information on dosing recommendations is available in Section 3.3.2.2.1.

2.1.7.1.4. Nevirapine

TMC114-C119

Module 5.3.3.4/TMC114-C119-CRR

2.1.7.1.4.1. Objective

To investigate the PK interaction between NVP and DRV.

2.1.7.1.4.2. Subjects and Methods

This was a Phase 1, open-label, randomized, crossover study in HIV-1 infected subjects to investigate the PK interaction between NVP (an NNRTI and CYP3A substrate and inducer[53]) and DRV coadministered with rtv.

The study population consisted of 2 panels of a total of 19 HIV-1 infected subjects, who were on stable therapy with NVP 200 mg twice daily for at least 16 weeks. Two further panels, each consisting of 4 other HIV-infected subjects who were on stable therapy of NVP were added to the study. The study was divided into 2 sessions of 14 days each, in which Treatment A and Treatment B or Treatment B2 were administered in a randomized order. There was no washout period between the sessions. In Treatment A, subjects continued their usual HIV therapy consisting of NVP and at least 2 NRTIs. Treatment B consisted of 300 mg DRV (oral solution formulation TF019), together with 100 mg rtv, twice daily in addition to the usual NVP/NRTI therapy. Treatment B2 consisted of 400 mg DRV (400-mg tablet formulation F001), together with 100 mg rtv, twice daily in addition to the usual NVP/NRTI therapy. All subjects received Treatment A in 1 session (N=17) and then either Treatment B (N=11) or B2 (N=8) in the other session. All treatments were administered for 13 days twice daily, with an additional morning dose on Day 14, under fed conditions.

To investigate the effect of NVP on the PK of DRV administered as an oral solution together with rtv, the results of Treatment B were compared with the results from historical data (Module 5.3.5.1/TMC114-C207-CRR), in which DRV/rtv was administered at the same dosing regimen, but without NVP.

To investigate the effect of NVP on the PK of DRV administered as a tablet together with rtv, the results of Treatment B2 were compared with the results from historical data (study TMC114-C137[10]), in which DRV/rtv was administered at the same dosing regimen, but without NVP.

2.1.7.1.4.3. Results

2.1.7.1.4.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV (TF019)/rtv 300/100 mg twice daily was coadministered with NVP relative to administration of DRV (TF019)/rtv 300/100 mg twice daily alone were 84% and 109%, respectively. When DRV (F001)/rtv 400/100 mg twice daily was coadministered with NVP, relative to administration of DRV (TF036)/rtv alone, the LS means ratios were 140% and 124%, respectively (Table 36). For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125.00% with the exception of C_{max} following administration of the 300/100 mg twice daily dosing regimen. There was no relevant difference in the median t_{max} of DRV administered at 300 mg twice daily with or without NVP or between DRV administered at 400 mg twice daily with or without NVP.

Table 36: PK Parameters of DRV Following Coadministration of DRV/rtv with NVP Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C119)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	**Reference**	
	Treatment B DRV (TF019)/rtv 300/100 mg bid + NVP 200 mg bid	**Study TMC114-C207 DRV (TF019)/rtv 300/100 mg bid**	
N	8	13	
t_{max}, h	0.5 (0.5-3.0)	0.50 (0.25-1.00)	-
C_{min}, ng/mL	1,400 (282)	1,175 (371)	123.0 (98.0; 154)
C_{max}, ng/mL	3,534 (741)	4,440 (2,112)	84.22 (64.5; 110)
AUC_{12h} ng.h/mL	26,588 (4,533)	25,030 (7,044)	108.7 (89.0; 133)
	Treatment B2 DRV (F001)/rtv 400/100 mg bid + NVP 200 mg bid	**Study TMC114-C137 DRV (TF036) [a]/rtv 400/100 mg bid**	
N	8	8	
t_{max}, h	3.0 (2.0-4.0)	2.5 (1.0-3.0)	-
C_{min}, ng/mL	1,894 (524)	1,848 (528)	102.1 (78.7; 132)
C_{max}, ng/mL	5,530 (1,357)	3,913 (873)	140.3 (114; 173)
AUC_{12h} ng.h/mL	41,361 (10,625)	33,511 (9,540)	123.5 (97.2; 157)

bid=twice daily; N=maximum number of subjects with data.
[a] TF036 is the earlier designation for tablet formulation F001.
Source: Module 5.3.3.4/TMC114-C119-CRR/Table 11, Table 12, and Table 13

2.1.7.1.4.3.2. NVP PK

The LS mean ratios for C_{max} and AUC_{12h} of NVP when NVP was coadministered with DRV (TF019)/rtv 300/100 mg twice daily relative to administration of NVP alone were 114% and 127%, respectively. When NVP was coadministered with DRV (F001)/rtv 400/100 mg twice daily, relative to administration of NVP alone, the LS means ratios were 118% and 127%, respectively (Table 37). For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125.00%. There median t_{max} of NVP was later when NVP was coadministered with DRV/rtv.

Based on the fact that the 300 and 400 mg twice daily doses of DRV induced identical increases in exposure to NVP, a comparable increase in exposure to NVP is expected when the 600/100 mg twice daily dose of DRV/rtv is coadministered.

Table 37: PK Parameters of NVP Following Administration of NVP in the Absence and Presence of DRV/rtv (Study TMC114-C119)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B: NVP 200 mg bid + DRV (TF019) /rtv 300/100 mg bid	**Treatment A, Panels 1 and 2: NVP 200 mg bid**	
N	8	9	
t_{max}, h	4.5 (0.5-9.0)	1.5 (0.0-12.0)	-
C_{min}, ng/mL	7,031 (4,804)	5,192 (2,137)	118.0 (92.6; 150)
C_{max}, ng/mL	10,670 (6,579)	8,064 (2,531)	114.1 (91.7; 142)
AUC_{12h} ng.h/mL	109,749 (68,732)	76,570 (29,948)	126.7 (106; 151)
	Treatment B2: NVP 200 mg bid + DRV (F001)/rtv 400/100 mg bid	**Treatment A, Panels 3 and 4: NVP 200 mg bid**	
N	8	8	
t_{max}, h	4.0 (2.0-5.0)	3.0 (0.5 - 6.0)	-
C_{min}, ng/mL	6,220 (2,589)	4,273 (1,614)	147.4 (120; 182)
C_{max}, ng/mL	8,560 (3,178)	7,005 (1,348)	118.3 (102; 137)
AUC_{12h} ng.h/mL	88,148 (33,335)	66,933 (14,441)	127.3 (112; 144)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C119-CRR/Table 8, Table 9, and Table 10

2.1.7.1.4.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV (TF019)/rtv 300/100 mg twice daily was coadministered with NVP relative to administration of DRV (TF019)/rtv alone were 86% and 84%, respectively. When DRV (F001)/rtv 400/100 mg twice daily was coadministered with NVP relative to administration of DRV (TF036)/rtv alone, the LS means ratios were 123% and 110%, respectively (Table 38). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There were no relevant differences in the median t_{max} of DRV between the 2 comparisons.

Table 38: PK Parameters of rtv Following Coadministration of DRV/rtv With NVP Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C119)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	**Reference**	
	Treatment B DRV (TF019)/rtv 300/100 mg bid + NVP 200 mg bid	**DRV (TF019)/rtv 300/100 mg bid (Study TMC114-C207)**	
N	8	13	
t_{max}, h	3.0 (0.0-5.0)	3.00 (0.50-6.00)	-
C_{min}, ng/mL	103 (51.7)	127 (63.1)	82.75 (57.6; 119)
C_{max}, ng/mL	569 (370)	667 (430)	86.19 (53.2; 140)
AUC_{12h} ng.h/mL	3,280 (1,449)	3,786 (1,401)	84.02 (59.2; 119)
	Treatment B2 DRV (F001)/rtv 400/100 mg bid + NVP 200 mg bid	**DRV (TF036) [a]/rtv 400/100 mg bid (Study TMC114-C137)**	
N	8	8	
t_{max}, h	5.0 (4.0 - 5.0)	4.0 (4.0 - 6.0)	-
C_{min}, ng/mL	189 (95.1)	199 (113)	98.06 (61.2; 157)
C_{max}, ng/mL	967 (601)	792 (461)	123.3 (75.6; 201)
AUC_{12h} ng.h/mL	5,781 (3,011)	5,464 (3,037)	109.7 (70.9; 170)

bid=twice daily; N=maximum number of subjects with data.
[a] TF036 is the earlier designation for tablet formulation F001.
Source: Module 5.3.3.4/TMC114-C119-CRR/Table 14, Table 15, and Table 16

2.1.7.1.4.4. Conclusion

The mean exposure (AUC_{12h}) to DRV, coadministered with rtv, was slightly increased when DRV/rtv was coadministered with NVP, and the mean exposure (AUC_{12h}) to NVP was slightly increased when NVP was coadministered with DRV/rtv. These changes were not considered clinically relevant.

Information on dosing recommendations is available in Section 3.3.2.2.3.

2.1.7.1.5. Etravirine

TMC125-C176

Module 5.3.3.4/TMC125-C176-CRR

2.1.7.1.5.1. Objective

To investigate the PK interaction between steady-state concentrations of etravirine and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.1.5.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-period crossover study in 32 healthy subjects to investigate the PK interaction between steady-state DRV, administered as the 400-mg tablet F001 and the 200-mg tablet F002, together with rtv, and etravirine (a CYP3A and CYP2C

substrate and CYP3A inducer[23]). For all subjects, 2 treatment sessions were scheduled: Session A and Session B1 for Panel 1 and Session A and Session B2 for Panel 2:

- Session A: Etravirine 100 mg twice daily for 7 days, with an additional morning dose on Day 8.
- Session B1: DRV/rtv 600/100 mg twice daily on Days 1 to 15, with an additional morning dose on Day 16, and etravirine 100 mg twice daily on Days 9 to 15, with an additional morning dose on Day 16.
- Session B2: DRV/rtv 600/100 mg twice daily on Days 1 to 15, with an additional morning dose on Day 16, and etravirine 200 mg twice daily on Days 9 to 15, with an additional morning dose on Day 16.

Subsequent sessions were separated by a washout period of at least 14 days. All treatments were administered under fed conditions within 15 minutes after a meal.

2.1.7.1.5.3. Results

2.1.7.1.5.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with etravirine 100 mg twice daily relative to administration of DRV/rtv alone were 103% and 106%, respectively; the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds (Table 39). Following coadministration of etravirine 200 mg twice daily with DRV/rtv, relative to administration of DRV/rtv alone, the LS means ratios for C_{max} and AUC_{12h} of DRV were 111% and 115%; the 90% CI of the LS means ratio for C_{max} was within the 80.00% to 125.00% bounds, while for AUC_{12h}, the upper limit of the 90% CI was just above 125.00%. There was no relevant change in the median t_{max} of DRV in Panel 1 or Panel 2.

Table 39: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Etravirine (Study TMC125-C176)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	**Reference**	
	Panel 1, Session B1 Day 16 DRV/rtv 600/100 mg bid + Etravirine 100 mg bid	**Panel 1, Session B1 Day 8 DRV/rtv 600/100 mg bid**	
N	13	14	
t_{max}, h	3.0 (1.0-4.0)	2.0 (1.5-4.0)	-
C_{0h}, ng/mL	2,429 (631)	2,625 (934)	-
C_{min}, ng/mL	2,217 (541)	2,254 (834)	102 (89; 117)
C_{max}, ng/mL	5,804 (1,269)	5,599 (1,104)	103 (98; 109)
AUC_{12h} ng.h/mL	45,199 (11,583)	42,982 (12,666)	106 (100; 113)
FI, %	96.5 (20.2)	99.5 (31.5)	-
	Panel 2, Session B2 Day 16 DRV/rtv 600/100 mg bid + Etravirine 200 mg bid	**Panel 2, Session B2 Day 8 DRV/rtv 600/100 mg bid**	
N	10	15	
t_{max}, h	3.0 (1.0-3.0)	3.0 (1.0-4.0)	-
C_{0h}, ng/mL	2,805 (758)	2,683 (820)	-
C_{min}, ng/mL	2,301 (738)	2, 337 (631)	102 (90; 117)
C_{max}, ng/mL	5,746 (1,232)	5,234 (1,060)	111 (101; 122)
AUC_{12h} ng.h/mL	45,449 (10,864)	41,135 (9,579)	115 (105; 126)
FI, %	93.0 (15.7)	86.6 (16.1)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125-C176-CRR/Table 9 and Table 10

2.1.7.1.5.3.2. Etravirine PK

The LS mean ratios for C_{max} and AUC_{12h} of etravirine when etravirine 100 mg twice daily was coadministered with DRV/rtv relative to administration of etravirine 100 mg twice daily alone were 68% and 63%, respectively (Table 40). When etravirine 200 mg twice daily was coadministered with DRV/rtv, relative to administration of etravirine 100 mg twice daily alone, the LS means ratios for C_{max} and AUC_{12h} of etravirine were 181% and 180%. There was no relevant change in the median t_{max} of etravirine in Panel 1 or Panel 2.

Table 40: PK Parameters of Etravirine Following Administration of Etravirine in the Absence and Presence of DRV/rtv (Study TMC125-C176)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Panel 1, Session B1 Etravirine 100 mg bid + DRV/rtv 600/100 mg bid	**Panel 1, Session A Etravirine 100 mg bid**	
N	13	14	
t_{max}, h	3.0 (2.0-4.0)	3.0 (1.5-6.0)	-
C_{0h}, ng/mL	112 (67)	198 (101)	-
C_{min}, ng/mL	94 (49)	189 (95)	51 (44; 61)
C_{max}, ng/mL	313 (118)	452 (122)	68 (57; 82)
AUC_{12h} ng.h/mL	2,204 (952)	3,592 (1,388)	63 (54; 73)
FI, %	125 (35.4)	96.9 (32.7)	-
	Panel 2, Session B2 Etravirine 200 mg bid + DRV/rtv 600/100 mg bid	**Panel 2, Session A Etravirine 100 mg bid**	
N	10	11	
t_{max}, h	3.0 (1.5-4.0)	3.0 (1.5-6.0)	-
C_{0h}, ng/mL	289 (157)	161 (48)	-
C_{min}, ng/mL	268 (151)	156 (50)	167 (138; 203)
C_{max}, ng/mL	734 (305)	405 (118)	181 (156; 211)
AUC_{12h} ng.h/mL	5,519 (2,452)	3,062 (816)	180 (156; 208)
FI, %	107 (30.6)	98.8 (24.7)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125-C176-CRR/Table 7 and Table 8

2.1.7.1.5.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with etravirine 100 mg twice daily relative to administration of DRV/rtv alone were 93% and 86%, respectively; the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds (Table 41). Following coadministration of etravirine 200 mg twice daily with DRV/rtv, relative to administration of DRV/rtv alone, the LS means ratios for C_{max} and AUC_{12h} of rtv were 90% and 89%; the lower limit of the 90% CI of the LS means ratio for C_{max} was below 80.00%, while for AUC_{12h}, the 90% CI was within the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of rtv in Panel 1 or Panel 2.

Table 41: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Etravirine (Study TMC125-C176)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	**Reference**	
	Panel 1, Session B1 Day 16 DRV/rtv 600/100 mg bid + Etravirine 100 mg bid	**Panel 1, Session B1 Day 8 DRV/rtv 600/100 mg bid**	
N	13	14	
t_{max}, h	4.0 (1.0-6.0)	4.0 (1.5-6.0)	-
C_{0h}, ng/mL	190 (70)	226 (135)	-
C_{min}, ng/mL	142 (56)	163 (86)	91 (81; 102)
C_{max}, ng/mL	766 (184)	830 (239)	93 (80; 108)
AUC_{12h} ng.h/mL	4,396 (1,087)	5,217 (1,763)	86 (76; 97)
FI, %	172 (24.1)	158 (31.5)	-
	Panel 2, Session B2 Day 16 DRV/rtv 600/100 mg bid + Etravirine 200 mg bid	**Panel 2, Session B2 Day 8 DRV/rtv 600/100 mg bid**	
N	10	15	
t_{max}, h	4.0 (3.0-4.0)	4.0 (3.0-6.0)	-
C_{0h}, ng/mL	275 (130)	269 (120)	-
C_{min}, ng/mL	206 (85)	192 (85)	101 (86; 117)
C_{max}, ng/mL	974 (351)	1,061 (461)	90 (74; 108)
AUC_{12h} ng.h/mL	5,742 (1,970)	6,129 (2,218)	89 (82; 98)
FI, %	161 (20.2)	169 (53.0)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125-C176-CRR/Table 11 and Table 12

2.1.7.1.5.4. Conclusion

When DRV/rtv was coadministered with etravirine 100 mg twice daily, exposure (C_{max} and AUC_{12h}) to DRV was unaffected. When DRV/rtv was coadministered with etravirine 200 mg twice daily, the mean AUC_{12h} was increased 1.15-fold, while C_{max} was unaffected. Exposure (AUC_{12h}) to etravirine was decreased by 37% and increased 1.80-fold when etravirine was coadministered with DRV/rtv at doses of 100 mg twice daily and 200 mg twice daily, respectively (in both cases compared with administration of etravirine 100 mg twice daily). The mean exposure to rtv was decreased by 14% and 11% after coadministration of etravirine 100 mg and 200 mg twice daily, respectively.

Information on dosing recommendations is available in Section 3.3.2.2.2.

2.1.7.1.6. Rilpivirine

TMC278-C112

Module 5.3.3.4/TMC278-C112-CRR-CRR

2.1.7.1.6.1. Objective

To investigate the PK interaction between steady-state concentrations of rilpivirine and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.1.6.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-period crossover study in 16 healthy subjects to investigate the PK interaction between rilpivirine (a substrate and mild inducer of CYP3A) and DRV, administered as the 400-mg tablet formulation F021, together with rtv. In each of 2 sessions, which were separated by a washout period of at least 14 days, subjects received the following treatments:

- Treatment A: Rilpivirine 150 mg once daily on Days 1 to 11.
- Treatment B: DRV/rtv 800/100 mg once daily on Days 1 to 22, and rilpivirine 150 mg once daily on Days 12 to 22.

All treatments were taken under fed conditions within 10 minutes after breakfast.

2.1.7.1.6.3. Results

2.1.7.1.6.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{24h} of DRV when DRV/rtv was coadministered with rilpivirine relative to administration of DRV/rtv alone were 90% and 89%, respectively (Table 42). For C_{max} and AUC_{24h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds; for C_{min}, the lower limit of the 90% CIs was below 80.00%. There was no relevant change in the median t_{max} of DRV.

Table 42: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Rilpivirine (Study TMC278-C112)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B (Day 22) DRV/rtv 800/100 mg qd + Rilpivirine 150 mg qd	Treatment B (Day 11) DRV/rtv 800/100 mg qd	
N	14	15	
t_{max}, h	3.0 (1.0-4.0)	2.0 (1.0-5.0)	-
C_{0h}, ng/mL	1,890 (1,330)	1,887 (1,010)	-
C_{min}, ng/mL	1,388 (615)	1,714 (916)	89 (68; 116)
C_{max}, ng/mL	6,676 (1,374)	7,586 (1,988)	90 (81; 100)
AUC_{24h} ng.h/mL	71,930 (21,350)	82,780 (24,980)	89 (81; 99)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC278-C112-CRR/Table 9 and Table 10

2.1.7.1.6.3.2. Rilpivirine PK

The LS mean ratios for C_{max} and AUC_{24h} of rilpivirine when rilpivirine was coadministered with DRV/rtv relative to administration of rilpivirine alone were 179% and 230%, respectively (Table 43). There was no change in the median t_{max} of rilpivirine.

Table 43: PK Parameters of Rilpivirne Following Administration of Rilpivirine in the Absence and Presence of DRV/rtv (Study TMC278-C112)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B (Day 22) Rilpivirine 150 mg qd + DRV/rtv 800/100 mg qd	Treatment A (Day 11) Rilpivirine 150 mg qd	
N	14	14	
t_{max}, h	4.0 (4.0-24.0)	4.0 (1.0-5.0)	-
C_{0h}, ng/mL	1,233 (474)	416 (104)	
C_{min}, ng/mL	1,013 (408)	360 (91.6)	278 (239; 324)
C_{max}, ng/mL	1,860 (673)	991 (208)	179 (156; 206)
AUC_{24h} ng.h/mL	30,630 (11,230)	12,740 (2,008)	230 (198; 267)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC278-C112-CRR/Table 7 and Table 8

2.1.7.1.6.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{24h} of rtv when DRV/rtv was coadministered with rilpivirine relative to administration of DRV/rtv alone were 83% and 85%, respectively (Table 44). For all comparisons, the lower limit of the 90% CIs was below 80.00%. There was no relevant change in the median t_{max} of rtv.

Table 44: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Rilpivirine (Study TMC278-C112)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B (Day 22) DRV/rtv 800/100 mg qd + Rilpivirine 150 mg qd	Treatment B (Day 11) DRV/rtv 800/100 mg qd	
N	14	15	
t_{max}, h	4.5 (2.0-6.0)	4.0 (1.0-6.0)	-
C_{0h}, ng/mL	37.6 (25.8)	43.3 (16.0)	-
C_{min}, ng/mL	27.7 (14.3)	35.7 (15.1)	78 (68; 90)
C_{max}, ng/mL	558 (277)	690 (293)	83 (72; 95)
AUC_{24h} ng.h/mL	4,060 (1,537)	5,201 (2,381)	85 (78; 91)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC278-C112-CRR/Table 11 and Table 12

2.1.7.1.6.4. Conclusion

The mean exposure (AUC_{24h}) to DRV, coadministered with rtv, was unaffected by the presence of rilpivirine. The mean exposure (AUC_{24h}) to rilpivirine was increased 2.3-fold when rilpivirine was coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.2.4.

2.1.7.1.7. Raltegravir

TMC114-MK0518

Module 5.3.3.4/TMC114-MK0518-CSR

2.1.7.1.7.1. Objective

To investigate the effect of DRV/rtv on the PK of raltegravir.

2.1.7.1.7.2. Subjects and Methods

This was a Phase 1, open-label, sequential, 2-period crossover study in 18 healthy subjects to investigate the PK interaction between raltegravir (an HIV integrase strand transfer inhibitor, metabolized primarily through glucuronidation by UGT1A1[24]) and DRV (administered as the 300-mg tablet formulation F016) together with rtv (rtv is an inducer of glucuronidation[33]). Each subject received the following treatments in 2 periods, with Period 2 immediately following Period 1:

- Period 1: Raltegravir 400 mg twice daily for 4 days.
- Period 2: DRV/rtv 600/100 mg twice daily and raltegravir 400 mg twice daily for 12 days. No evening dose was administered on Day 12.

DRV, rtv, and raltegravir were administered within 15 minutes after completion of a meal.

2.1.7.1.7.3. Results

2.1.7.1.7.3.1. DRV and rtv PK

The PK parameters of DRV and rtv after administration of DRV/rtv in the presence of raltegravir are shown in Table 45.

Table 45: PK Parameters of DRV and rtv Following Coadministration of DRV/rtv With Raltegravir (Study TMC114-MK0518)

Parameter	Mean (SD); t_{max}: Median (Range)	
	DRV/rtv 600/100 mg bid + Raltegravir 400 mg bid	**DRV/rtv 600/100 mg bid + Raltegravir 400 mg bid**
N	6	6
C_{0h}, ng/mL	3,042 (946)	290 (120)
C_{12h} ng/mL	2,798 (1,116)	245 (79)
C_{max}, ng/mL	6,020 (1,659)	716 (352)
AUC_{12h}, ng.h/mL	50,320 (17,076)	5,082 (2,248)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-MK0518-CSR/Table 11-3

2.1.7.1.7.3.2. Raltegravir PK

The LS mean ratios for C_{max} and AUC_{12h} of raltegravir when raltegravir was coadministered with DRV/rtv relative to administration of raltegravir alone were 67% and 71%, respectively (Table 46). There was no relevant change in the median t_{max} of raltegravir.

Table 46: PK Parameters of Raltegravir Following Administration of Raltegravir in the Absence and Presence of DRV/rtv (Study TMC114-MK0518)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Raltegravir 400 mg bid + DRV/rtv 600/100 mg bid	Raltegravir 400 mg bid	
N	6	12	
t_{max}	1.75 (0.0-10.0)	1.25 (0.0-10.0)	
C_{12h}, nM	263 (233)	561 (771)	138 (16; 1,212)
C_{max}, µM	1.18 (0.63)	1.89 (1.5)	67 (33; 137)
AUC_{12h} µM.h	8.54 (5.93)	4.98 (1.9)	71 (38; 133)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-MK0518-CSR/Table 11-1 and Table 11-2

2.1.7.1.7.4. Conclusion

Due to an insufficient number of evaluable subjects and greater than anticipated variability, no PK conclusions for the effect of DRV/rtv on raltegravir may be drawn from this study.

Information on dosing recommendations is available in Section 3.3.2.5.3.

2.1.7.1.8. Maraviroc

TMC114-A4001052

Module 5.3.3.4/TMC114-A4001052-CRR

2.1.7.1.8.1. Objective

To investigate the effect of steady-state concentrations of DRV, coadministered with rtv, on the PK of maraviroc at steady-state.

2.1.7.1.8.2. Subjects and Methods

This was a Phase 1, open-label, randomized, placebo-controlled, 2-way crossover study in 16 healthy subjects to investigate the PK interaction between DRV, administered as the 300-mg tablet formulation F016, together with rtv, and the CCR5 agonist maraviroc (a CYP3A and P-gp substrate) at steady-state. In 2 sessions, each subject received Treatment A and B, as follows, with subsequent sessions separated by a washout period of at least 14 days:

- Treatment A: Maraviroc 150 mg twice daily on Days 1 to 9, and a single dose on the morning of Day 10.
- Treatment B: Maraviroc 150 mg twice daily and DRV/rtv 600/100 mg twice daily on Days 1 to 9. A single dose of both maraviroc and DRV/rtv were administered on the morning of Day 10.

Maraviroc administration took place under fasting conditions, whereas administration of DRV and rtv took place under fed conditions. On each day, subjects fasted from at least 2 hours before until 1 hour after maraviroc dosing. Standard breakfast and dinner were served at least 1 hour

after maraviroc administration, and DRV and rtv were administered within 15 minutes after completing a meal. Darunavir was taken within 5 minutes after rtv intake.

2.1.7.1.8.3. Results

2.1.7.1.8.3.1. DRV and rtv PK

The PK parameters of DRV and rtv after administration of DRV/rtv in the presence of maraviroc are shown in Table 47.

Table 47: PK Parameters of DRV and rtv Following Coadministration of DRV/rtv With Maraviroc (Study TMC114-A4001052)

Parameter	Mean (SD); t_{max}: Median (Range)	
	DRV/rtv 600/100 mg bid + Maraviroc 150 mg bid	DRV/rtv 600/100 mg bid + Maraviroc 150 mg bi
N	15	15
t_{max}, h	3.30	4.57
C_{min}, ng/mL	2.685	236
C_{max}, ng/mL	5,820	859
$AUC_{10.5h}$, ng.h/mL	43,929	5,404

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-A4001052-CRR/Table 10

2.1.7.1.8.3.2. Maraviroc PK

The LS mean ratios for C_{max} and AUC_{12h} of maraviroc when maraviroc was coadministered with DRV/rtv relative to administration of maraviroc alone were 229% and 405%, respectively (Table 48). There was no relevant change in the median t_{max} of maraviroc.

Table 48: PK Parameters of Maraviroc Following Administration of Maraviroc in the Absence and Presence of DRV/rtv (Study TMC114-A4001052)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Maraviroc 150 mg bid + DRV/rtv 600/100 mg bid	Maraviroc 150 mg bid	
N	13	15	
C_{max}, ng/mL	279	629	229 (146; 359)
AUC_{12h}, ng.h/mL	885	3,701	405 (294; 559)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-A4001052-CRR/Table 7 and Table 8

2.1.7.1.8.4. Conclusion

The mean exposure (C_{max} and AUC_{12h}) to maraviroc was increased when maraviroc was coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.4.

2.1.7.2. Other Drugs

2.1.7.2.1. Ranitidine and Omeprazole

TMC114-C122

Module 5.3.3.4/TMC114-C122-CRR

2.1.7.2.1.1. Objective

To investigate the effect of omeprazole and ranitidine on the PK of DRV at steady-state, coadministered with rtv.

2.1.7.2.1.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-way crossover study in 18 healthy subjects to investigate the effect of ranitidine and omeprazole (2 gastrointestinal agents that inhibit acid secretion and elevate intragastric pH [35,57]) on the PK of DRV (400-mg tablet formulation F001), coadministered with rtv, after repeated dosing. In 3 sessions, each subject received DRV/rtv 400/100 mg twice daily (Treatment A), DRV/rtv 400/100 mg twice daily and ranitidine 150 mg twice daily (Treatment B), and DRV/rtv 400/100 mg twice daily and omeprazole 20 mg once daily (Treatment C). All treatments were administered for 4 days with an additional morning dose on Day 5. Subsequent sessions were separated by a washout period of at least 7 days. Omeprazole was taken before breakfast, ranitidine was taken before breakfast and dinner, and DRV and rtv were taken after breakfast and dinner.

2.1.7.2.1.3. Results

2.1.7.2.1.3.1. DRV PK

The PK of DRV was unaffected by coadministration of ranitidine or omeprazole. The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with ranitidine relative to administration of DRV/rtv alone were 96% and 95%, respectively (Table 49). For all comparisons, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of DRV following coadministration with ranitidine. When DRV/rtv was coadministered with omeprazole, relative to administration of DRV/rtv alone, the LS mean ratios for C_{max} and AUC_{12h} of DRV were 102% and 104%, respectively (Table 49). For all comparisons, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds. There was no change in the median t_{max} of DRV following coadministration with omeprazole.

Table 49: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Ranitidine or Omeprazole (Study TMC114-C122)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B: DRV/rtv 400/100 mg bid + Ranitidine 150 mg bid	**Treatment A: DRV/rtv 400/100 mg bid**	
N	16	16	
t_{max}, h	3.5 (3.0-5.0)	4.0 (1.5-4.0)	-
C_{min}, ng/mL	2,696 (1,151)	2,851 (1,172)	94.20 (89.6; 99.1)
C_{max}, ng/mL	5,743 (1,878)	5,834 (1,415)	96.48 (89.1; 105)
AUC_{12h} ng.h/mL	47,258 (16,340)	48,905 (14,352)	95.45 (90.4; 101)
	Treatment C: DRV/rtv 400/100 mg bid + Omeprazole 20 mg qd	**Treatment A: DRV/rtv 400/100 mg bid**	
N	17	16	
t_{max}, h	4.0 (2.0-5.0)	4.0 (1.5-4.0)	-
C_{min}, ng/mL	3,121 (1,416)	2,851 (1,172)	107.7 (92.8-125)
C_{max}, ng/mL	6,009 (1,844)	5,834 (1,415)	101.5 (94.9-109)
AUC_{12h} ng.h/mL	51,505 (18,930)	48,905 (14,352)	103.8 (95.7-113)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C122-CRR/Table 8, Table 9, and Table 10

2.1.7.2.1.3.2. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with ranitidine relative to administration of DRV/rtv alone were 119% and 106%, respectively (Table 50). For C_{min} and AUC_{12h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds, while the upper limit of the 90% CI of C_{max} was above the 125.00% bound. There was no change in the median t_{max} of rtv following coadministration with ranitidine. When DRV/rtv was coadministered with omeprazole, relative to administration of DRV/rtv alone, the LS mean ratios for C_{max} and AUC_{12h} of rtv were 103% and 92%, respectively, and the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds (Table 50). For C_{min}, the lower limit of the 90% CI was below 80.00%. There was no change in the median t_{max} of rtv following coadministration with omeprazole.

Table 50: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Ranitidine or Omeprazole (Study TMC114-C122)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B: DRV/rtv 400/100 mg bid + Ranitidine 150 mg bid	**Treatment A: DRV/rtv 400/100 mg bid**	
N	16	16	
t_{max}, h	4.0 (0.0-6.0)	4.0 (1.0-5.0)	-
C_{min}, ng/mL	442 (209)	437 (184)	98.40 (85.5; 113)
C_{max}, ng/mL	2,395 (1,040)	1,906 (560)	119.4 (103; 139)
AUC_{12h} ng.h/mL	12,922 (4,439)	11,670 (3,039)	106.1 (99.2; 113)
	Treatment C: DRV/rtv 400/100 mg bid + Omeprazole 20 mg qd	**Treatment A: DRV/rtv 400/100 mg bid**	
N	17	16	
t_{max}, h	4.0 (4.0-6.0)	4.0 (1.0-5.0)	-
C_{min}, ng/mL	351 (199)	437 (184)	74.29 (61.1; 90.3)
C_{max}, ng/mL	2,031 (987)	1,906 (560)	102.7 (88.2; 120)
AUC_{12h} ng.h/mL	10,945 (4,009)	11,670 (3,039)	92.01 (83.0; 102)

bid=twice daily; N=maximum number of subjects with data, qd=once daily.
Source: Module 5.3.3.4/TMC114-C122-CRR/Table 11, Table 12, and Table 13

2.1.7.2.1.4. Conclusion

Systemic exposure to DRV and rtv was not considerably affected when ranitidine or omeprazole was given with DRV coadministered with rtv.

Information on dosing recommendations is available in Section 3.3.2.6.2.

2.1.7.2.2. Digoxin

TMC114-C150

Module 5.3.3.4/TMC114-C150-CRR

2.1.7.2.2.1. Objective

To investigate the effect of steady-state concentrations of DRV, coadministered with rtv, on the PK of a single dose of digoxin.

2.1.7.2.2.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-way crossover study in 17 healthy subjects to investigate the PK interaction between DRV, administered as the 300-mg tablet formulation F016, together with rtv, and digoxin at steady-state. In 2 sessions, each subject received Treatment A and B, with subsequent sessions separated by a washout period of at least 14 days:

- Treatment A: Digoxin 0.4 mg single dose on Day 8.
- Treatment B: DRV/rtv 600/100 mg twice daily on Days 1 to 11 and digoxin 0.4 mg single dose on Day 8.

Darunavir, rtv, and digoxin were administered within 15 minutes after completing a meal. Darunavir was taken within 5 minutes after rtv intake. In case of coadministration of DRV/rtv and digoxin (Day 8 of Treatment B), rtv had to be taken first, followed by DRV (within 5 minutes), and digoxin (within 5 minutes).

2.1.7.2.2.3. Results

2.1.7.2.2.3.1. DRV and rtv PK

The PK parameters of DRV and rtv after administration of DRV/rtv in the presence of digoxin are shown in Table 51.

Table 51: PK Parameters of DRV and rtv Following Coadministration of DRV/rtv With Digoxin (Study TMC114-C150)

Parameter	Mean (SD); t_{max}: Median (Range)	
	DRV/rtv 600/100 mg bid + Digoxin 0.4 mg	**DRV/rtv 600/100 mg bid + Digoxin 0.4 mg**
N	14	14
t_{max}, h	3.0 (1.0-5.0)	4.5 (4.0-6.0)
C_{0h}, ng/mL	4,208 (1,015)	561 (423)
C_{min}, ng/mL	3,426 (900)	372 (282)
C_{max}, ng/mL	7,729 (1,072)	1,436 (682)
AUC_{12h}, ng.h/mL	63,830 (10,830)	8,582 (4,486)
$C_{ss,av}$, ng/mL	5,323 (906)	716 (374)
FI, %	82.4 (25.8)	146 (52.6)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C150-CRR/Table 6 and Table 7

2.1.7.2.2.3.2. Digoxin PK

The LS mean ratios for C_{max} and AUC_{24h} of digoxin when digoxin was coadministered with DRV/rtv relative to administration of digoxin alone were 129% and 135%, respectively (Table 52). The 90% CIs of the LS means ratios were large because of the substantial intersubject variability (ISV). When the results of the subject with the highest individual ratios were excluded from the analysis of AUC_{last}, the LS means ratio was 161%, with a 90% CI of 131% to 198% (refer to Module 5.3.3.4/TMC114-C150-CRR/Table 9). There was no relevant change in the median t_{max} of digoxin.

Table 52: PK Parameters of Digoxin Following Administration of Digoxin in the Absence and Presence of DRV/rtv (Study TMC114-C150)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Digoxin 0.4 mg + DRV/rtv 600/100 mg bid	Digoxin 0.4 mg	
N	14[a]	9	
t_{max}, h	1.5 (0.5-2.0)	1.0 (0.5-2.0)	-
C_{max}, ng/mL	2.28 (0.712)	1.97 (0.940)	128.7 (92.25; 179.4)
AUC_{24h}, ng.h/mL	12.11 (3.54)	9.69 (3.69)	135.0 (100.2; 182.0)
AUC_{last}, ng.h/mL [b]	21.6 (6.49)	16.8 (7.78)	177.4 (89.87; 350.3)
AUC_{∞}, ng.h/mL [c]	34.7 (12.3)	25.2 (9.76)	-
$t_{1/2,term}$, h [c]	45.3 (6.02)	42.0 (21.2)	-
$D_{urine,total}$, %	35.0 (10.1)	29.3 (9.79)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C150-CRR/Table 8 and Table 9

2.1.7.2.2.4. Conclusion

The mean exposure (AUC_{12h}) to digoxin was increased when digoxin was coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.3.

2.1.7.2.3. Clarithromycin

TMC114-C142

Module 5.3.3.4/TMC114-C142-CRR

2.1.7.2.3.1. Objective

To investigate the PK interaction between steady-state concentrations of clarithromycin and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.3.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-way crossover study in 18 healthy subjects to investigate the PK interaction between clarithromycin (a substrate of CYP3A and P-gp and a mild inhibitor of P-gp[7]) and DRV (400-mg tablet formulation F001), in combination with rtv, all at steady-state. In 3 sessions, each subject received DRV/rtv 400/100 mg twice daily (Treatment A), clarithromycin 500 mg twice daily (Treatment B), and 500 mg clarithromycin twice daily and DRV/rtv 400/100 mg twice daily (Treatment C). Treatments A and B were administered for 6 days with an additional morning dose on Day 7. Treatment C was administered for 6 days with an additional morning dose on Day 7, and an evening dose of DRV/rtv only on Day 7. Subsequent sessions were separated by a washout period of at least 7 days. All treatments were administered under fed conditions.

2.1.7.2.3.3. Results

2.1.7.2.3.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with clarithromycin relative to administration of DRV/rtv alone were 83% and 87%, respectively (Table 53). The 90% CIs of the LS means ratios for C_{max} and AUC_{12h} were outside of the 80.00% to 125.00% bounds; for C_{min}, the upper limit of the 90% CI was just above the 125.00% bound. There was no change in the median t_{max} of DRV.

Table 53: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Clarithromycin (Study TMC114-C142)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment C DRV/rtv 400/100 mg bid + Clarithromycin 500 mg bid	Treatment A DRV/rtv 400/100 mg bid	
N	17	17	
t_{max}, h	3.0 (1.5-5.0)	3.0 (1.5-5.0)	-
C_{min}, ng/mL	1,612 (564)	1,613 (566)	101 (81; 126)
C_{max}, ng/mL	3,506 (1,015)	4,108 (874)	83 (72; 96)
AUC_{12h} ng.h/mL	29,154 (8,471)	32,734 (7,915)	87 (75; 101)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C142-CRR/Table 9 and Table 10

2.1.7.2.3.3.2. Clarithromycin and 14-Hydroxy Clarithromycin PK

The LS mean ratios for C_{max} and AUC_{12h} of clarithromycin when clarithromycin was coadministered with DRV/rtv relative to administration of clarithromycin alone were 126% and 157%, respectively (Table 54). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There was no relevant change in median t_{max} of clarithromycin. Plasma concentrations of the metabolite 14-hydroxy clarithromycin were reduced to below the LLOQ in the presence of DRV/rtv, which was likely due to inhibition of CYP3A by DRV and rtv.

Table 54: PK Parameters of Clarithromycin and 14-Hydroxy Clarithromycin Following Administration of Clarithromycin in the Absence and Presence of DRV/rtv (Study TMC114-C142)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment C Clarithromycin 500 mg bid + DRV/rtv 400/100 mg bid	Treatment B Clarithromycin 500 mg bid	
Clarithromycin			
N	17	16	
t_{max}, h	2.0 (1.0-5.0)	3.0 (1.0-6.0)	-
C_{min}, ng/mL	1,298 (466)	501 (196)	274 (230; 326)
C_{max}, ng/mL	2,711 (887)	2,261 (826)	126 (103; 154)
AUC_{12h} ng.h/mL	23,867 (6,169)	15,619 (4,395)	157 (135; 184)
14-Hydroxy Clarithromycin			
N	17	16	
t_{max}, h	-	3.0 (1.5-6.0)	-
C_{min}, ng/mL	< LLOQ	319 (122)	-
C_{max}, ng/mL	< LLOQ	666 (269)	-
AUC_{12h} ng.h/mL	< LLOQ	5,981 (2,255)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C142-CRR/Section Table 13, Table 14, and Table 15

2.1.7.2.3.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with clarithromycin relative to administration of DRV/rtv alone were 98% and 100%, respectively (Table 55). The 90% CIs of the LS means ratios for C_{max} and AUC_{12h} were within the 80.00% to 125.00% bounds; for C_{min}, the upper limit of the 90% CI was above the 125.00% bound. There was no relevant change in the median t_{max} of rtv.

Table 55: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Clarithromycin (Study TMC114-C142)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment C DRV/rtv 400/100 mg bid + Clarithromycin 500 mg bid	Treatment A DRV/rtv 400/100 mg bid	
N	17	17	
t_{max}, h	4.0 (1.5-5.0)	3.0 (1.0-5.0)	-
C_{min}, ng/mL	235 (182)	197 (121)	124 (94; 164)
C_{max}, ng/mL	1,153 (585)	1,096 (393)	98 (84; 115)
AUC_{12h} ng.h/mL	7,139 (3,699)	6,838 (2,849)	100 (86; 117)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C142-CRR/Table 11 and Table 12

2.1.7.2.3.4. Conclusion

The mean exposure (C_{max} and AUC_{12h}) to DRV was decreased when DRV/rtv was coadministered with clarithromycin; exposure to rtv was unaffected. The mean exposure to clarithromycin was increased when clarithromycin was coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.4.

2.1.7.2.4. Carbamazepine

TMC114-C172

Module 5.3.3.4/TMC114-C172-CRR

2.1.7.2.4.1. Objective

To investigate the PK interaction between steady-state concentrations of carbamazepine and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.4.2. Subjects and Methods

This was a Phase 1, open-label, 2-panel crossover study in 32 healthy subjects to investigate the PK interaction between DRV (administered as the 300-mg tablet formulation F016), together with rtv, and the anticonvulsant carbamazepine at steady-state. Concentrations of the metabolite carbamazepine epoxide were also assessed. Subjects received the following treatments:

Panel 1 (N=16)

- Days 1 to 7: DRV/rtv 600/100 mg twice daily.
- Days 8 to 10: DRV/rtv 600/100 mg twice daily plus carbamazepine 200 mg once daily.
- Days 11 to 29: DRV/rtv 600/100 mg twice daily plus carbamazepine 200 mg twice daily.
- Day 30: Morning dose of DRV/rtv 600/100 mg plus carbamazepine 200 mg.

Panel 2 (N=16):

- Days 1 to 3: Carbamazepine 200 mg once daily.
- Days 4 to 23: Carbamazepine 200 mg twice daily.
- Days 24 to 29: Carbamazepine 200 mg twice daily plus DRV/rtv 600/100 mg twice daily.
- Day 30: Morning dose of carbamazepine 200 mg plus DRV/rtv 600/100 mg.

DRV, rtv, and carbamazepine were administered within 10 minutes after a meal. Darunavir was taken within 5 minutes after rtv intake. On days of coadministration of DRV/rtv and carbamazepine, carbamazepine had to be taken first, followed by rtv (within 5 minutes), and DRV (within 5 minutes).

2.1.7.2.4.3. Results

2.1.7.2.4.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with carbamazepine relative to administration of DRV/rtv alone were 104% and 99%, respectively

(Table 56). For C_{max} and AUC_{24h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds; for C_{min}, the lower limit of the 90% CIs was below 80.00%. There was no relevant change in the median t_{max} of DRV.

Table 56: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Carbamazepine - Panel 1 (Study TMC114-C172)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 600/100 mg bid + Carbamazepine 200 mg bid	DRV/rtv 600/100 mg bid	
N	11	16	
t_{max}, h	3.0 (1.0-5.0)	2.0 (0.5-5.0)	-
C_{0h}, ng/mL	3,125 (1,008)	3,527 (860)	-
C_{min}, ng/mL	2,509 (772)	2,901 (714)	85.45 (73.33; 99.57)
C_{max}, ng/mL	6,551 (1,384)	6,262 (1,148)	103.7 (93.14; 115.5)
AUC_{12h} ng.h/mL	51,800 (10,800)	52,310 (9,557)	98.79 (90.30; 108.1)
$C_{ss,av}$, ng/mL	4,316 (900)	4,359 (796)	-
FI, %	94.2 (23.7)	77.7 (12.0)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C172-CRR/Table 5 and Table 6

2.1.7.2.4.3.2. Carbamazepine and Carbamazepine Epoxide PK

The LS mean ratios for C_{max} and AUC_{12h} of carbamazepine when carbamazepine was coadministered with DRV/rtv relative to administration of carbamazepine alone were 143% and 145%, respectively (Table 57). There was no relevant change in the median t_{max} of carbamazepine.

The LS mean ratios for C_{max} and AUC_{12h} of the metabolite carbamazepine epoxide when carbamazepine was coadministered with DRV/rtv relative to administration of carbamazepine alone were both 46% (Table 57). There was no change in the median t_{max} of carbamazepine epoxide.

Table 57: PK Parameters of Carbamazepine and Carbamazepine Epoxide Following Administration of Carbamazepine in the Absence and Presence of DRV/rtv - Panel 2 (Study TMC114-C172)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Carbamazepine 200 mg bid + DRV/rtv 600/100 mg bid	Carbamazepine 200 mg bid	
Carbamazepine			
N	16	16	
t_{max}, h	5.0 (1.5-8.0)	4.5 (2.0-8.0)	-
C_{0h}, µg/mL	8.68 (2.52)	5.33 (1.40)	-
C_{min}, µg/mL	7.77 (2.35)	5.01 (1.23)	154.3 (141.3; 168.4)
C_{max}, µg/mL	9.97 (2.58)	6.95 (1.54)	142.9 (133.7; 152.7)
AUC_{12h} µg.h/mL	105.2 (28.9)	72.1 (16.2)	145.3 (134.5; 157.1)
$C_{ss,av}$, µg/mL	8.77 (2.41)	6.00 (1.35)	-
FI, %	25.8 (7.70)	32.8 (7.84)	-
Carbamazepine Epoxide			
N	16	16	
t_{max}, h	5.0 (0.0-12.0)	5.0 (3.0-8.0)	-
C_{0h}, µg/mL	0.315 (0.077)	0.640 (0.167)	-
C_{min}, µg/mL	0.270 (0.079)	0.555 (0.129)	47.78 (45.07; 50.66)
C_{max}, µg/mL	0.351 (0.098)	0.762 (0.176)	45.60 (42.52; 48.90)
AUC_{12h} µg.h/mL	3.67 (0.982)	7.86 (1.79)	46.31 (43.88; 48.88)
$C_{ss,av}$, µg/mL	0.306 (0.082)	0.655 (0.149)	-
FI, %	26.8 (9.35)	31.3 (9.52)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C172-CRR/Table 9, Table 10, Table 11, and Table 12

2.1.7.2.4.3.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with carbamazepine relative to administration of DRV/rtv alone were 56% and 51%, respectively (Table 58). There was no relevant change in the median t_{max} of rtv.

Table 58: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Carbamazepine - Panel 1 (Study TMC114-C172)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 600/100 mg bid + Carbamazepine 200 mg bid	DRV/rtv 600/100 mg bid	
N	11	16	
t_{max}, h	5.0 (2.0-8.0)	4.0 (1.5-6.0)	-
C_{0h}, ng/mL	173.1 (78.4)	386 (198)	-
C_{min}, ng/mL	113 (44.2)	256 (104)	44.22 (37.05; 52.78)
C_{max}, ng/mL	517 (148)	935 (249)	56.17 (49.48; 63.77)
AUC_{12h} ng.h/mL	3,281 (914)	6,540 (2,087)	51.17 (46.54; 56.25)
$C_{ss,av}$, ng/mL	273 (76.2)	545.0 (174)	-
FI, %	149 (31.8)	129 (29.2)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C172-CRR/Table 7 and Table 8

2.1.7.2.4.4. Conclusion

The mean exposure (AUC_{12h}) to DRV, coadministered with rtv, was generally unaffected by the presence of carbamazepine. The mean exposure to carbamazepine was increased 1.45-fold in the presence of DRV/rtv, while the mean exposure to the carbamazepine metabolite, carbamazepine epoxide, was decreased by 54%. The parent-to-metabolite ratio of carbamazepine to carbamazepine epoxide decreased from a mean of 11.1% when carbamazepine was administered alone to 3.51% when coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.7.

2.1.7.2.5. Paroxetine and Sertraline

TMC114-C121

Module 5.3.3.4/TMC114-C121-CRR

2.1.7.2.5.1. Objective

To investigate the PK interaction between the selective serotonin reuptake inhibitors (SSRIs) paroxetine and sertraline at steady-state and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.5.2. Subjects and Methods

This was a Phase 1, open-label, controlled, randomized, crossover study in healthy subjects to investigate the PK interaction between repeated doses of paroxetine (a CYP2D6 substrate and inhibitor[36]) or sertraline (a CYP3A substrate[34]) and DRV, administered as the 400-mg tablet formulation F001, together with rtv. The study population consisted of 36 healthy subjects, equally divided into 2 panels. Panel 1 received in 3 sessions: DRV/rtv 400/100 mg twice daily (Treatment A), paroxetine 20 mg once daily (Treatment B), and 20 mg paroxetine once daily coadministered with DRV/rtv 400/100 mg twice daily (Treatment C). Panel 2 received in 3 sessions DRV/rtv 400/100 mg twice daily (Treatment A), sertraline 50 mg once daily

(Treatment D), and 50 mg sertraline once daily coadministered with DRV/rtv 400/100 mg twice daily (Treatment E). Treatment A was administered for 6 days with an additional morning dose on Day 7. Treatments B, C, D, and E were administered for 7 days. Subsequent sessions were separated by a washout period of at least 7 days. All treatments were administered under fed conditions.

2.1.7.2.5.3. Results

2.1.7.2.5.3.1. DRV PK

The PK of DRV was unaffected by coadministration of paroxetine or sertraline. The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with paroxetine relative to administration of DRV/rtv alone were 97% and 102%, respectively (Table 59). For all comparisons, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds. There was no change in the median t_{max} of DRV following coadministration with paroxetine.

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with sertraline relative to administration of DRV/rtv alone were 101% and 98%, respectively (Table 59). For all comparisons, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds. There was no change in the median t_{max} of DRV following coadministration with sertraline.

Table 59: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Paroxetine or Sertraline (Study TMC114-C121)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment C DRV/rtv 400/100 mg bid. + Paroxetine 20 mg qd	**Treatment A DRV/rtv 400/100 mg bid**	
N	16	31	
t_{max}, h	4.0 (2.0-9.0)	4.0 (0.0-5.0)	-
C_{min}, ng/mL	2,091 (652)	2,324 (1,174)	106.6 (95.7; 119)
C_{max}, ng/mL	3,958 (699)	4,479 (1,543)	96.89 (91.9; 102)
AUC_{12h} ng.h/mL	35,127 (7,368)	39,038 (16,211)	101.8 (94.6; 110)
	Treatment E: DRV/rtv 400/100 mg bid + Sertraline 50 mg qd	**Treatment A: DRV/rtv 400/100 mg bid**	
N	16	31	
t_{max}, h	4.0 (0.0-5.0)	4.0 (0.0-5.0)	-
C_{min}, ng/mL	2,527 (904)	2,324 (1,174)	94.11 (76.4; 116)
C_{max}, ng/mL	5,099 (1,455)	4,479 (1,543)	100.8 (89.3; 114)
AUC_{12h} ng.h/mL	43,780 (13,932)	39,038 (16,211)	97.98 (83.9; 114)

bid=twice daily; N=maximum number of subjects with data, qd=once daily.
Source: Module 5.3.3.4/TMC114-C121-CRR/Table 9, Table 10, and Table 11

2.1.7.2.5.3.2. Paroxetine PK

The LS mean ratios for C_{max} and AUC_{24h} of paroxetine when paroxetine was coadministered with DRV/rtv relative to administration of paroxetine alone were 65% and 61%, respectively (Table 60). There was no change in the median t_{max} of paroxetine.

Table 60: PK Parameters of Paroxetine Following Administration of Paroxetine in the Absence and Presence of DRV/rtv (Study TMC114-C121)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment C Paroxetine 20 mg qd + DRV/rtv 400/100 mg bid	Treatment B Paroxetine 20 mg qd	
N	16	18	
t_{max}, h	6.0 (3.0-12.0)	6.0 (5.0-9.0)	-
C_{min}, ng/mL	6.76 (3.78)	11.4 (7.23)	63.2 (55.1-72.5)
C_{max}, ng/mL	15.6 (8.11)	24.0 (11.5)	64.5 (58.8-70.7)
AUC_{24h} ng.h/mL	253 (122)	433 (234)	60.7 (55.5-66.3)

bid=twice daily; N=maximum number of subjects with data, qd=once daily.
Source: Module 5.3.3.4/TMC114-C121-CRR/Table 17 and Table 18

2.1.7.2.5.3.3. Sertraline PK

The LS mean ratios for C_{max} and AUC_{24h} of sertraline when sertraline was coadministered with DRV/rtv relative to administration of sertraline alone were 56% and 51%, respectively, (Table 61). There was no change in the median t_{max} of sertraline.

Table 61: PK Parameters of Sertraline Following Administration of Sertraline in the Absence and Presence of DRV/rtv (Study TMC114-C121)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment E Sertraline 50 mg qd + DRV/rtv 400/100 mg bid	Treatment D Sertraline 50 mg qd	
N	16	15	
t_{max}, h	6.0 (0.0-9.0)	6.0 (4.0-9.0)	-
C_{min}, ng/mL	7.37 (3.28)	12.8 (4.80)	50.69 (45.3; 56.7)
C_{max}, ng/mL	18.7 (7.44)	28.9 (8.40)	55.54 (48.7; 63.3)
AUC_{24h} ng.h/mL	284 (115)	485 (167)	51.20 (45.6; 57.5)

bid=twice daily; N=maximum number of subjects with data, qd=once daily.
Source: Module 5.3.3.4/TMC114-C121-CRR/Table 15 and Table 16

2.1.7.2.5.3.4. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with paroxetine relative to administration of DRV/rtv alone were 117% and 134%, respectively, (Table 62). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of rtv following coadministration with paroxetine.

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with sertraline, relative to administration of DRV/rtv alone, were 101% and 89%, respectively (Table 62). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There was no change in the median t_{max} of rtv following coadministration with sertraline.

Table 62: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Paroxetine or Sertraline (Study TMC114-C121)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment C DRV/rtv 400/100 mg bid. + Paroxetine 20 mg qd	**Treatment A DRV/rtv 400/100 mg bid**	
N	16	31	
t_{max}, h	4.5 (4.0-9.0)	4.0 (3.0-9.0)	-
C_{min}, ng/mL	407 (184)	319 (158)	152.5 (134; 174)
C_{max}, ng/mL	1,689 (742)	1,591 (802)	117.3 (100; 137)
AUC_{12h} ng.h/mL	11,071 (5,546)	9,059 (3,666)	134.3 (122; 147)
	Treatment E: DRV/rtv 400/100 mg bid + Sertraline 50 mg qd	**Treatment A: DRV/rtv 400/100 mg bid**	
N	16	31	
t_{max}, h	4.0 (1.5-5.0)	4.0 (3.0-9.0)	-
C_{min}, ng/mL	315 (172)	319 (158)	80.99 (71.5; 91.7)
C_{max}, ng/mL	1,770 (814)	1,591 (802)	100.9 (80.0; 127)
AUC_{12h} ng.h/mL	9,434 (3,657)	9,059 (3,666)	89.07 (75.1; 106)

bid=twice daily; N=maximum number of subjects with data, qd=once daily.
Source: Module 5.3.3.4/TMC114-C121-CRR/Table 12, Table 13, and Table 14

2.1.7.2.5.4. Conclusion

The exposure to DRV, coadministered with rtv, was unaffected by coadministration of paroxetine or sertraline. For sertraline and paroxetine, approximately 50% and 40% decreases in exposure, respectively, were observed upon coadministration of DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.8.

2.1.7.2.6. Ketoconazole

TMC114-C129

Module 5.3.3.4/TMC114-C129-CSR

2.1.7.2.6.1. Objective

To investigate the PK interaction between steady-state concentrations of ketoconazole and steady-state concentrations of DRV.

2.1.7.2.6.2. Subjects and Methods

This was a Phase 1, open-label, controlled, randomized, crossover study in healthy subjects to investigate the PK interaction between repeated doses of DRV (200-mg tablet formulation

F002), with and without coadministration of rtv, and ketoconazole. Ketoconazole is an antifungal agent and a potent CYP3A inhibitor. The study population consisted of 26 healthy subjects, divided into 8 subjects in Panel 1 and 18 subjects in Panel 2. Panel 1 received DRV 400 mg twice daily (Treatment A) and DRV 400 mg twice daily coadministered with ketoconazole 200 mg twice daily (Treatment B) in 2 sessions. Panel 2 received DRV/rtv 400/100 mg twice daily (Treatment C), ketoconazole 200 mg twice daily (Treatment D), and DRV/rtv 400/100 mg twice daily coadministered with ketoconazole 200 mg twice daily (Treatment E) in 3 sessions. All treatments were administered under fed conditions for 6 days, with an additional single dose on Day 7. Subsequent sessions were separated by a washout period of at least 7 days.

2.1.7.2.6.3. Results

2.1.7.2.6.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV alone was coadministered with ketoconazole relative to administration of DRV in the absence of ketoconazole were 178% and 255%, respectively (Table 63). The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with ketoconazole relative to administration of DRV/rtv in the absence of ketoconazole were 121% and 142%, respectively. For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125.00%. There was no relevant change in the median t_{max} of DRV.

Table 63: PK Parameters of DRV Following Administration of DRV or DRV/rtv in the Absence and Presence of Ketoconazole (Study TMC114-C129)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B DRV400 mg bid + Ketoconazole 200 mg bid	**Treatment A DRV 400 mg bid**	
N	6	7	
t_{max}, h	3.0 (2.0-4.0)	2.0 (2.0-5.0)	-
C_{min}, ng/mL	235 (154)	68.2 (26.8)	279.3 (158; 493)
C_{max}, ng/mL	2,788 (912)	1,808 (871)	177.6 (128; 247)
AUC_{12h} ng.h/mL	15,505 (7,589)	6,478 (3,341)	254.8 (180; 361)
	Treatment E DRV/rtv 400/100 mg bid + Ketoconazole 200 mg bid	**Treatment C DRV/rtv 400/100 mg bid**	
N	17	14	
t_{max}, h	3.0 (0.0-6.0)	2.5 (1.0-5.0)	-
C_{min}, ng/mL	3,582 (966)	2,209 (1,143)	172.8 (139; 214)
C_{max}, ng/mL	6,394 (1,445)	5,209 (1,625)	120.9 (104; 140)
AUC_{12h} ng.h/mL	60,690 (14,174)	42,707 (16,234)	142.4 (123; 165)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C129-CSR/Table 9, Table 10, and Table 11

2.1.7.2.6.3.2. Ketoconazole PK

The LS mean ratios for C_{max} and AUC_{12h} of ketoconazole when ketoconazole was coadministered with DRV/rtv relative to administration of ketoconazole in the absence of

DRV/rtv were 211% and 312%, respectively (Table 64). There was no change in the median t_{max} of ketoconazole.

Table 64: PK Parameters of Ketoconazole Following Administration of Ketoconazole in the Absence and Presence of DRV or DRV/rtv (Study TMC114-C129)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment E Ketoconazole 200 mg bid + DRV/rtv 400/100 mg bid	Treatment D Ketoconazole 200 mg bid	
N	17	15	
t_{max}, h	3.0 (1.0-5.0)	3.0 (1.0-4.0)	-
C_{min}, ng/mL	5,354 (1,627)	831 (794)	968.0 (644; 1,455)
C_{max}, ng/mL	10,501 (2,524)	5,311 (2,018)	210.5 (181; 244)
AUC_{12h} ng.h/mL	94,343 (25,129)	33,098 (16,014)	312.1 (265; 368)
	Treatment B Ketoconazole 200 mg bid + DRV400 mg bid		
N	6		
t_{max}, h	3.0 (2.0-3.0)		
C_{min}, ng/mL	692 (565)		
C_{max}, ng/mL	5,458 (747)		
AUC_{12h} ng.h/mL	35,292 (7,209)		

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C129-CSR/Table 12 and Table 13

2.1.7.2.6.3.3. RTV PK

There was no change in the median t_{max} of rtv when DRV/rtv was coadministered with ketoconazole relative to administration of DRV/rtv in the absence of ketoconazole (Table 65). The systemic exposure to rtv coadministered with DRV was unaffected by the presence of ketoconazole.

Table 65: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Ketoconazole (Study TMC114-C129)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment E DRV/rtv 400/100 mg bid + Ketoconazole 200 mg bid	Treatment C DRV/rtv 400/100 mg bid
N	17	14
t_{max}, h	4.0 (1.0-5.0)	4.0 (1.0-5.0)
C_{min}, ng/mL	287 (129)	215 (142)
C_{max}, ng/mL	1,368 (553)	1,232 (750)
AUC_{12h} ng.h/mL	8,515 (3,646)	7,556 (4,721)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C129-CSR/Table 14

2.1.7.2.6.4. Conclusion

The presence of ketoconazole significantly increased exposure to DRV coadministered with rtv. The exposure to ketoconazole was also significantly increased when coadministered with DRV and rtv.

Information on dosing recommendations is available in Section 3.3.2.6.10.

2.1.7.2.7. Artemether/Lumefantrine

TMC125VIR1001

Module 5.3.3.4/TMC125VIR1001-CSR

2.1.7.2.7.1. Objective

To investigate the PK interaction between multiple doses of artemether/lumefantrine and single and multiple doses of DRV/rtv.

2.1.7.2.7.2. Subjects and Methods

This was a Phase 1, open-label, 2-panel, 2-period crossover study in healthy subjects to investigate the PK interaction between DRV (administered as the commercial 600-mg tablet F032) together with rtv or etravirine and the antimalarial schizontocides, artemether and lumefantrine at steady-state. Artemether is extensively metabolized by CYP3A and to a lesser extent by CYP2B6, CYP2C9, and CYP2C19, in vitro. It has an active metabolite, dihydroartemisinin (DHA). Artemisinin derivatives are inducers of CYP3A, CYP2B6, and CYP2C19. Lumefantrine is primarily metabolized by CYP3A to desbutyl-lumefantrine in vitro. In the DRV/rtv panel, the study population consisted of 16 healthy subjects (total study population: 33 subjects). All subjects received artemether/lumefantrine alone (Treatment A) and DRV/rtv alone and coadministered with artemether/lumefantrine (Treatment B), separated by a washout period of at least 4 weeks, as follows:

- Treatment A: 3 days of treatment with artemether/lumefantrine 80/480 mg (6 doses of 4 tablets [20/120-mg] at 0, 8, 24, 36, 48, and 60 hours).
- Treatment B: DRV/rtv 600/100 mg twice daily from Day 1 to Day 21, with a single 600/100 mg dose of DRV/rtv in the morning on Day 22. From Day 8, 3 days of treatment with artemether/lumefantrine 80/480 mg (6 doses of 4 tablets [20/120-mg] at 0, 8, 24, 36, 48, and 60 hours).

Darunavir/rtv and artemether/lumefantrine treatments were taken under fed conditions within 10 minutes after a meal.

2.1.7.2.7.3. Results

2.1.7.2.7.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with artemether/lumefantrine relative to administration of DRV/rtv alone were 100% and 96%, respectively (Table 66). For C_{max} and AUC_{12h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds; for C_{min}, the lower limit of the 90% CIs was slightly below 80.00%. There was no change in the median t_{max} of DRV.

Table 66: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Artemether/Lumefantrine (Study TMC125VIR1001)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B (Day 11) DRV/rtv 600/100 mg bid + Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	Treatment B (Day 8) DRV/rtv 600/100 mg bid	
N	14	14	
t_{max}, h	4.00 (1.00-4.00)	4.00 (0.50-4.00)	-
C_{0h}, ng/mL	3,451 (1,213)	3,930 (1,222)	-
C_{min}, ng/mL	2,629 (1,057)	2,886 (697)	87 (77; 98)
C_{max}, ng/mL	6,305 (1,493)	6,294 (1,428)	100 (93; 107)
AUC_{12h} ng.h/mL	51,271 (14,768)	52,526 (11,606)	96 (90; 103)
FI, %	89.1 (21.9)	77.3 (13.0)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125VIR1001-CSR/Table 24 and Table 25

2.1.7.2.7.3.2. Artemether and DHA PK

After single-dose administration of artemether/lumefantrine and DRV/rtv, the LS mean ratios for C_{max} and AUC_{8h} of artemether when artemether/lumefantrine was coadministered with DRV/rtv relative to administration of artemether/lumefantrine alone were 85% and 91%, respectively (Table 67). For both comparisons, the lower limit of the 90% CIs was below 80.00%. After repeated-dose administration, the LS mean ratios for C_{max} and AUC_{last} of artemether were 82% and 84%, and, for both comparisons, the lower limit of the 90% CIs was below 80.00%. For C_{min}, the 90% CI of the LS means ratio was contained within the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of artemether after single and repeated dosing.

Table 67: PK Parameters of Artemether Following Administration of Artemether/Lumefantrine in the Absence and Presence of DRV/rtv (Study TMC125VIR1001)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours + DRV/rtv 600/100 mg bid	Treatment A Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	
Single Dose: Treatment A (Day 1) vs. Treatment B (Day 8)			
N	14	15	
t_{max}, h	1.47 (0.47-5.97)	1.00 (0.50-4.00)	-
C_{6h}, ng/mL	8.03 (8.15)	7.14 (6.71)	-
C_{max}, ng/mL	56.0 (32.1)	63.4 (25.2)	85 (68; 105)
AUC_{8h} ng.h/mL	146 (66.6)	172 (82.5)	91 (78; 106)
Repeated Dose: Treatment A (Day 4) vs. Treatment B (Day 11)			
N	14	15	
t_{max}, h	1.47 (0.47-3.97)	1.00 (0.50-4.00)	-
C_{0h}, ng/mL	0 (-)	0 (-)	-
C_{min}, ng/mL	0 (-)	0 (-)	97 (90; 105)
C_{max}, ng/mL	17.9 (8.01)	25.3 (19.2)	82 (61; 111)
AUC_{last} ng.h/mL	65.7 (33.4)	92.2 (66.7)	84 (69; 102)
FI, %	339 (114)	354 (119)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125VIR1001-CSR/Table 16, Table 17, and Table 18

After single-dose administration of artemether/lumefantrine and DRV/rtv, the LS mean ratios for C_{max} and AUC_{8h} of the DHA metabolite of artemether when artemether/lumefantrine was coadministered with DRV/rtv relative to administration of artemether/lumefantrine alone were 106% and 112%, respectively (Table 68). For both comparisons, the upper limit of the 90% CIs was above the 125.00%. After repeated-dose administration, the LS mean ratios for C_{max} and AUC_{last} of DHA were both 82%; and, for both comparisons, the lower limit of the 90% CIs of the LS means ratio was below 80.00%. The 90% CI for C_{min} was contained within the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of DHA after single and repeated dosing.

Table 68: PK Parameters of Dihydroartemisinin (DHA) Following Administration of Artemether/Lumefantrine in the Absence and Presence of DRV/rtv (Study TMC125VIR1001)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours + DRV/rtv 600/100 mg bid	Treatment A Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	
Single Dose: Treatment A (Day 1) vs. Treatment B (Day 8)			
N	14	15	
t_{max}, h	1.47 (0.97-5.97)	2.00 (1.00-4.00)	-
C_{6h}, ng/mL	9.81 (5.66)	8.45 (6.84)	-
C_{max}, ng/mL	62.6 (29.5)	55.3 (18.4)	106 (82; 139)
AUC_{8h} ng.h/mL	184 (57.0)	164 (47.9)	112 (96; 130)
Repeated Dose: Treatment A (Day 4) vs. Treatment B (Day 11)			
N	14	15	
t_{max}, h	1.97 (0.47-3.97)	2.00 (1.00-4.00)	-
C_{0h}, ng/mL	1.08 (1.07)	1.19 (1.16)	-
C_{min}, ng/mL	1.01 (1.04)	1.14 (1.15)	100 (82; 122)
C_{max}, ng/mL	52.5 (25.9)	65.1 (26.1)	82 (66; 101)
AUC_{last} ng.h/mL	177 (46.9)	227 (74.9)	82 (74; 91)
FI, %	331 (95.2)	335 (76.4)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125VIR1001-CSR/Table 19, Table 20, and Table 21

2.1.7.2.7.3.3. Lumefantrine PK

After repeated-dose administration of artmether/lumefantrine, the LS mean ratios for C_{max} and AUC_{264h} of lumefantrine when artemether/lumefantrine was coadministered with DRV/rtv relative to administration of artemether/lumefantrine alone were 165% and 275%, respectively (Table 69). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of lumefantrine.

Table 69: PK Parameters of Lumefantrine Following Repeated-Dose Administration of Artemether/Lumefantrine in the Absence and Presence of DRV/rtv (Study TMC125VIR1001)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours + DRV/rtv 600/100 mg bid	Treatment A Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	
N	14	15	
t_{max}, h	5.97 (1.97-11.9)	6.00 (4.00-8.00)	-
C_{0h}, µg/mL	16.3 (6.59)	7.39 (3.88)	-
C_{min}, µg/mL	14.5 (5.49)	7.05 (3.56)	226 (192; 267)
C_{max}, µg/mL	20.4 (7.39)	12.8 (5.05)	165 (149; 183)
AUC_{264h} µg.h/mL	1,174 (628)	467 (275)	275 (246; 308)
FI, %	33.7 (9.23)	61.8 (27.0)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125VIR1001-CSR/Table 22 and Table 23

2.1.7.2.7.3.4. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with artemether/lumefantrine relative to administration of DRV/rtv alone were 85% and 90%, respectively (Table 70). For C_{min} and AUC_{12h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds; for C_{max}, the lower limit of the 90% CI was below 80.00%. There was no change in the median t_{max} of DRV.

Table 70: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Artemether/Lumefantrine (Study TMC125VIR1001)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B (Day 11) DRV/rtv 600/100 mg bid + Artemether/Lumefantrine 80/480 mg, 6 doses at 0, 8, 24, 36, 48, and 60 hours	Treatment B (Day 8) DRV/rtv 600/100 mg bid	
N	14	14	
t_{max}, h	4.00 (1.00-6.00)	4.00 (2.00-6.00)	-
C_{0h}, ng/mL	289 (93.7)	331 (147)	-
C_{min}, ng/mL	187 (54.9)	194 (87.0)	101 (88; 116)
C_{max}, ng/mL	783 (253)	945 (392)	85 (73; 99)
AUC_{12h} ng.h/mL	5,498 (1,757)	6,218 (2,431)	90 (80; 101)
FI, %	129 (19.5)	143 (27.8)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC125VIR1001-CSR/Table 26 and Table 27

2.1.7.2.7.4. Conclusion

The mean exposure (C_{max} and AUC_{12h}) to DRV, coadministered with rtv, was unaffected by the presence of artemether/lumefantrine. Coadministration of artemether/lumefantrine with DRV/rtv decreased the mean single-dose C_{max} and AUC_{8h} of artemether by 15% and 9%, respectively, and decreased the mean repeated-dose C_{max} and AUC_{last} of artemether by 18% and 16%,

respectively; the mean repeated-dose C_{min} of artemether was unaffected. Coadministration of artemether/lumefantrine with DRV/rtv increased the mean single-dose C_{max} and AUC_{8h} of the DHA metabolite 1.06- and 1.12-fold, respectively, and decreased both the mean repeated-dose C_{max} and AUC_{last} of DHA by 18%; the mean repeated dose C_{min} of DHA was unaffected. Coadministration of artemether/lumefantrine with DRV/rtv increased the mean C_{min}, C_{max}, and AUC_{264h} of lumefantrine 2.26-, 1.65-, and 2.75 fold, respectively.

Information on dosing recommendations is available in Section 3.3.2.6.12.

2.1.7.2.8. Rifabutin

TMC114-C107

Module 5.3.3.4/TMC114-C107-CRR

2.1.7.2.8.1. Objective

To investigate the PK interaction between steady-state concentrations of rifabutin and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.8.2. Subjects and Methods

This was a Phase 1, open-label, randomized, crossover study in healthy subjects to investigate the PK interaction between repeated doses of rifabutin (a substrate and inducer of CYP3A) and DRV (administered as the 400-mg tablet formulation F001), together with rtv. The study population was to consist of 16 healthy subjects, divided 1:1 into 2 panels. In 2 sessions, Panel 1 was to receive Treatments A and B1 and Panel 2 was to receive Treatments A and B2. In Treatment A, DRV/rtv 400/100 mg twice daily was to be administered from Day 1 to 9 with an additional morning dose on Day 10. In Treatment B1, rifabutin 300 mg once daily was to be administered from Day 1 to 10, immediately followed by a combined administration of rifabutin 150 mg once daily and DRV/rtv 400/100 mg twice daily from Day 11 to 20. In Treatment B2, the combination of rifabutin 150 mg once daily and DRV/rtv 400/100 mg twice daily was to be administered from Day 1 to 10, immediately followed by the administration of rifabutin 300 mg once daily alone from Day 11 to 20. Treatments were separated by a washout period of at least 14 days. All treatments were to be administered under fed conditions.

A total of 7 subjects discontinued the study during Session 1 due to AEs during treatment phases (including the rifabutin phase). Due to safety concerns, the sponsor decided to discontinue the study after Session 1. Furthermore, the objectives of the study concerning the PK of DRV, rtv, and rifabutin could not have been met even if the remaining 9 subjects had all completed Session 2. A second PK interaction study between DRV/rtv and rifabutin was completed (study TMC114-C163) and is described in Section 2.1.7.2.9.

2.1.7.2.8.3. Results

2.1.7.2.8.3.1. DRV PK

The PK parameters of DRV after administration of DRV/rtv in the presence and absence of rifabutin are shown in Table 71.

Table 71: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Rifabutin

	Mean (SD); t_{max}: Median (Range)		
Parameter	**Treatment A DRV/rtv 400/100 mg bid (Days 1-10)**	**Treatment B1 Rifabutin 300 mg qd (Days 1-10) + DRV/rtv 400/100 mg bid + Rifabutin 150 mg qd (Days 11-20)**	**Treatment B2 DRV/rtv 400/100 mg bid + Rifabutin 150 mg qd (Days 1-10) + Rifabutin 300 mg qd (Days 11-20)**
N	8	4	4
t_{max}, h	2.0 (1.5-5.0)	NA	NA
C_{0h}, ng/mL	NA	NA	NA
C_{min}, ng/mL	2,236 (665)	NA	NA
C_{max}, ng/mL	4,340 (786)	NA	NA
$C_{ss,av}$, ng/mL	3,151 (640)	NA	NA
AUC_{12h}, ng.h/mL	37,808 (7,682)	NA	NA

bid=twice daily; N=maximum number of subjects with data; NA=not assessable; qd=once daily.
Source: Module 5.3.3.4/TMC114-C107-CRR/Table 5

2.1.7.2.8.3.2. Rifabutin and 25-*O*-Desacetylrifabutin PK

The PK parameters of rifabutin and its metabolite 25-*O*-desacetylrifabutin after administration of rifabutin in the presence and absence of DRV/rtv are shown in Table 72.

The Day 10/Day 20 treatment ratios for 1 subject for rifabutin were 331% for C_{0h}, 296% for C_{min}, 128% for C_{max}, and 197% for AUC_{24h}, and for 25-*O*-desacetylrifabutin, the corresponding ratios were 6,493% for C_{0h}, 5,133% for C_{min}, 1,370% for C_{max}, and 2,619% for AUC_{24h}. Although, for this subject, increases in exposure to rifabutin and 25-*O*-desacetylrifabutin were seen when rifabutin was coadministered with DRV/rtv, no definite conclusions can be drawn from these limited data.

Table 72: PK Parameters of Rifabutin and 25-*O*-Desacetylrifabutin Following Administration of Rifabutin in the Absence and Presence of DRV/rtv

	Mean (SD); t_{max}: Median (Range)			
	Treatment B1 Rifabutin 300 mg qd (Days 1-10) + DRV/rtv 400/100 mg bid + Rifabutin 150 mg qd (Days 11-20)		Treatment B2: DRV/rtv 400/100 mg bid + Rifabutin 150 mg qd (Days 1-10) + Rifabutin 300 mg qd (Days 11-20)	
Parameter	Rifabutin	25-*O*-desacetylrifabutin	Rifabutin	25-*O*-desacetylrifabutin
N	4	4	4	4
t_{max}, h	3.0 (1.5-5.0)	3.5 (1.5-5.0)	NA	NA
C_{0h}, ng/mL	NA	NA	NA	NA
C_{min}, ng/mL	49.2 (16.8)	4.56 (1.87)	NA	NA
C_{max}, ng/mL	385 (157)	31.3 (19.6)	NA	NA
$C_{ss,av}$, ng/mL	149 (63.9)	13.6 (9.14)	NA	NA
AUC_{24h}, ng.h/mL	3,579 (1,535)	327 (219)	NA	NA

bid=twice daily; N=maximum number of subjects with data; NA=not assessable; qd=once daily.
Source: Module 5.3.3.4/TMC114-C107-CRR/Table 7 and Table 8

2.1.7.2.8.3.3. RTV PK

The PK parameters of rtv after administration of DRV/rtv in the presence and absence of rifabutin are shown in Table 73.

Table 73: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Rifabutin

	Mean (SD); t_{max}: Median (Range)		
Parameter	Treatment A DRV/rtv 400/100 mg bid (Days 1-10)	Treatment B1 Rifabutin 300 mg qd (Days 1-10) + DRV/rtv 400/100 mg bid + Rifabutin 150 mg qd (Days 11-20)	Treatment B2 DRV/rtv 400/100 mg bid + Rifabutin 150 mg qd (Days 1-10) + Rifabutin 300 mg qd (Days 11-20)
N	8	4	4
t_{max}, h	4.0 (4.0-5.0)	NA	NA
C_{0h}, ng/mL	NA	NA	NA
C_{min}, ng/mL	243 (99.3)	NA	NA
C_{max}, ng/mL	1,414 (507)	NA	NA
$C_{ss,av}$, ng/mL	654 (218)	NA	NA
AUC_{12h}, ng.h/mL	7,846 (2,617)	NA	NA

bid=twice daily; N=maximum number of subjects with data; NA=not assessable; qd=once daily.
Source: Module 5.3.3.4/TMC114-C107-CRR/Table 6

2.1.7.2.8.4. Conclusion

No firm conclusions on PK can be drawn due to the high number of subjects who discontinued the study prematurely. On the basis of data from an individual subject, the exposure to rifabutin and 25-*O*-desacetylrifabutin appeared to increase when rifabutin was coadministered with DRV/rtv.

Based on these limited data, a second Phase 1 study with DRV/rtv and rifabutin (TMC114-C163) was conducted to investigate the PK interaction (see Section 2.1.7.2.9).

2.1.7.2.9. Rifabutin

TMC114-C163

Module 5.3.3.4/TMC114-C163-CRR

To investigate the PK interaction between steady-state concentrations of rifabutin and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.9.1. Subjects and Methods

This was a Phase 1, open-label, randomized, 3-period crossover study in 27 healthy subjects to investigate the PK interaction between rifabutin (a substrate and inducer of CYP3A) and DRV (administered as the 300 mg tablet formulation F016), together with rtv, at steady-state. In 3 sessions, the following treatments were administered, with a washout period of at least 14 days between sessions:

- Treatment A: DRV/rtv 600/100 mg twice daily for 12 days, with an additional morning dose on Day 7.
- Treatment B: Rifabutin 300 mg once daily for 13 days.
- Treatment C: DRV/rtv 600/100 mg twice daily, and rifabutin 150 mg once every other day for 13 days.

Darunavir, rtv, and rifabutin had to be taken together within 10 minutes after a meal. On days of coadministration, rifabutin had to be taken first, followed by rtv (within 5 minutes), and DRV (within 5 minutes).

2.1.7.2.9.2. Results

2.1.7.2.9.2.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with rifabutin relative to administration of DRV/rtv alone were 142% and 157%, respectively (Table 74). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of DRV.

Table 74: PK Parameters of DRV on Day 13 Following Administration of DRV/rtv in the Absence and Presence of Rifabutin (Study TMC114-C163)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 600/100 mg bid + Rifabutin 150 mg qod	DRV/rtv 600/100 mg bid	
N	11	16	
t_{max}, h	3.0 (1.5-5.0)	4.0 (1.0-9.0)	-
C_{0h}, ng/mL	4,825 (2,140)	2,768 (1,077)	164.8 (97.53; 278.3)
C_{min}, ng/mL	4,322 (1,955)	2,349 (1,006)	174.5 (128.3; 237.4)
C_{max}, ng/mL	8,719 (2,942)	5,874 (1,637)	142.1 (121.3; 166.5)
AUC_{12h}, ng.h/mL	74,590 (25,630)	46,720 (15,430)	157.1 (128.1; 192.6)
$C_{ss,av}$, ng/mL	6,216 (2,136)	3,893 (1,286)	-
FI, %	74.7 (22.0)	93.8 (23.4)	-

bid=twice daily; N=maximum number of subjects with data; qod=every other day.
Source: Module 5.3.3.4/TMC114-C163-CRR/Table 6 and Table 7

2.1.7.2.9.2.2. Rifabutin and 25-*O*-Desacetylrifabutin PK

The LS mean ratios for C_{max} and area under the plasma concentration-time curve over the dosing interval ($AUC_{!}$) of rifabutin were when rifabutin was coadministered with DRV/rtv relative to administration of rifabutin alone were 72% and 93%, respectively (Table 75). The 90% CIs of the LS means ratios for AUC_{τ} and average plasma concentration at steady-state ($C_{ss,av}$) were within the 80.00% to 125.00% bounds, whereas the 90% CIs for all other comparisons were outside of the 80.00% to 125.00% bounds. There was an increase (1.5 hours) in the median t_{max} of rifabutin in the presence of DRV/rtv.

The LS mean ratios for C_{max} and $AUC_{!}$ of 25-*O*-desacetylrifabutin when rifabutin was coadministered with DRV/rtv relative to administration of rifabutin alone were 477% and 981%, respectively (Table 75). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. The metabolite-to-parent ratio of 25-*O*-desacetylrifabutin to rifabutin increased from a mean of 7.3% when rifabutin 300 mg once daily was administered alone to 73.0% when rifabutin 150 mg once every other day was coadministered with DRV/rtv. There was an increase (2.5 hours) in the median t_{max} of 25-*O*-desacetylrifabutin in the presence of DRV/rtv.

Table 75: PK Parameters of Rifabutin and 25-*O*-Desacetylrifabutin on Day 13 Following Administration of Rifabutin in the Absence and Presence of DRV/rtv (Study TMC114-C163)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Rifabutin 150 mg qod + DRV/rtv 600/100 mg bid	Rifabutin 300 mg qd	
Rifabutin			
N	11	15	
t_{max}, h	4.0 (2.0-5.0)	2.5 (1.0-6.0)	-
C_{0h}, ng/mL	116 (31.9)	67.5 (19.8)	173.0 (153.6; 194.8)
C_{min}, ng/mL	112 (34.6)	62.0 (14.2)	163.7 (148.1; 180.8)
C_{max}, ng/mL	620 (242)	565 (133)	71.71 (55.01; 93.48)
$AUC_{!}$, ng.h/mL[a]	10,790 (3,171)	4,659 (969)	93.27 (79.58; 109.3)
$C_{ss,av}$, ng/mL	225 (66.1)	194 (40.4)	93.28 (79.58; 109.3)
FI, %	216 (71.3)	260 (50.2)	-
25-*O*-Desacetylrifabutin			
N	11	15	
t_{max}, h	5.0 (2.5-12.0)	2.5 (1.5-6.0)	-
C_{0h}, ng/mL	121.0 (23.9)	4.15 (1.13)	2,897 (2,390; 3,511)
C_{min}, ng/mL	112 (26.6)	3.68 (1.11)	2,710 (2,215; 3,316)
C_{max}, ng/mL	237 (74.5)	41.0 (15.8)	476.7 (404.0; 562.5)
$AUC_{!}$, ng.h/mL[a]	7,497 (2,044)	339 (117)	981.2 (808.7; 1,191)
$AUC_{!,parent/metabolite}$ ng/mL[a]	18,670 (4,628)	5,016 (1,043)	312.8 (269.2; 363.4)
$C_{ss,av}$, ng/mL	156 (42.6)	14.1 (4.86)	981.2 (808.8; 1,190)
FI, %	78.5 (26.7)	261 (41.4)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily; qod=every other day.

[a] $AUC_{!}$ is 24h for reference and 48h for test; before statistical analysis, $AUC_{!}$ was corrected for these differences in dosage interval.

Source: Module 5.3.3.4/TMC114-C163-CRR/Table 10, Table 11, Table 12, and Table 13

2.1.7.2.9.2.3. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with rifabutin relative to administration of DRV/rtv alone were 168% and 166%, respectively (Table 76). For all comparisons, the 90% CIs of the LS means ratios were outside the 80.00% to 125.00% bounds. There was no relevant change in the median t_{max} of rtv.

Table 76: PK Parameters of rtv on Day 13 Following Administration of DRV/rtv in the Absence and Presence of Rifabutin (Study TMC114-C163)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	DRV/rtv 600/100 mg bid + + Rifabutin 150 mg qod	DRV/rtv 600/100 mg bid	
N	11	16	
t_{max}, h	4.0 (1.0-6.0)	4.5 (1.5-5.0)	-
C_{0h}, ng/mL	330 (252)	293.6 (154.7)	111.4 (54.43; 228.1)
C_{min}, ng/mL	233 (131)	176 (87.6)	130.7 (87.73; 194.6)
C_{max}, ng/mL	1,379 (641)	918 (404)	168.2 (123.6; 228.9)
AUC_{12h}, ng.h/mL	8,335 (3,772)	5,394 (2,281)	165.7 (127.1; 215.9)
$C_{ss,av}$, ng/mL	695 (314)	450 (190)	-
FI, %	170 (33.5)	165 (47.8)	-

bid=twice daily; N=maximum number of subjects with data; qod=every other day.
Source: Module 5.3.3.4/TMC114-C163-CRR/Table 8 and Table 9

2.1.7.2.9.3. Conclusion

The coadministration of rifabutin 150 mg every other day with DRV/rtv 600/100 mg twice daily. increased the mean exposure (AUC_{12h}) to DRV 1.57-fold relative to DRV/rtv 600/100 mg twice daily without rifabutin. Following coadministration with DRV/rtv, the mean exposure (AUC_{τ}) to rifabutin 150 mg every other day was decreased slightly (by 7%), compared to rifabutin 300 mg once daily without DRV/rtv; the mean exposure to 25-*O*-desacetylrifabutin was increased 9.8-fold in the presence of DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.13.

2.1.7.2.10. Ethinyl Estradiol/Norethindrone

TMC114-C131

Module 5.3.3.4/TMC114-C131-CRR

2.1.7.2.10.1. Objective

To investigate the effect of multiple doses of DRV/rtv on the steady-state PK of ethinyl estradiol and norethindrone.

2.1.7.2.10.2. Subjects and Methods

This was a Phase 1, open-label study in 19 healthy female subjects on stable oral contraceptives to investigate the PK interaction between ethinyl estradiol/norethindrone and DRV (administered as the 300-mg tablet formulation F016), together with rtv. In 2 consecutive 28 day sessions, subjects received treatments for 2 oral contraceptive cycles (Treatment A and B in a randomized sequence) separated by 7 days without oral contraceptive treatment as follows:

- Treatment A: Ethinyl estradiol/norethindrone 35 µg/1 mg once daily on Days 1 to 21.

- Treatment B: Ethinyl estradiol/norethindrone 35 µg/1 mg once daily on Days 1 to 21, and DRV/rtv 600/100 mg twice daily on Days 1 to 14.

Oral contraceptive treatment had to be administered in the morning. Darunavir and rtv were administered within 15 minutes after completing a meal. Darunavir was taken within 5 minutes after rtv intake. In case of coadministration of DRV/rtv and ethinyl estradiol/norethindrone, the oral contraceptive had to be taken first, followed by rtv (within 5 minutes), and DRV (within 5 minutes).

2.1.7.2.10.3. Results

2.1.7.2.10.3.1. DRV and rtv PK

The PK parameters of DRV and rtv after administration of DRV/rtv in the presence of ethinyl estradiol/norethindrone are shown in Table 77.

Table 77: PK Parameters of DRV and rtv on Day 14 Following Coadministration of DRV/rtv With Ethinyl Estradiol/Norethindrone (Study TMC114-C131)

Parameter	Mean (SD); t_{max}: Median (Range)	
	DRV/rtv 600/100 mg bid + Ethinyl Estradiol/Norethindrone 0.035/1 mg qd	**DRV/rtv 600/100 mg bid + Ethinyl Estradiol/Norethindrone 0.035/1 mg qd**
N	11	11
t_{max}, h	4.0 (1.5-4.0)	4.0 (3.0-5.0)
C_{0h}, ng/mL	3,583 (1,554)	534 (254)
C_{12h}, ng/mL	2,855 (1,033)	454 (260)
C_{min}, ng/mL	2,594 (1,090)	285 (129)
C_{max}, ng/mL	8,073 (988)	1,780 (864)
AUC_{12h}, ng.h/mL	55,920 (11,290)	8,548 (3,112)
$C_{ss,av}$, ng/mL	4,660 (941)	712 (259)
FI, %	122 (34.04)	207 (72.5)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C131-CRR/Table 10 and Table 12

2.1.7.2.10.3.2. Ethinyl Estradiol PK

The LS mean ratios for C_{max} and AUC_{24h} of ethinyl estradiol when ethinyl estradiol/norethindrone was coadministered with DRV/rtv relative to administration of ethinyl estradiol/norethindrone alone were 68% and 56%, respectively (Table 78).

Table 78: PK Parameters of Ethinyl Estradiol Following Administration of Ethinyl Estradiol/Norethindrone in the Absence and Presence of DRV/rtv (Study TMC114-C131)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Ethinyl Estradiol/ Norethindrone 0.035/1 mg qd + DRV/rtv 600/100 mg bid	Ethinyl Estradiol/ Norethindrone 0.035/1 mg qd	
N	11	13	
t_{max}, h	3.0 (1.0-4.0)	2.0 (1.0-4.0)	-
C_{0h}, pg/mL	9.63 (4.68)	23.7 (11.9)	-
C_{24h} pg/mL	9.43 (3.58)	24.0 (11.6)	-
C_{min}, pg/mL	8.08 (3.86)	22.3 (11.1)	38.18 (27.26; 53.46)
C_{max}, pg/mL	73.7 (17.0)	105 (29.0)	67.58 (61.40; 74.38)
AUC_{24h}, pg.h/mL	609 (151)	1,095 (400)	56.25 (50.41; 62.77)
$C_{ss,av}$, pg/mL	25.4 (6.29)	45.6 (16.7)	-
FI, %	266 (68.7)	193 (43.8)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C131-CRR/Table 6 and Table 7

2.1.7.2.10.3.3. Norethindrone PK

The LS mean ratios for C_{max} and AUC_{24h} of norethindrone when ethinyl estradiol/norethindrone was coadministered with DRV/rtv relative to administration of ethinyl estradiol/norethindrone alone were 90% and 86%, respectively (Table 79). For C_{max}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds; for C_{min} and AUC_{24h}, the lower limit of the 90% CIs was below 80.00%.

Table 79: PK Parameters of Norethindrone Following Administration of Ethinyl Estradiol/Norethindrone in the Absence and Presence of DRV/rtv (Study TMC114-C131)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Ethinyl Estradiol/ Norethindrone 0.035/1 mg qd + DRV/rtv 600/100 mg bid	Ethinyl Estradiol/ Norethindrone 0.035/1 mg qd	
N	11	13	
t_{max}, h	2.0 (1.0-4.0)	2.0 (1.0-3.0)	-
C_{0h}, ng/mL	1.58 (0.979)	2.38 (1.25)	-
$C_{24h,}$ ng/mL	1.51 (0.830)	2.32 (1.32)	-
C_{min}, ng/mL	1.42 (0.903)	2.24 (1.27)	70.09 (50.76; 96.79)
C_{max}, ng/mL	15.4 (3.85)	17.2 (4.72)	89.90 (83.08; 97.28)
AUC_{24h}, ng.h/mL	113 (33.7)	144 (54.6)	85.67 (74.60; 98.39)
$C_{ss,av}$, ng/mL	4.69 (1.41)	6.01 (2.27)	-
FI, %	308 (76.5)	266 (65.4)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C131-CRR/Table 8 and Table 9

2.1.7.2.10.4. Conclusion

Systemic exposures (AUC_{24h}) to ethinyl estradiol and norethindrone decreased by 44% and 14%, respectively, when DRV/rtv was coadministered with ethinyl estradiol/norethindrone at steady-state.

Information on dosing recommendations is available in Section 3.3.2.6.17.

2.1.7.2.11. Telaprevir

VX950-C124

Module 5.3.3.4/VX950-C124-CRR

2.1.7.2.11.1. Objective

To investigate the PK interaction between steady-state concentrations of telaprevir and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.11.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-panel, 2-way crossover study in 40 healthy subjects to investigate the PK interaction between telaprevir (a CYP3A substrate and inhibitor) and DRV/rtv (Panel 1, 20 subjects) at steady-state and between telaprevir and fosamprenavir/rtv (Panel 2) at steady-state. Darunavir was administered as the 300-mg tablet F016. Subjects were randomized to 2 panels in a 1:1 ratio. Two treatment sessions were scheduled for all subjects (for Panel 1 [DRV/rtv panel]: Treatments A and B). All subjects in Panel 1 received telaprevir alone (Treatment A) and DRV/rtv alone and coadministered with telaprevir (Treatment B), separated by a washout period of at least 13 days, as follows:

- Treatment A: Telaprevir 750 mg every 8 hours from Day 1 to Day 10 and telaprevir 1,125 mg every 12 hours from Day 11 to Day 13, with an additional dose on the morning of Day 14.
- Treatment B: DRV/rtv 600/100 mg twice daily from Day 1 to Day 23, with a single 600/100 mg dose of DRV/rtv in the morning on Day 24. Telaprevir 750 mg every 8 hours from Day 11 to Day 20, and telaprevir 1,125 mg every 12 hours from Day 21 to Day 23, with an additional dose on the morning of Day 24.

All treatments were taken under fed conditions.

2.1.7.2.11.3. Results

2.1.7.2.11.3.1. DRV PK

The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with telaprevir 750 mg every 8 hours relative to administration of DRV/rtv alone were both 60% (Table 80). The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with telaprevir 1,125 mg every 12 hours relative to administration of DRV/rtv alone were 53% and 49%, respectively. Across all treatments, there was no relevant change in the median t_{max} of DRV.

Table 80: PK Parameters of DRV Following Administration of DRV/rtv in the Absence and Presence of Telaprevir (Study VX950-C124)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Day 20 DRV/rtv 600/100 mg bid + Telaprevir 750 mg q8h	**Day 10 DRV/rtv 600/100 mg bid**	
N	14	16	
t_{max}, h	3.0 (2.0-4.0)	3.0 (1.0-4.0)	-
C_{0h}, ng/mL	1,995 (784)	3,329 (1,213)	-
C_{min}, ng/mL	1,794 (869)	2,964 (1,122)	57.56 (52.20; 63.47)
C_{max}, ng/mL	3,984 (1,061)	6,522 (1,280)	59.76 (55.92; 63.87)
AUC_{12h} ng.h/mL	32,120 (9,713)	51,940 (14,290)	59.62 (56.55; 62.86)
$C_{ss,av}$, ng/mL	2,677 (809)	4,329 (1,191)	-
FI, %	97.13 (29.37)	87.6 (27.4)	-
	Day 24 DRV/rtv 600/100 mg bid + Telaprevir 1,125 mg q12h	**Day 10 DRV/rtv 600/100 mg bid**	
N	15	16	
t_{max}, h	3.0 (1.0-4.0)	3.0 (1.0-4.0)	-
C_{0h}, ng/mL	1,777 (964)	3,329 (1,213)	-
C_{min}, ng/mL	1,392 (805)	2,964 (1,122)	42.24 (35.08; 50.87)
C_{max}, ng/mL	3,657 (1,569)	6,522 (1,280)	53.01 (47.36; 59.33)
AUC_{12h} ng.h/mL	26,780 (11,110)	51,940 (14,290)	48.56 (43.15; 54.64)
$C_{ss,av}$, ng/mL	2,232 (926)	4,329 (1,191)	-
FI, %	108 (27.5)	87.6 (27.4)	-

bid=twice daily; N=maximum number of subjects with data; q8h=every 8 hours; q12h=every 12 hours.
Source: Module 5.3.3.4/VX950-C124-CRR/Table 12 and Table 13

2.1.7.2.11.3.2. Telaprevir PK

Following an every 8 hour dosing regimen of telaprevir, the LS mean ratios for C_{max} and AUC_{8h} of telaprevir when telaprevir was coadministered with DRV/rtv relative to administration of telaprevir alone were 64% and 65%, respectively (Table 81). Following an every 12 hour dosing regimen of telaprevir, the LS mean ratios for C_{max} and AUC_{12h} of telaprevir when telaprevir was coadministered with DRV/rtv relative to administration of telaprevir alone were 65% and 69%, respectively (Table 81). For both comparisons, there was no relevant change in the median t_{max} of telaprevir. A statistically significant sequence effect was observed for the C_{max} comparison of the every 12 hour dosing regimen. This was considered not to have had an influence on the outcome of the study.

Table 81: PK Parameters of Telaprevir Following Administration of Telaprevir in the Absence and Presence of DRV/rtv (Study VX950-C124)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Day 20 Telaprevir 750 mg q8h + DRV/rtv 600/100 mg bid	**Day 10 Telaprevir 750 mg q8h**	
N	14	16	
t_{max}, h	3.75 (0.0-5.0)	4.0 (2.0-5.0)	-
C_{0h}, ng/mL	1,657 (285)	2,261 (446)	-
C_{min}, ng/mL	1,237 (207)	1,835 (381)	67.86 (62.54; 73.63)
C_{max}, ng/mL	2,000 (399)	3,061 (580)	64.24 (61.20; 67.43)
AUC_{8h} ng.h/mL	12,560 (1,909)	19,480 (3,734)	64.91 (61.23; 68.82)
$C_{ss,av}$, ng/mL	1,570 (239)	2,436 (467)	-
FI, %	47.7 (11.4)	50.6 (8.19)	-
	Day 24 Telaprevir 1,125 mg q12h + DRV/rtv 600/100 mg bid	**Day 14 Telaprevir 1,125 mg q12h**	
N	15	15	
t_{max}, h	4.0 (2.0-5.0)	3.5 (1.5-5.0)	-
C_{0h}, ng/mL	1,536 (344)	2,183 (618)	-
C_{min}, ng/mL	1,063 (241)	1,410 (373)	78.58 (71.50; 86.37)
C_{max}, ng/mL	2,193 (491)	3,429 (634)	64.99 (59.14; 71.42)
AUC_{12h} ng.h/mL	18,430 (3,550)	27,460 (5,375)	68.98 (64.08; 74.24)
$C_{ss,av}$, ng/mL	1,536 (296)	2,289 (448)	-
FI, %	73.5 (15.7)	89.7 (23.4)	-

bid=twice daily; N=maximum number of subjects with data; q8h=every 8 hours; q12h=every 12 hours.
Source: Module 5.3.3.4/VX950-C124-CRR/Table 6 and Table 7

2.1.7.2.11.3.3. VRT-127394 PK

Following an every 8 hour dosing regimen of telaprevir, the LS mean ratios for C_{max} and AUC_{8h} of VRT-127394 (R-diastereomer of telaprevir) when telaprevir was coadministered with DRV/rtv relative to administration of telaprevir alone were 72% and 71%, respectively (Table 82). There was no relevant change in the median t_{max} of VRT-127394 with the every 8 hour dosing regimen. Following an every 12 hour dosing regimen of telaprevir, the LS mean ratios for C_{max} and AUC_{12h} of VRT-127394 when telaprevir was coadministered with DRV/rtv relative to administration of telaprevir alone were 74% and 77%, respectively (Table 82). There was no change in the median t_{max} of VRT-127394 with the every 12 hour dosing regimen. A statistically significant sequence effect was observed for the C_{min} and C_{max} comparisons of the every 12 hour dosing regimen. This was considered not to have had an influence on the outcome of the study.

Table 82: PK Parameters of the Telaprevir R-Diastereomer VRT-127394 Following Administration of Telaprevir in the Absence and Presence of DRV/rtv (Study VX950-C124)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Day 20 Telaprevir 750 mg q8h + DRV/rtv 600/100 mg bid	**Day 10 Telaprevir 750 mg q8h**	
N	14	16	
t_{max}, h	3.75 (0.0-6.0)	4.0 (0.0-5.0)	-
C_{0h}, ng/mL	1,395 (228)	1,857 (461)	-
C_{min}, ng/mL	972 (169)	1,463 (315)	66.92 (58.01; 77.19)
C_{max}, ng/mL	1,502 (248)	2,088 (456)	71.68 (66.40; 77.39)
AUC_{8h} ng.h/mL	9,923 (1,152)	13,960 (2,929)	71.30 (65.38; 77.75)
$C_{ss,av}$, ng/mL	1,240 (144)	1,747 (366)	-
FI, %	43.6 (15.0)	35.6 (12.0)	-
	Day 24 Telaprevir 1,125 mg q12h + DRV/rtv 600/100 mg bid	**Day 14 Telaprevir 1,125 mg q12h**	
N	15	15	
t_{max}, h	3.5 (0.0-8.0)	4.0 (0.0-5.0)	-
C_{0h}, ng/mL	1,275 (278)	1,704 (531)	-
C_{min}, ng/mL	943 (203)	1,218 (357)	80.83 (72.97; 89.54)
C_{max}, ng/mL	1,512 (390)	2,091 (579)	74.09 (69.56; 78.91)
AUC_{12h} ng.h/mL	14,440 (3,145)	19,310 (4,517)	76.79 (72.37; 81.48)
$C_{ss,av}$, ng/mL	1,203 (262)	1,609 (376)	-
FI, %	46.4 (15.1)	54.9 (17.7)	-

bid=twice daily; N=maximum number of subjects with data; q8h=every 8 hours; q12h=every 12 hours.
Source: Module 5.3.3.4/VX950-C124-CRR/Table 9 and Table 10

2.1.7.2.11.3.4. RTV PK

The LS mean ratios for C_{max} and AUC_{12h} of rtv when DRV/rtv was coadministered with telaprevir 750 mg every 8 hours relative to administration of DRV/rtv alone were 137% and 148%, respectively (Table 83). When DRV/rtv was coadministered with telaprevir 1,125 mg every 12 hours, the LS mean ratios for C_{max} and AUC_{12h} of rtv were 117% and 116%, respectively; for all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125.00% (Table 83). For all treatments, there was no change in the median t_{max} of rtv.

Table 83: PK Parameters of rtv Following Administration of DRV/rtv in the Absence and Presence of Telaprevir (Study VX950-C124)

Parameter	Mean (SD); t_{max}: Median (Range) Test	Reference	Test/Reference Least Square Means Ratio, % (90% CI)
	Day 20 DRV/rtv 600/100 mg bid + Telaprevir 750 mg q8h	**Day 10 DRV/rtv 600/100 mg bid**	
N	14	16	
t_{max}, h	4.0 (2.0-12.0)	4.0 (2.0-5.0)	-
C_{0h}, ng/mL	486 (337)	281 (143)	-
C_{min}, ng/mL	289 (153)	200 (97.1)	137.6 (109.7; 172.8)
C_{max}, ng/mL	1,407 (485)	1,080 (457)	137.3 (121.4; 155.3)
AUC_{12h} ng.h/mL	8,662 (3,137)	6,012 (2,411)	147.5 (130.6; 166.7)
$C_{ss,av}$, ng/mL	722 (261)	501 (201)	-
FI, %	161 (37.1)	176 (43.3)	-
	Day 24 DRV/rtv 600/100 mg bid + Telaprevir 1,125 mg q12h	**Day 10 DRV/rtv 600/100 mg bid**	
N	15	16	
t_{max}, h	4.0 (4.0-5.0)	4.0 (2.0-5.0)	-
C_{0h}, ng/mL	371 (218)	281 (143)	-
C_{min}, ng/mL	230 (122)	200 (97.1)	109.1 (90.86; 131.0)
C_{max}, ng/mL	1,268 (537)	1,080 (457)	117.0 (97.23; 140.9)
AUC_{12h} ng.h/mL	6,972 (2,241)	6,012 (2,411)	115.5 (102.1; 130.6)
$C_{ss,av}$, ng/mL	581 (187)	501 (201)	-
FI, %	184 (71.0)	176 (43.3)	-

bid=twice daily; N=maximum number of subjects with data; q8h=every 8 hours; q12h=every 12 hours.
Source: Module 5.3.3.4/VX950-C124-CRR/Table 14 and Table 15

2.1.7.2.11.4. Conclusion

The mean exposure (C_{max} and AUC_{12h}) to DRV, coadministered with rtv, was decreased by approximately 40% in the presence of telaprevir 750 mg every 8 hours and was decreased by approximately 50% in the presence of telaprevir 1,125 mg every 12 hours. The mean exposure to telaprevir administered at either 750 mg every 8 hours or 1,125 mg every 12 hours was decreased approximately 30% to 35% in the presence of DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.23.

2.1.7.2.12. Atorvastatin

TMC114-C133

Module 5.3.3.4/TMC114-C133-CRR

2.1.7.2.12.1. Objective

To investigate the PK interaction between repeated doses of atorvastatin and repeated doses of DRV/rtv.

2.1.7.2.12.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 1-period crossover study in 16 healthy subjects to investigate the PK interaction between the 3-hydroxy-3-methylglutary coenzyme A (HMG-CoA) reductase inhibitor atorvastatin (a substrate of CYP3A) and DRV/rtv. Subjects were randomized to receive the following treatments in 2 sessions: atorvastatin 40 mg once daily for 4 days (Treatment A), and DRV/rtv 300/100 mg twice daily for 9 days (DRV administered as the 20 mg/mL oral solution TF019) coadministered with atorvastatin 10 mg once daily from Days 4 to 7 (Treatment B). Subsequent sessions were separated by a washout period of 6 days. All treatments were administered under fed conditions.

2.1.7.2.12.3. Results

2.1.7.2.12.3.1. DRV PK

The PK parameters of DRV after administration of DRV/rtv in the presence of atorvastatin relative to historical values in the absence of atorvastatin are shown in Table 84. The median t_{max} of DRV when DRV/rtv was coadministered with atorvastatin was slightly later relative to administration of DRV/rtv alone. The mean C_{min} and AUC_{12h} values for DRV when DRV/rtv was coadministered with atorvastatin were approximately 1.39- and 1.29-fold higher, respectively, relative to administration of DRV/rtv alone. The mean C_{max} was comparable for both treatments.

Table 84: PK Parameters of DRV Following Coadministration of DRV/rtv With Atorvastatin Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C133)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment B DRV/rtv 300/100 mg bid + Atorvastatin 10 mg qd	**Study TMC114-C124 DRV/rtv 300/100 mg bid**
N	15	12
t_{max}, h	1.5 (0.5-4.0)	0.5 (0.5-4.0)
C_{min}, ng/mL	2,569 (716)	1,845 (842)
C_{max}, ng/mL	4,121 (734)	3,971 (1,385)
AUC_{12h}, ng.h/mL	38,385 (9,235)	29,837 (10,345)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C133-CRR/Table 6; Module 5.3.3.4/TMC114-C124-CRR/Table 7

2.1.7.2.12.3.2. Atorvastatin and Atorvastatin Metabolite PK

The LS mean ratios for C_{max} and AUC_{24h} of atorvastatin when atorvastatin was coadministered with DRV/rtv relative to administration of atorvastatin alone were 56% and 85%, respectively (Table 85). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. The LS mean ratios for the C_{max} and AUC_{24h} of the metabolite atorvastatin lactone were 85% and 107%, respectively (Table 85). For AUC_{24h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds and, for C_{min} and C_{max}, the 90% CIs were outside of the 80.00% to 125.00% bounds.

The active metabolites 2- and 4-hydroxy-atorvastatin were not detected in plasma when atorvastatin was coadministered with DRV/rtv.

Table 85: PK Parameters of Atorvastatin and Atorvastatin Lactone Following Administration of Atorvastatin in the Absence and Presence of DRV/rtv (Study TMC114-C133)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B DRV/rtv 300/100 mg bid + Atorvastatin 10 mg qd	Treatment A Atorvastatin 40 mg qd	
Atorvastatin			
N	15	15	
t_{max}, h	4.0 (1.0-6.0)	1.5 (0.5-3.0)	-
C_{min}, ng/mL	1.16 (0.441)	0.668 (0.615)	181.0 (137; 240)
C_{max}, ng/mL	9.58 (4.96)	17.4 (7.93)	56.46 (47.5; 67.2)
AUC_{24h} ng.h/mL	84.4 (30.3)	102 (43.1)	85.42 (75.6; 96.5)
$t_{1/2,term}$, h	11.7 (5.83)	6.98 (1.94)	-
Atorvastatin Lactone			
N	15	15	
t_{max}, h	4.0 (3.0-6.0)	3.0 (1.5-4.0)	-
C_{min}, ng/mL	1.10 (0.518)	NQ	208.1 (163; 265)
C_{max}, ng/mL	5.61 (2.69)	6.84 (3.74)	85.43 (76.1; 95.9)
AUC_{24h} ng.h/mL	66.1 (25.2)	63.1 (29.1)	107.0 (96.3; 119)
$t_{1/2,term}$, h	12.9 (8.87)	7.57 (2.60)	-

bid=twice daily; N=maximum number of subjects with data; NQ=not quantifiable; qd=once daily.
Source: Module 5.3.3.4/TMC114-C133-CRR/Table 8, Table 9, Table 10, and Table 11

2.1.7.2.12.3.3. RTV PK

The PK parameters of rtv after administration of DRV/rtv in the presence of atorvastatin relative to historical values in the absence of atorvastatin are shown in Table 86. The median t_{max} of rtv when DRV/rtv was coadministered with atorvastatin was later relative to administration of DRV/rtv alone. The mean C_{min} and AUC_{12h} values for rtv when DRV/rtv was coadministered with atorvastatin were approximately 1.5- and 1.2-fold higher, respectively, relative to administration of DRV/rtv alone. The mean C_{max} was comparable for both treatments.

Table 86: PK Parameters of rtv Following Coadministration of DRV/rtv With Atorvastatin Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C133)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment B DRV/rtv 300/100 mg bid + Atorvastatin 10 mg qd	Study TMC114-C124 DRV/rtv 300/100 mg bid
N	15	12
t_{max}, h	6.0 (4.0-10.0)	4.0 (2.0-6.0)
C_{min}, ng/mL	265 (69.9)	174 (84.6)
C_{max}, ng/mL	1,049 (445)	1,030 (343)
AUC_{12h}, ng.h/mL	6,906 (2,266)	5,811 (1,960)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.3.4/TMC114-C133-CRR/Table 7

2.1.7.2.12.4. Conclusion

The mean exposure (AUC_{24h}) to atorvastatin was decreased by 15% when atorvastatin was coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.25.

2.1.7.2.13. Pravastatin

TMC114-C120

Module 5.3.3.4/TMC114-C120-CRR

2.1.7.2.13.1. Objective

To investigate the PK interaction between a single dose of pravastatin and repeated doses of DRV/rtv.

2.1.7.2.13.2. Subjects and Methods

This was a Phase 1, open-label, randomized, crossover study in 14 healthy subjects to investigate the PK interaction between the HMG-CoA reductase inhibitor pravastatin (a substrate of CYP3A) and DRV (administered as the oral solution TF019), together with rtv. Most HMG-CoA reductase inhibitors, like lovastatin and simvastatin, should not be coadministered with PIs used for treating HIV because both drug types are metabolized by CYP3A.[29,59] Subjects were randomized to 1 of 2 groups. Group 1 received a single dose of 40 mg pravastatin (Treatment A) in Session 1. In Session 2, DRV/rtv 600/100 mg twice daily was administered for 7 days. On Day 7, a single dose of pravastatin 40 mg was coadministered with DRV/rtv (Treatment B). Group 2 received Treatment B in Session 1 and Treatment A in Session 2. Subsequent sessions were separated by a washout period of at least 6 days. All treatments were administered under fed conditions.

2.1.7.2.13.3. Results

2.1.7.2.13.3.1. DRV PK

The PK of DRV, coadministered with rtv, in the absence and presence of pravastatin are shown in Table 87. To assess the effect of pravastatin on the PK of DRV, parameters from the current study were compared with historical data from study TMC114-C207, in which subjects were also treated with DRV/rtv 600/100 mg twice daily (Module 5.3.5.1/TMC114-C207-CRR). Study TMC114-C207 was performed in highly experienced HIV-1 infected subjects, and the PK of DRV were determined on Day 14. Although study TMC114-C207 was performed in HIV-1 infected subjects, there is no indication that coadministration of a single dose of pravastatin had a relevant impact on the PK of DRV coadministered with rtv.

Table 87: PK Parameters of DRV Following Administration of DRV/rtv With Pravastatin Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C120)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment B DRV/rtv 600/100 mg bid + Pravastatin 40 mg Day 7 (Healthy Subjects)	Study TMC114-C207 DRV/rtv 600/100 mg bid Day 14 (HIV-1 Infected Subjects)
N	14	11
t_{max}, h	0.5 (0.5-4.0)	0.5 (0.5-1.0)
C_{min}, ng/mL	2,393 (988)	1,928 (1,223)
C_{max}, ng/mL	5,447 (1,703)	6,008 (1,617)
AUC_{12h}, ng.h/mL	40,355 (13,559)	36,986 (16,444)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C120-CRR/Table 7

2.1.7.2.13.3.2. Pravastatin PK

The LS mean ratios for C_{max} and AUC_{24h} of pravastatin when pravastatin was coadministered with DRV/rtv relative to administration of pravastatin alone were 163% and 181%, respectively (Table 88). There was no relevant change in the median t_{max} of DRV.

Table 88: PK Parameters of Pravastatin Following Administration of Pravastatin in the Absence and Presence of DRV (Study TMC114-C120)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B Pravastatin 40 mg + DRV/rtv 600/100 mg bid	Treatment A Pravastatin 40 mg	
N	14	14	
t_{max}, h	1.5 (1.0-3.0)	1.0 (0.5-3.0)	-
C_{max}, ng/mL	86.9 (88.4)	50.9 (67.6)	163.4 (94.9; 282)
AUC_{last} ng.h/mL	175 (159)	92.0 (86.4)	181.0 (123; 266)
$t_{1/2,term}$, h	1.30 (0.296)	1.79 (0.757)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C120-CRR/Table 5 and Table 6

2.1.7.2.13.3.3. RTV PK

The PK of rtv, coadministered with DRV, in the absence and presence of pravastatin are shown in Table 89. When compared with historical data from studies TMC114-C207 (in HIV-1 infected subjects) and TMC114-C112 (in healthy subjects), the coadministration of pravastatin did not appear to affect the PK of rtv.

Table 89: PK Parameters of rtv Following Administration of DRV/rtv With Pravastatin Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C120)

Parameter	Mean (SD); t_{max}: Median (Range)		
	Study TMC114-C120 Treatment B DRV/rtv 600/100 mg bid + Pravastatin 40 mg (Healthy Subjects)	**Study TMC114-C207 DRV/rtv 600/100 mg bid Day 14 (HIV-1 Infected Subjects)**	**Study TMC114-C112 DRV/rtv 300/100 mg bid Day 7 (Healthy Subjects)**
N	14	11	8
t_{max}, h	6.0 (1.5-6.0)	3.0 (0.5-8.0)	6.0 (4.0-9.0)
C_{min}, ng/mL	137 (103)	113 (43.7)	118 (56.4)
C_{max}, ng/mL	582 (354)	423 (275)	514 (149)
AUC_{12h}, ng.h/mL	3,894 (2,156)	3,113 (1,377)	3,806 (1,194)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C120-CRR/Table 8

2.1.7.2.13.4. Conclusion

The mean exposure (AUC_{24h}) to pravastatin was increased in the presence of DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.25.

2.1.7.2.14. Buprenorphine/Naloxone

TMC114-C171

Module 5.3.3.4/TMC114-C171-CRR

2.1.7.2.14.1. Objective

To investigate the PK interaction between steady-state concentrations of buprenorphine/naloxone and steady-state concentrations of DRV, coadministered with rtv.

2.1.7.2.14.2. Subjects and Methods

This was a Phase 1, open-label, add-on study in 17 non-HIV-1 infected subjects who were on stable buprenorphine/naloxone maintenance therapy to investigate the PK interaction between buprenorphine/naloxone and DRV, administered as the 300-mg tablet formulation F016, together with rtv, at steady-state. All subjects received DRV/rtv at 600/100 mg twice daily on Days 1 to 7 added to their buprenorphine/naloxone therapy (maximum dose of 24/6 mg once daily [sublingual]).

Buprenorphine/naloxone was taken before noon from Day #14 until Day #3. On Day #2, buprenorphine/naloxone intake took place between 7:30 and 9:30 a.m. On Days #1 to 8, buprenorphine/naloxone was taken within 10 minutes after completion of a breakfast and immediately after DRV/rtv intake, if applicable (ie, on Days 1 to 7). Darunavir and rtv (Days 1 to 7) were administered within 10 minutes after a meal. Darunavir was taken within 5 minutes after rtv intake.

2.1.7.2.14.3. Results

2.1.7.2.14.3.1. DRV PK

The PK parameters of DRV after administration of DRV/rtv in the presence of buprenorphine/naloxone relative to historical values in the absence of buprenorphine/naloxone are shown in Table 90. There was no relevant change in the median t_{max} of DRV when DRV/rtv was coadministered with buprenorphine/naloxone relative to administration of DRV/rtv alone. Exposure to DRV when DRV/rtv was coadministered with buprenorphine/naloxone was comparable to historical values.

Table 90: PK Parameters of DRV Following Coadministration of DRV/rtv With Buprenorphine/ Naloxone Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C171)

Parameter	Mean (SD); t_{max}: Median (Range)		
	DRV/rtv 600/100 mg bid + Buprenorphine/Naloxone	DRV/rtv 600/100 mg bid (Historical data: TMC114-C123)	DRV/rtv 600/100 mg bid (Historical data: TMC114-C163)
N	17	17	16
t_{max}, h	3.0 (1.0-5.0)	3.0 (2.0-5.0)	4.0 (1.0-9.0)
C_{0h}, ng/mL	3,450 (944)	2,742 (625)	2,768 (1,077)
C_{min}, ng/mL	3,132 (1,006)	2,353 (744)	2,349 (1,006)
C_{max}, ng/mL	6,894 (1,654)	5,908 (917)	5,874 (1,637)
AUC_{12h}, ng.h/mL	58,550 (17,200)	44,750 (7,773)	46,720 (15,430)
$C_{ss,av}$, ng/mL	4,879 (1,434)	3,729 (648)	3,893 (1,286)
FI, %	80.3 (24.5)	98.4 (29.4)	93.80 (23.4)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C171-CRR/Table 6

2.1.7.2.14.3.2. Buprenorphine PK

The LS mean ratios for C_{max} and AUC_{24h} of buprenorphine when buprenorphine/naloxone was coadministered with DRV/rtv relative to administration of buprenorphine alone were 92% and 89%, respectively (Table 91). The 90% CIs for the LS mean ratios for C_{min} were within the 80.00% to 125.00% bounds, whereas the 90% CIs for all other comparisons were marginally outside the 80.00% to 125.00% range. The ISV for the PK parameters was comparable between the treatments, with values ranging from 50% to 69% (refer to Module 5.3.3.4/TMC114-C171-CRR/Section 4.2.6.2). These high ISV values are partly related to the difference in administered dose between subjects (8 or 16 mg for buprenorphine). The dose normalized %CV values ranged from 38% to 51%. There was no change in the median t_{max} of buprenorphine.

The LS mean ratios for C_{max} and AUC_{24h} of the buprenorphine metabolite norbuprenorphine when buprenorphine/naloxone was coadministered with DRV/rtv relative to administration of buprenorphine/naloxone alone were 136% and 146%, respectively (Table 91). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. The ISV for these PK parameters was comparable between the treatments, with values ranging from 87% to 102% (refer to Module 5.3.3.4/TMC114-C171-CRR/Section 4.2.7.2). These high values are partly related to the difference in administered dose between subjects (8 or 16 mg for buprenorphine). The dose normalized %CV values ranged from 61% to 70%.

Table 91: PK Parameters of Buprenorphine and Norbuprenorphine Following Administration of Buprenorphine/Naloxone in the Absence and Presence of DRV/rtv (Study TMC114-C171)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Buprenorphine/Naloxone + DRV/rtv 600/100 mg bid	Buprenorphine/Naloxone	
Buprenorphine			
N	17	18	
t_{max}, h	2.0 (1.0-3.0)	2.0 (1.0-9.0)	-
C_{0h}, ng/mL	0.840 (0.550)	0.887 (0.611)	92.21 (76.04; 111.8)
C_{min}, ng/mL	0.751 (0.503)	0.730 (0.452)	97.69 (82.27; 116.0)
C_{max}, ng/mL	3.99 (2.30)	3.90 (1.98)	92.06 (78.60; 107.8)
AUC_{24h}, ng.h/mL	38.2 (25.0)	37.5 (18.7)	89.40 (78.13; 102.3)
$C_{ss,av}$, ng/mL	1.59 (1.04)	1.56 (0.777)	-
FI, %	206 (75.5)	207 (66.8)	-
Norbuprenorphine			
N	17	18	
t_{max}, h	6.0 (0.5-24.0)	7.0 (1.0-24.0)	
C_{0h}, ng/mL	3.94 (3.99)	1.96 (1.97)	184.5 (138.0; 246.6)
C_{min}, ng/mL	3.28 (2.95)	1.80 (1.82)	171.3 (129.4; 226.8)
C_{max}, ng/mL	5.58 (5.71)	3.56 (3.24)	135.8 (106.3; 173.5)
AUC_{24h}, ng.h/mL	103 (96.4)	61.4 (53.5)	145.6 (114.6; 184.9)
Ratio $AUC_{24h, Metabolite/Parent}$ (%)	278 (138)	171 (111)	-
$C_{ss,av}$, ng/mL	4.31 (4.02)	2.56 (2.23)	-
FI, %	50.3 (24.9)	69.3 (18.5)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C171-CRR/Table 8, Table 10, Table 11, and Table 13

2.1.7.2.14.3.3. Naloxone PK

The PK parameters of naloxone after administration of DRV/rtv in the presence of buprenorphine/naloxone are shown in Table 92. Mean C_{max} and AUC_{24h} for naloxone were comparable when buprenorphine/naloxone was coadministered with DRV/rtv, compared to administration of buprenorphine/naloxone alone. The ISV for C_{max} increased from 28% to 68%, and the ISV for AUC_{24h} increased from 55% to 73% when buprenorphine/naloxone was coadministered with DRV/rtv relative to administration of buprenorphine/naloxone alone (refer to Module 5.3.3.4/TMC114-C171-CRR/Section 4.2.8.2).

Table 92: PK Parameters of Naloxone Following Administration of Buprenorphine/Naloxone in the Absence and Presence of DRV/rtv (Study TMC114-C171)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Test	Reference
	DRV/rtv 600/100 mg bid + Buprenorphine/Naloxone	Buprenorphine/Naloxone
N	11	12
t_{max}, h	1.0 (0.5-1.5)	0.75 (0.5-2.0)
C_{0h}, ng/mL	NQ	NQ
C_{min}, ng/mL	NQ	NQ
C_{max}, ng/mL	0.242 (0.163)	0.204 (0.056)
AUC_{24h}, ng.h/mL	0.401 (0.292)	0.354 (0.196)

bid=twice daily; N=maximum number of subjects with data; NQ=not quantifiable.
Source: Module 5.3.3.4/TMC114-C171-CRR/Table 14

2.1.7.2.14.3.4. RTV PK

The PK parameters of rtv after administration of DRV/rtv in the presence of buprenorphine/naloxone relative to historical values in the absence of buprenorphine/naloxone are shown in Table 93. Exposure to rtv when DRV/rtv was coadministered with buprenorphine/naloxone was comparable to historical values.

Table 93: PK Parameters of rtv Following Coadministration of DRV/rtv With Buprenorphine/Naloxone Compared With Historical Data for DRV/rtv Administration Alone (Study TMC114-C171)

Parameter	Mean (SD); t_{max}: Median (Range)		
	DRV/rtv bid 600/100 mg + Buprenorphine/Naloxone	DRV/rtv 600/100 mg bid (Historical data: TMC114-C123)	DRV/rtv 600/100 mg bid (Historical data: TMC114-C163)
N	17	16	16
t_{max}, h	5.0 (1.0-12.0)	4.0 (1.0-5.0)	4.5 (1.5-5.0)
C_{0h}, ng/mL	326 (169)	235 (124)	294 (155)
C_{min}, ng/mL	216 (108)	162 (78.9)	176 (87.6)
C_{max}, ng/mL	825 (374)	1,063 (488)	918 (404)
AUC_{12h}, ng.h/mL	5,452 (1,895)	5,787 (2,427)	5,394 (2,281)
$C_{ss,av}$, ng/mL	454 (158)	482 (202)	450 (190)
FI, %	133 (52.4)	185 (32.9)	165 (47.8)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C171-CRR/Table 7

2.1.7.2.14.4. Conclusion

The mean exposure (AUC_{24h}) to buprenorphine and naloxone was generally comparable when administered in the presence and absence of DRV/rtv. In contrast, mean norbuprenorphine C_{max} and AUC_{24h} were increased 1.36- and 1.46-fold, respectively, when buprenorphine/naloxone was coadministered with DRV/rtv. Mean DRV and rtv exposures in the presence of buprenorphine/naloxone were comparable with historical data. None of the subjects required a dose adjustment of buprenorphine/naloxone during coadministration with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.29.

2.1.7.2.15. Methadone

TMC114-C127

Module 5.3.3.4/TMC114-C127-CRR

2.1.7.2.15.1. Objective

To investigate the effect of DRV/rtv on methadone PK.

2.1.7.2.15.2. Subjects and Methods

This was a Phase 1, open-label, add-on study to investigate the PK interaction between steady-state DRV (administered as the 300-mg tablet formulation F016), together with rtv, and methadone in subjects on stable methadone therapy. Methadone is primarily metabolized by *N*-demethylation to an inactive metabolite, 2 ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidene (EDDP). Many methadone interactions are substantial and clinically relevant, such as the marked decrease in methadone concentrations that is seen when EFV is coadministered.[2,8] Such interactions can induce withdrawal symptoms and warrant close monitoring. While the metabolism of methadone is variable and not fully understood, CYP enzymes, primarily CYP3A and to a lesser extent CYP2D6 and 2B6, have been associated with the conversion of methadone to EDDP and other inactive metabolites, which are excreted mainly in urine.[28]

A total of 16 non-HIV-1 infected subjects on stable methadone therapy received DRV/rtv 600/100 mg twice daily for 7 days added to their current, individualized methadone therapy (doses ranged from 55 to 150 mg/day, refer to Module 5.3.3.4/TMC114-C127-CRR/Section 4.1.5). Darunavir/rtv was administered under fed conditions within 10 minutes after a meal. Methadone was administered immediately after DRV/rtv intake.

2.1.7.2.15.3. Results

2.1.7.2.15.3.1. DRV and rtv PK

The PK parameters of DRV and rtv after administration of DRV/rtv in the presence of methadone are shown in Table 94.

Table 94: PK Parameters of DRV and rtv Following Coadministration of DRV/rtv With Methadone in Subjects on Stable Methadone Therapy (Study TMC114-C127)

Parameter	Mean (SD); t_{max}: Median (Range)	
	DRV/rtv 600/100 mg bid	DRV/rtv 600/100 mg bid
N	16	16
t_{max}, h	3.0 (1.5-5.0)	4.0 (3.0-6.0)
C_{min}, ng/mL	3,064 (1,461)	202 (104)
C_{max}, ng/mL	6,762 (1,730)	861 (648)
AUC_{12h}, ng.h/mL	55,130 (18,870)	5,659 (3,256)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C127-CRR/Table 11 and Table 12

2.1.7.2.15.3.2. R(-) Methadone and S(+) Methadone PK

The LS mean ratios for C_{max} and AUC_{24h} when methadone was coadministered with DRV/rtv relative to administration of methadone alone were 76% and 85%, respectively, for R(-) methadone and 56% and 64%, respectively, for S(+) methadone (Table 95). For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds. There was no change in the median t_{max} of R(-) methadone and no relevant change in the median t_{max} of S(+) methadone.

Table 95: PK Parameters of R(-) and S(+) Methadone in Subjects on Stable Methadone Therapy in the Absence and Presence of DRV/rtv (Study TMC114-C127)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Methadone [a] + DRV/rtv 600/100 mg bid	Methadone [a]	
R(-) Methadone			
N	16	16	
t_{max}, h	4.0 (2.0-6.0)	4.0 (1.5-6.0)	-
C_{min}, ng/mL	125 (66.4)	140 (53.7)	85.24 (77.36; 93.92)
C_{max}, ng/mL	184 (84.4)	237 (86.8)	75.99 (71.17; 81.12)
AUC_{24h}, ng.h/mL	3,657 (1,825)	4,161 (1,542)	84.50 (78.18; 91.33)
S(+) Methadone			
N	16	16	
t_{max}, h	4.0 (1.0-6.0)	3.0 (1.5-6.0)	-
C_{min}, ng/mL	84.5 (53.4)	134 (70.5)	60.15 (52.59; 68.81)
C_{max}, ng/mL	163 (84.9)	275 (111)	56.34 (50.90; 62.37)
AUC_{24h}, ng.h/mL	2,898 (1,607)	4,318 (1,994)	64.10 (57.72; 71.19)

bid=twice daily; N=maximum number of subjects with data.
[a] Subjects received individualized doses of methadone, ranging from 55 to 150 mg/day (Module 5.3.3.4/TMC114-C127-CRR/Section 4.1.5).
Source: Module 5.3.3.4/TMC114-C127-CRR/Table 7, Table 8, Table 9, and Table 10

2.1.7.2.15.4. Pharmacodynamic Assessment of Methadone Withdrawal

There were no increases in symptoms of opiate withdrawal during the study, and no methadone dose adjustments were needed during the coadministration phase, indicating the lack of any clinically relevant interaction when DRV/rtv was coadministered with methadone (Module 5.3.3.4/TMC114-C127-CRR/Section 4.3.5.1.2).

2.1.7.2.15.5. Conclusion

The mean exposure (AUC_{24h}) to the biologically active R(-) methadone was decreased by 15% when methadone was coadministered with DRV/rtv, and the mean exposure to the biologically inactive S(+) methadone was decreased by 36% when methadone was coadministered with DRV/rtv. However, there were no increases in symptoms of opiate withdrawal.

Information on dosing recommendations is available in Section 3.3.2.6.29.

2.1.7.2.16. Sildenafil

TMC114-C128

Module 5.3.3.4/TMC114-C128-CRR

2.1.7.2.16.1. Objective

To investigate the effect of steady-state concentrations of DRV, coadministered with rtv, on the PK of a single-dose of sildenafil.

2.1.7.2.16.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-way crossover study in 16 healthy male subjects to investigate the effect of repeated doses of DRV (400-mg tablet formulation F001), coadministered with rtv, on the PK of sildenafil (a CYP3A substrate[52]) and its active metabolite *N*-desmethyl sildenafil. In 2 sessions, each subject received the following treatments: sildenafil administered as a single dose of 100 mg (Treatment A) and DRV/rtv 400/100 mg twice daily for 8 days, with a single dose of 25 mg sildenafil coadministered on Day 7 (Treatment B). Subsequent sessions were separated by a washout period of 7 days. All treatments were administered under fed conditions.

2.1.7.2.16.3. Results

2.1.7.2.16.3.1. DRV and rtv PK

The PK parameters of DRV and rtv after administration of DRV/rtv in the presence of sildenafil are shown in Table 96.

Table 96: PK Parameters of DRV and rtv Following Coadministration of DRV/rtv With Sildenafil (Study TMC114-C128)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment B DRV/rtv 400/100 mg bid + Sildenafil 25 mg	Treatment B DRV/rtv 400/100 mg bid + Sildenafil 25 mg
N	16	16
t_{max}, h	3.0 (1.0-5.0)	5.0 (1.0-5.0)
C_{min}, ng/mL	2,271 (1,062)	287 (127)
C_{max}, ng/mL	5,053 (1,255)	1,386 (883)
AUC_{12h}, ng.h/mL	41,033 (13,944)	7,789 (3,188)

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C128-CRR/Table 6 and Table 7

2.1.7.2.16.3.2. Sildenafil and *N*-Desmethyl Sildenafil PK

The LS mean ratios for C_{max} and AUC_{last} of sildenafil when sildenafil was coadministered with DRV/rtv relative to administration of sildenafil alone were 62% and 97%, respectively (Table 97). The 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds for C_{max} and contained within the 80.00% to 125.00% bounds for AUC_{last}. There was no change in the median t_{max} of sildenafil. The LS mean ratios for C_{max} and AUC_{last} of *N*-desmethyl sildenafil when sildenafil was coadministered with DRV/rtv relative to administration of sildenafil alone were 4.6% and 5.4%, respectively (Table 97). The median t_{max} of *N*-desmethyl sildenafil was later when sildenafil was coadministered with DRV/rtv relative to administration of sildenafil alone (4.0 hours versus 2.5 hours).

Table 97: PK Parameters of Sildenafil and *N*-Desmethyl Sildenafil Following Administration of Sildenafil in the Absence and Presence of DRV/rtv (Study TMC114-C128)

Parameter	Mean (SD); t_{max}: Median (Range)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B DRV/rtv 400/100 mg bid + Sildenafil 25 mg	Treatment A Sildenafil 100 mg	
Sildenafil			
N	16	16	
t_{max}, h	3.0 (1.5-4.0)	3.0 (1.0-4.0)	-
C_{max}, ng/mL	181 (90.5)	283 (84.0)	62.08 (54.8; 70.3)
AUC_{last} ng.h/mL	1,173 (481)	1,197 (377)	97.10 (86.4; 109)
$t_{1/2,term}$, h	4.36 (0.955)	3.10 (0.759)	-
***N*-Desmethyl Sildenafil**			
N	16	16	
t_{max}, h	4.0 (2.0-16.0)	2.5 (1.0-4.0)	-
C_{max}, ng/mL	4.32 (2.39)	95.8 (49.0)	4.57 (3.87; 5.40)
AUC_{last} ng.h/mL	31.7 (27.4)	401 (195)	5.42 (3.50; 8.40)
$t_{1/2,term}$, h	-	4.06 (1.11)	-

bid=twice daily; N=maximum number of subjects with data.
Source: Module 5.3.3.4/TMC114-C128-CRR/Table 8, Table 9, Table 10, and Table 11

2.1.7.2.16.4. Conclusion

The mean C_{max} of sildenafil was decreased when sildenafil was coadministered with DRV/rtv, and the mean AUC_{last} was unaffected. The mean exposure (C_{max} and AUC_{last}) to the active metabolite, *N*-desmethyl sildenafil, was considerably decreased when sildenafil was coadministered with DRV/rtv.

Information on dosing recommendations is available in Section 3.3.2.6.31.

2.1.8. Extrinsic Factor PK: Concomitant Administration of COBI With Other Drugs

2.1.8.1. CYP and P-gp Probe Substrates

GS-US-216-0112

Module 5.3.3.4/GS-US-216-0112-CSR

2.1.8.1.1. Objective

To investigate the effect of COBI on CYP isoforms 2B6 and 2D6, and the drug efflux transporter P-gp using validated phenotyping probes.

2.1.8.1.2. Subjects and Methods

This was a Phase 1, open-label, crossover study in 53 healthy subjects to assess the effects of COBI (150-mg tablet) on selected CYPs (2D6 and 2B6) and on the drug efflux transporter P-gp. Subjects were enrolled into 1 of 3 cohorts. Within each cohort, subjects were randomized to 1 of 2 treatment sequences to receive the following treatments:

Cohort 1 (CYP2D6):

- Treatment A (reference): Desipramine 50 mg, administered orally as a single dose in the morning.
- Treatment B (test): COBI 150 mg, administered orally once daily in the morning for 10 consecutive days, and desipramine 50 mg administered orally as a single dose in the morning on Day 10.

Cohort 2 (P-gp):

- Treatment C (reference): Digoxin 0.5 mg, administered orally as a single dose in the morning.
- Treatment D (test): COBI 150 mg, administered orally once daily in the morning for 10 consecutive days, and digoxin 0.5 mg administered orally as a single dose in the morning on Day 10.

Cohort 3 (CYP2B6):

- Treatment E (reference): EFV 600 mg, administered orally as a single dose in the morning.
- Treatment F (test): COBI 150 mg, administered orally once daily in the morning for 10 consecutive days, and EFV 600 mg, administered orally as a single dose in the morning on Day 10.

All treatments were administered under fed conditions within 5 minutes after a meal.

2.1.8.1.3. Results

2.1.8.1.3.1. PK of COBI

The PK parameters of COBI following administration of COBI in the presence of CYP2D6, CYP2B6, and P-gp probe substrates are shown in Table 98.

Table 98: PK Parameters of COBI Following Coadministration of Multiple Doses of COBI With a Single Dose of Desipramine, Digoxin, or EFV (Study GS-US-216-0112)

Parameter	Mean (%CV)		
	COBI 150 mg qd + Desipramine 50 mg	COBI 150 mg qd + Digoxin 0.5 mg	COBI 150 mg qd + EFV 600 mg
N	9	22	17
C_{24h}, ng/mL[a]	146 (63.5)	116 (75.1)	104 (87.9)
C_{max}, ng/mL	1,905 (16.2)	1,817 (22.1)	1,693 (19.9)
AUC_{24h}, ng.h/mL[b]	17,850 (25.5)	15,638 (30.6)	14,784 (32.5)

qd=once daily.
[a] Reported as C_{τ}.
[b] Reported as AUC_{τ}.
Source: Module 5.3.3.4/GS-US-216-0112-CSR

2.1.8.1.3.2. Desipramine, Digoxin, and EFV PK

The LS mean ratios for C_{max}, AUC_{last}, and AUC_{∞} of desipramine when desipramine was coadministered with COBI relative to administration of desipramine alone were 124%, 158%, and 165%, respectively (Table 99). The LS mean ratios for C_{max}, AUC_{last}, and AUC_{∞} of digoxin when digoxin was coadministered with COBI relative to administration of digoxin alone were 141%, 120%, and 108%, respectively. The LS mean ratios for C_{max}, AUC_{last}, and AUC_{∞} of EFV when EFV was coadministered with COBI relative to administration of EFV alone were 87%, 93%, and 93%, respectively. Values for EFV were similar when 1 outlier was excluded from this cohort (ie, Cohort 3).

Table 99: PK Parameters of Desipramine, Digoxin, and EFV Following Single-Dose Administration of Desipramine, Digoxin, and EFV in the Absence and Presence of COBI (Study GS-US-216-0112)

Parameter	Mean (%CV)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Desipramine 50 mg + COBI 150 mg qd	**Desipramine 50 mg**	
N	8	8	
C_{max}, ng/mL	33.2 (28.2)	27.9 (43.6)	124.31 (107.54; 143.68)
AUC_{last}, ng.h/mL	970 (51.2)	651 (66.3)	157.52 (134.88; 183.95)
AUC_{∞}, ng.h/mL	1,205 (64.7)	752 (83.3)	165.41 (135.76; 201.54)
	Digoxin 0.5 mg + COBI 150 mg qd	**Digoxin 0.5 mg**	
N	22	22	
C_{max}, ng/mL	2.5 (32.3)	1.7 (24.9)	140.95 (128.52; 154.58)
AUC_{last}, ng.h/mL	26.5 (28.1)	22.0 (28.2)	119.60 (109.98; 130.06)
AUC_{∞}, ng.h/mL	34.7 (26.6)	31.9 (24.1)	107.73 (99.58; 116.55)
	EFV 600 mg + COBI 150 mg qd	**EFV 600 mg**	
N	17	17	
C_{max}, ng/mL	3,866 (20.6)	4,400.2 (14.4)	86.62 (79.59; 94.27)
AUC_{last}, ng.h/mL	129,807 (29.1)	139,120 (26.2)	92.84 (89.70; 96.09)
AUC_{∞}, ng.h/mL	150,255 (27.2)	161,454 (25.5)	92.88 (89.22; 96.69)

qd=once daily.
Source: Module 5.3.3.4/GS-US-216-0112-CSR

2.1.8.1.4. Conclusion

Coadministration of COBI with desipramine resulted in CYP2D6 inhibition, as indicated by 1.24- to 1.65-fold increases in desipramine exposure (C_{max} and AUC values, respectively). Cobicistat may be classified as a mild CYP2D6 inhibitor based on the less than 2-fold increase in desipramine exposure parameters with coadministration as per Committee for Human Medicinal Products guidelines.[16] Coadministration of COBI and digoxin may have resulted in transient inhibition of gut P-gp, as evidenced by a 1.41-fold increase in digoxin C_{max}. A small reduction (13%) in the C_{max} of EFV was observed upon coadministration with COBI.

Information on dosing recommendations for digoxin is available in Section 3.3.2.6.3. Information on dosing recommendations for EFV is available in Section 3.3.2.2.1. Information on dosing recommendations for desipramine is available in Section 3.3.2.6.8.

2.1.8.2. EVG

GS-US-201-0104

Module 5.3.3.4/GS-US-201-0104-CSR

2.1.8.2.1. Objective

To investigate the PK of DRV when administered alone or coadministered with both COBI and EVG.

2.1.8.2.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-way, crossover study in 18 healthy subjects to evaluate the single-dose PK and safety of DRV alone and the multiple-dose PK and safety of DRV and EVG when coadministered with COBI (150-mg tablet). The investigational PI GS-8374 was also assessed in this study, but these data are not presented, as they are not relevant to the current submission. Subjects were randomized to 1 of 2 treatment sequences (ACD or BDC) in a 1:1 ratio and received the following treatments:

- Treatment A: GS-8374 600 mg single dose on the morning of Day 1.
- Treatment B: DRV 800 mg single dose on the morning of Day 1.
- Treatment C: GS-8374 600 mg, EVG 150 mg, and COBI 150 mg administered together once daily in the morning for 10 consecutive days (Days 2 to 11 for Treatment Sequence 1, and Days 13 to 22 for Treatment Sequence 2).
- Treatment D: DRV 800 mg, EVG 150 mg, and COBI 150 mg, administered together orally once daily in the morning for 10 consecutive days (Days 2 to 11 for Treatment Sequence 2, and Days 13 to 22 for Treatment Sequence 2)

All treatments were administered under fed conditions within 5 minutes after a meal.

2.1.8.2.3. Results

2.1.8.2.3.1. PK of COBI

The PK of COBI when coadministered with DRV and EVG are shown in Table 100.

Table 100: PK Parameters of COBI Following Coadministration of Multiple Doses of COBI With DRV and EVG (Study GS-US-201-0104)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)
	COBI 150 mg qd +DRV 800 mg qd + EVG 150 mg qd
N	18
t_{max}, h	4.00 (3.50; 4.50)
C_{24h}, ng/mL[a]	15.5 (93.6)
C_{max}, ng/mL	1,257 (18.7)
AUC_{24h}, ng.h/mL[b]	8,677 (24.3)
$t_{1/2,term}$, h	2.8 (2.6; 2.9)
CL/F, mL/h	18,151 (21.2)

Q=quartile; qd=once daily.
[a] Reported as C_{τ}.
[b] Reported as AUC_{τ}.
Source: Module 5.3.3.4/GS-US-201-0104-CSR/Table 4.6

2.1.8.2.3.2. PK of DRV

Following multiple-dose coadministration of DRV with EVG and COBI, the mean AUC_{24h} of DRV was increased approximately 6-fold relative to the mean AUC_{∞} of DRV following single-dose administration of DRV alone; mean C_{max} was increased 2.5-fold (Table 101). There was no relevant change in the median t_{max} of DRV.

Table 101: PK Parameters of DRV Following a Single Dose of DRV Alone or Multiple-Doses of DRV Coadministered With EVG and COBI (Study GS-US-201-0104)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)	
	DRV 800 mg Single Dose	**DRV 800 mg qd + COBI 150 mg qd + EVG 150 mg qd**
N	9	18
t_{max}, h	3.00 (2.00; 3.50)	3.75 (3.00; 4.50)
C_{24h}, ng/mL[a]	-	1,046 (69.8)
C_{max}, ng/mL	3,369 (38.6)	8,515 (17.3)
AUC_{24h}, ng.h/mL[b]	-	78,909 (27.3)
AUC_{last}, ng.h/mL	11,806 (47.0)	-
AUC_{∞}, ng.h/mL	13,269 (44.1)	-
$t_{1/2,term}$, h	8.6 (4.8; 10.4)	7.0 (5.7; 8.5)
CL/F, mL/h	72,728 (58.4)	11,010 (33.1)

Q=quartile; qd=once daily.
[a] Reported as C_{τ}.
[b] Reported as AUC_{τ}.
Source: Module 5.3.3.4/GS-US-201-0104-CSR/Table 4.3 and Table 4.4

2.1.8.2.3.3. PK of EVG

The PK of EVG when coadministered with DRV and COBI are shown in Table 102.

Table 102: PK Parameters of EVG Following Coadministration of Multiple Doses of EVG With DRV and COBI (Study GS-US-201-0104)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)
	EVG 150 mg qd + COBI 150 mg qd + DRV 800 mg qd
N	18
t_{max}, h	4.00 (4.00; 4.50)
C_{24h}, ng/mL[a]	242 (36.4)
C_{max}, ng/mL	2,091 (32.3)
AUC_{24h}, ng.h/mL[b]	18,067 (20.8)
$t_{1/2,term}$, h	7.2 (6.2; 8.9)
CL/F, mL/h	8,661 (21.5)

Q=quartile; qd=once daily.
[a] Reported as C_τ.
[b] Reported as AUC_τ.
Source: Module 5.3.3.4/GS-US-201-0104-CSR/Table 4.5

2.1.8.2.4. Conclusion

Exposure to DRV when coadministered with EVG and COBI was increased relative to single-dose administration of DRV alone.

Information on dosing recommendations is available in Section 3.3.2.5.2.

2.1.8.3. Famotidine and Omeprazole

GS-US-216-0120

Module 5.3.3.4/GS-US-216-0120-CSR

2.1.8.3.1. Objective

To investigate the effect of famotidine and omeprazole on the PK of EVG/COBI at steady-state.

2.1.8.3.2. Subjects and Methods

This was a Phase 1, open-label, randomized, crossover study in 33 healthy subjects to investigate the effect of famotidine (a representative H_2-receptor agonist) and omeprazole (a representative proton-pump inhibitor) on the bioavailability and PK of EVG/COBI (COBI 150-mg tablet). Subjects were randomized to 1 of 3 treatment sequences (AB, AC, or AD) and received the following treatments:

- Treatment A: COBI 150 mg and EVG 150 mg once daily in the morning with a meal for 8 days.
- Treatment B: COBI 150 mg and EVG 150 mg once daily in the morning with a meal for 8 days; famotidine 40 mg once daily in the evening with a meal, 12 hours after EVG/COBI administration, for 8 days.
- Treatment C: COBI 150 mg and EVG 150 mg once daily in the morning with a meal for 8 days; omeprazole 20 mg once daily in the morning

in the fasted state, 2 hours before EVG/COBI administration, for 8 days.

- Treatment D: COBI 150 mg and EVG 150 mg coadministered orally once daily in the morning with a meal for 8 days; omeprazole 20 mg in the evening in the fasted state, 12 hours after EVG/COBI administration, for 8 days.

2.1.8.3.3. Results

2.1.8.3.3.1. COBI PK

The PK of COBI was unaffected by coadministration of famotidine or omeprazole (Table 103). The LS means ratios for C_{max} and AUC_{24h} of COBI when EVG/COBI was coadministered with famotidine relative to administration of EVG/COBI alone were 104% and 105%, respectively. The LS means ratios for C_{max} and AUC_{24h} of COBI when EVG/COBI was coadministered with omeprazole (morning or evening) relative to administration of EVG/COBI alone were between 90% and 99%.

Table 103: PK Parameters of COBI Following Administration of EVG/COBI in the Absence and Presence of Famotidine or Omeprazole (Study GS-US-216-0120)

Parameter	Mean (%CV) Test	Mean (%CV) Reference	Test/Reference Least Square Means Ratio, % (90% CI)
	Treatment B: EVG/COBI 150/150 mg qd + Famotidine 40 mg qd	**Treatment A: EVG/COBI 150/150 mg qd**	
N	10	10	
C_{24h}, ng/mL[a]	39.3 (131)	35.3 (140)	115.41 (105.70; 126.00)
C_{max}, ng/mL	1,767 (30.5)	1,728 (37.2)	103.60 (99.07; 108.34)
AUC_{24h}, ng.h/mL[b]	12,692 (45.1)	12,318 (51.3)	104.54 (101.51; 107.65)
	Treatment C: EVG/COBI 150/150 mg qd + Omeprazole 20 mg qd in the mornings	**Treatment A: EVG/COBI 150/150 mg qd**	
N	11	11	
C_{24h}, ng/mL[a]	28.5 (96.1)	34.6 (110)	92.76 (73.56;116.98)
C_{max}, ng/mL	1,569 (24.4)	1,737 (21.4)	90.16 (81.82; 99.34)
AUC_{24h}, ng.h/mL[b]	10,817 (35.9)	11,567 (29.8)	92.36 (84.79; 100.59)
	Treatment D: EVG/COBI 150/150 mg qd + Omeprazole 20 mg qd in the evening	**Treatment A: EVG/COBI 150/150 mg qd**	
N	11	11	
C_{24h}, ng/mL[a]	25.9 (69.0)	27.0 (81.9)	102.04 (81.58; 127.64)
C_{max}, ng/mL	1,516 (25.8)	1,573 (15.1)	94.39 (85.10; 104.70)
AUC_{24h}, ng.h/mL[b]	10,136 (26.2)	10,133 (20.2)	98.70 (88.98; 109.49)

qd=once daily.

[a] Reported as C_{τ}.

[b] Reported as AUC_{τ}.

Source: Module 5.3.3.4/GS-US-216-0120-CSR/Table 4.2 and Table 5

2.1.8.3.3.2. EVG PK

The PK of EVG was unaffected by coadministration of famotidine or omeprazole (Table 104). The LS means ratios for C_{max} and AUC_{24h} of EVG when EVG/COBI was coadministered with famotidine relative to administration of EVG/COBI alone were 102% and 103%, respectively. The LS means ratios for C_{max} and AUC_{24h} of EVG when EVG/COBI was coadministered with omeprazole (morning or evening) relative to administration of EVG/COBI alone were between 103% and 116%.

Table 104: PK Parameters of EVG Following Administration of EVG/COBI in the Absence and Presence of Famotidine or Omeprazole (Study GS-US-216-0120)

Parameter	Mean (%CV) Test	Mean (%CV) Reference	Test/Reference Least Square Means Ratio, % (90% CI)
	Treatment B: EVG/COBI 150/150 mg qd + Famotidine 40 mg qd	**Treatment A: EVG/COBI 150/150 mg qd**	
N	10	10	
C_{24h}, ng/mL[a]	526 (37.1)	441 (33.5)	117.90 (105.13; 132.23)
C_{max}, ng/mL	2,200 (23.6)	2,139 (23.0)	102.31 (89.42; 117.06)
AUC_{24h}, ng.h/mL[b]	23,537 (20.4)	22,726 (18.9)	103.39 (94.87; 112.68)
	Treatment C: EVG/COBI 150/150 mg qd + Omeprazole 20 mg qd in the mornings	**Treatment A: EVG/COBI 150/150 mg qd**	
N	11	11	
C_{24h}, ng/mL[a]	475 (46.6)	419 (48.1)	113.16 (95.85; 133.59)
C_{max}, ng/mL	2,767 (24.5)	2,392 (27.8)	116.35 (103.76; 130.46)
AUC_{24h}, ng.h/mL[b]	25,116 (22.5)	22,875 (22.9)	109.95 (101.64; 118.94)
	Treatment D: EVG/COBI 150/150 mg qd + Omeprazole 20 mg qd in the evening	**Treatment A: EVG/COBI 150/150 mg qd**	
N	11	11	
C_{24h}, ng/mL[a]	429 (37.5)	388 (35.2)	110.18 (91.90; 132.10)
C_{max}, ng/mL	2,414 (28.5)	2,332 (26.8)	102.99 (91.88; 115.45)
AUC_{24h}, ng.h/mL[b]	24,871 (26.9)	23,558 (21.7)	104.57 (92.85; 117.78)

qd=once daily.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.3.4/GS-US-216-0120-CSR/Table 4.1 and Table 5

2.1.8.3.4. Conclusion

Systemic exposure to COBI and EVG was not affected when famotidine or omeprazole was given with EVG/COBI.

Information on dosing recommendations is available in Section 3.3.2.6.2.

2.1.8.4. Famotidine

GS-US-216-0122

Module 5.3.3.4/GS-US-216-0122-CSR

2.1.8.4.1. Objective

To investigate the effect of simultaneous coadministration of famotidine and EVG/COBI on the bioavailability of EVG/COBI.

2.1.8.4.2. Subjects and Methods

This was a Phase 1, open-label, randomized, 2-way crossover study in 16 healthy subjects to investigate the effect of famotidine (a representative H_2-receptor agonist) on the bioavailability

of EVG/COBI (COBI 150-mg tablet) when coadministered simultaneously. Subjects were randomized to 1 of 2 treatment sequences (AB or BA) and received the following treatments:

- Treatment A: EVG 150 mg and COBI 150 mg once daily in the morning with a meal for 8 consecutive days (Days 1 to 8 for Treatment Sequence AB, and Days 9 to 16 for Treatment Sequence BA).
- Treatment B: EVG 150 mg, COBI 150 mg, and famotidine 40 mg once daily, all coadministered simultaneously in the morning with a meal for 8 consecutive days (Days 1 to 8 for Treatment Sequence BA, and Days 9 to 16 for Treatment Sequence AB).

2.1.8.4.3. Results

2.1.8.4.3.1. COBI and EVG PK

The PK of COBI and EVG were unaffected by coadministration of famotidine; the lower bounds of the 2-sided 90% CIs of all LS means ratios were >70% for both COBI and EVG (Table 105).

Table 105: PK Parameters of COBI and EVG Following Administration of EVG/COBI in the Absence and Presence of Famotidine (Coadministered Simultaneously With EVG/COBI) (Study GS-US-216-0122)

Parameter	Mean (%CV)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Treatment B: EVG/COBI 150/150 mg qd + Famotidine 40 mg qd	**Treatment A: EVG/COBI 150/150 mg qd**	
N	16	16	
C_{24h}, ng/mL[a]	25.7 (78.4)	22.1 (72.7)	111.34 (99.81; 124.20)
C_{max}, ng/mL	1,632 (21.7)	1,533 (20.7)	106.04 (99.40; 113.12)
AUC_{24h}, ng.h/mL[b]	10,465 (24.2)	10,002 (19.9)	103.49 (96.77; 110.68)
	Treatment B: EVG/COBI 150/150 mg qd + Famotidine 40 mg qd	**Treatment A: EVG/COBI 150/150 mg qd**	
N	16	16	
C_{24h}, ng/mL[a]	458 (38.5)	420 (32.1)	107.13 (98.45; 116.57)
C_{max}, ng/mL	2,269 (28.6)	2,239 (26.2)	100.48 (91.66; 110.15)
AUC_{24h}, ng.h/mL[b]	24,947 (20.6)	23,996 (15.8)	103.07 (98.10; 108.29)

qd=once daily.
[a] Reported as C_{τ}.
[b] Reported as AUC_{τ}.
Source: Module 5.3.3.4/GS-US-216-0122-CSR/Table 4.1,Table 4.2, and Table 5

2.1.8.4.4. Conclusion

Systemic exposure to COBI and EVG was not affected when famotidine was coadministered simultaneously with EVG/COBI.

Information on dosing recommendations is available in Section 3.3.2.6.2.

2.1.8.5. Atazanavir, Rosuvastatin, and Rifabutin

GS-US-216-0123

Module 5.3.3.4/GS-US-216-0123-CSR

2.1.8.5.1. Objective

To investigate the effect of EVG and ATV co-boosted with COBI on the PK of EVG and ATV; to investigate the effect of COBI-boosted EVG on the PK of EVG and rosuvastatin; to investigate the effect of COBI-boosted EVG on the PK of EVG and rifabutin.

2.1.8.5.2. Subjects and Methods

This was a Phase 1, open-label, partially randomized, crossover study in 34 healthy subjects to investigate the PK of EVG/COBI (COBI 150-mg tablet) coadministered once daily with ATV (a CYP3A substrate and P-gp inhibitor), rosuvastatin (an OATP1B1, OATP1B3, and BCRP substrate), or rifabutin (a substrate and inducer of CYP3A). Subjects were randomized to 1 of 3 cohorts and received the following treatments:

Cohort 1:

- Days 1 to 3: Rosuvastatin 10 mg single dose with food (Day 1), followed by 2-day washout period (Days 2 and 3).
- Days 4 to 14: EVG 85 mg and COBI 150 mg plus ATV 300 mg administered once daily in the morning with food (Days 4 to 13), followed by a 1-day washout period (Day 14).
- Day 15 to 24: EVG 150 mg and COBI 150 mg administered once daily in the morning with food.
- Day 25: EVG 150 mg and COBI 150 mg plus rosuvastatin 10 mg administered as a single dose in the morning with food.

Cohort 2:

- Days 1 to 3: No study treatment.
- Days 4 to 14: EVG 85 mg and COBI 150 mg plus ATV 300 mg administered once daily in the morning with food (Days 4 to 13), followed by a 1-day washout period (Day 14).
- Days 15 to 24: ATV 300 mg and rtv 100 mg administered once daily in the morning with food.

Cohort 3:

- Days 1 to 10: EVG 150 mg and COBI 150 mg administered once daily in the morning with food.
- Days 11 to 33: EVG 150 mg and COBI 150 mg administered once daily plus rifabutin 150 mg administered once every other day in the

morning with food (Days 11 to 23), followed by a 10-day washout period (Days 24 to 33).

- Day 34 to 46: Rifabutin 300 mg administered once daily in the morning with food.

All study drugs were administered within 5 minutes after a meal.

2.1.8.5.3. Results

2.1.8.5.3.1. COBI PK

Cobicistat AUC_{24h} and C_{max} values were generally similar across all treatments (Table 106). Cobicistat C_{24h} values were also similar across treatments except following coadministration of EVG/COBI with rifabutin, which resulted in markedly decreased COBI C_{24h}.

Table 106: PK Parameters of COBI Following Administration of EVG/COBI in the Presence or Absence of Rosuvastatin, ATV, or Rifabutin (Study GS-US-216-0123)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)					
	Cohort 1 EVG/COBI 150/150 mg qd	Cohort 1 EVG/COBI 150/150 mg qd + Rosuvastatin 10 mg Single Dose	Cohort 1 EVG/COBI 85/150 mg qd + ATV 300 mg qd	Cohort 2 EVG/COBI 85/150 mg qd + ATV 300 mg qd	Cohort 3 EVG/COBI 150/150 mg qd	Cohort 3 EVG/COBI 150/150 mg qd + Rifabutin 300 mg qd
N	10	10	10	8	12	12
t_{max}, h	4.25 (3.00; 4.50)	3.00 (2.00; 4.50)	3.00 (3.00; 3.50)	2.00 (2.00; 3.75)	3.00 (3.00; 4.00)	3.00 (2.00; 3.25)
C_{24h}, ng/mL[a]	32.3 (123)	34.2 (113)	46.6 (106)	32.3 (38.0)	22.8 (61.2)	6.5 (71.7)
C_{max}, ng/mL	1,400 (32.3)	1,451 (25.2)	1,612 (24.3)	1,836 (21.7)	1,642 (19.0)	1,877 (28.8)
AUC_{24h}, ng.h/mL[b]	10,389 (38.6)	11,066 (38.1)	12,148 (30.7)	12,942 (20.7)	11,215 (18.5)	11,410 (29.2)
$t_{1/2,term}$, h	3.1 (3.0; 3.4)	3.2 (3.1; 3.9)	3.7 (3.3; 3.8)	3.5 (3.3; 3.6)	3.3 (2.8; 3.7)	2.5 (2.1; 2.6)

Q=quartile; qd=once daily.

[a] Reported as C_{τ}.

[b] Reported as AUC_{τ}.

Source: Module 5.3.3.4/GS-US-216-0123-CSR/Table 4.4 and Appendix 16.2, Listing 8.4

2.1.8.5.3.2. EVG PK

Exposure to EVG (AUC_{24h} and C_{max}) when EVG/COBI was coadministered with rosuvastatin was bioequivalent to exposure to EVG when EVG/COBI was administered alone (Table 107). The LS means ratios for C_{max} and AUC_{24h} of EVG when EVG/COBI was coadministered with rosuvastatin relative to administration of EVG/COBI alone were 94% and 102%, respectively.

The LS means ratios for AUC_{24h} of EVG when EVG/COBI was coadministered with ATV (Cohorts 1 and 2) relative to administration of EVG/COBI alone (Cohort 1) were 115% (Cohort 1 versus Cohort 1) and 117% (Cohorts 1 and 2 versus Cohort 1) (Table 107). The LS mean ratios for C_{max} were approximately 85% for both comparisons.

The LS mean ratios for C_{max} and AUC_{24h} of EVG when EVG/COBI was coadministered with rifabutin relative to administration of EVG/COBI alone were 91% and 79%, respectively (Table 107).

Table 107: PK Parameters of EVG Following Administration of EVG/COBI in the Absence and Presence of Rosuvastatin, ATV, or Rifabutin (Study GS-US-216-0123)

Parameter	LS Means		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Cohort 1 EVG/COBI 150/150 mg qd + Rosuvastatin 10 mg Single Dose	**Cohort 1 EVG/COBI 150/150 mg qd**	
N	10	10	
C_{24h}, ng/mL[a]	262	267	98.20 (83.42; 115.60)
C_{max}, ng/mL	1,843	1,962	93.94 (82.61; 106.82)
AUC_{24h}, ng.h/mL[b]	17,724	17,348	102.17 (91.44; 114.15)
	Cohort 1 EVG/COBI 85/150 mg qd + ATV 300 mg qd	**Cohort 1 EVG/COBI 150/150 mg qd**	
N	10	10	
C_{24h}, ng/mL[a]	512	267	191.80 (163.43; 225.10)
C_{max}, ng/mL	1,661	1,962	84.68 (75.34; 95.18)
AUC_{24h}, ng.h/mL[b]	19,938	17,348	114.93 (108.14; 122.16)
	Cohort 1 and 2 EVG/COBI 85/150 mg qd + ATV 300 mg qd	**Cohort 1 EVG/COBI 150/150 mg qd**	
N	18	10	
C_{24h}, ng/mL[a]	489	267	183.34 (117.38; 286.37)
C_{max}, ng/mL	1,651	1,962	84.15 (61.79; 114.61)
AUC_{24h}, ng.h/mL[b]	20,329	17,348	117.19 (88.30; 155.53)
	Cohort 3 EVG/COBI 150/150 mg qd + Rifabutin 300 mg qd	**Cohort 3 EVG/COBI 150/150 mg qd**	
N	12	12	
C_{24h}, ng/mL[a]	134	407	32.85 (26.93; 40.07)
C_{max}, ng/mL	1,981	2,174	91.14 (83.56; 99.40)
AUC_{24h}, ng.h/mL[b]	17,726	22,326	79.40 (74.10; 85.07)

qd=once daily.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.3.4/GS-US-216-0123-CSR/Table 5

2.1.8.5.4. Rosuvastatin PK

When rosuvastatin was coadministered with EVG/COBI, exposure to rosuvastatin was modestly increased relative to when rosuvastatin was administered alone (Table 108). The LS means ratios for C_{max} and AUC_{24h} of rosuvastatin when rosuvastatin was coadministered with EVG/COBI relative to administration of rosuvastatin alone were 189% and 138%, respectively.

Table 108: PK Parameters of Rosuvastatin Following Administration of Rosuvastatin in the Absence and Presence of EVG/COBI (Study GS-US-216-0123)

Parameter	LS Means		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Cohort 1 Rosuvastatin 10 mg Single Dose + EVG/COBI 150/150 mg qd	Cohort 1 Rosuvastatin 10 mg Single Dose	
N	10	10	
C_{last}, ng/mL	0.14	0.10	143.10 (108.22; 189.22)
C_{max}, ng/mL	4.46	2.35	189.31 (148.19; 241.84)
AUC_{∞}, ng.h/mL	35.0	25.4	137.98 (113.83; 167.25)

qd=once daily.
Source: Module 5.3.3.4/GS-US-216-0123-CSR/Table 5

2.1.8.5.5. ATV PK

When ATV was coadministered with EVG/COBI (Cohorts 1 and 2), ATV exposure was modestly decreased relative to when ATV was coadministered with rtv (Cohort 2) (Table 109). The LS mean ratios for C_{max} and AUC_{24h} of ATV when ATV was coadministered with EVG/COBI relative to administration of ATV alone were between 76% and 90%.

Table 109: PK Parameters of ATV Following Administration of ATV With EVG/COBI or With rtv (Study GS-US-216-0123)

Parameter	LS Means		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Cohort 2 ATV 300 mg qd + EVG/COBI 85/150 mg qd	Cohort 2 ATV/rtv 300/100 mg qd	
N	7	7	
C_{24h}, ng/mL[a]	458	709	64.55 (51.43; 81.02)
C_{max}, ng/mL	4,436	5,623	78.89 (58.13; 107.07)
AUC_{24h}, ng.h/mL[b]	38,438	43,483	88.40 (71.44; 109.37)
	Cohort 1 and 2 ATV 300 mg qd + EVG/COBI 85/150 mg qd	Cohort 2 ATV/rtv 300/100 mg qd	
N	18	7	
C_{24h}, ng/mL[a]	571	709	80.51 (55.58; 116.62)
C_{max}, ng/mL	4,276	5,623	76.05 (59.07; 97.92)
AUC_{24h}, ng.h/mL[b]	39,339	43,483	90.47 (73.39; 111.52)

qd=once daily.
[a] Reported as C_{τ}.
[b] Reported as AUC_{τ}.
Source: Module 5.3.3.4/GS-US-216-0123-CSR/Table 5

2.1.8.5.6. Rifabutin PK

When rifabutin was coadministered with EVG/COBI, exposure to rifabutin was comparable to when rifabutin was administered alone (Table 110). The LS mean ratios for C_{max} and AUC_{τ} of rifabutin when rifabutin was coadministered with EVG/COBI relative to administration of rifabutin alone were 109% and 92%, respectively. Exposure to the metabolite of rifabutin,

25-*O*-desacetylrifabutin, was increased considerably when rifabutin was coadministered with EVG/COBI; the LS mean ratios for C_{max} and AUC_{τ} were 484% and 625%, respectively.

Table 110: PK Parameters of Rifabutin and 25-*O*-Desacetylrifabutin Following Administration of Rifabutin in the Absence and Presence of EVG/COBI (Study GS-US-216-0123)

Parameter	LS Means		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Cohort 3 Rifabutin 300 mg qod + EVG/COBI 150/150 mg qd	Cohort 3 Rifabutin 300 mg qd	
Rifabutin			
N	12	12	
C_{τ}, ng/mL	70.2	74.7	93.90 (84.77; 104.01)
C_{max}, ng/mL	558	513	108.87 (98.48; 120.37)
AUC_{τ}, ng.h/mL	8,302	8,985	92.40 (82.86; 103.04)
25-*O*-Desacetylrifabutin			
N	12	12	
C_{τ}, ng/mL	16.9	3.43	494.20 (404.20; 604.24)
C_{max}, ng/mL	146	30.2	484.43 (408.94; 573.85)
AUC_{τ}, ng.h/mL	2,955	473	625.07 (508.37; 768.57)

qd=once daily; qod=every other day.
Source: Module 5.3.3.4/GS-US-216-0123-CSR/Table 5

2.1.8.5.7. Conclusion

Coadministration of EVG/COBI 85/150 mg once daily with ATV 300 mg once daily did not result in clinically relevant changes in EVG, ATV, or COBI exposures. Coadministration of EVG/COBI 150/150 mg once daily with a single dose of rosuvastatin 10 mg did not affect EVG or COBI exposures; transient increases in rosuvastatin exposure (primarily C_{max}) were observed. Coadministration of EVG/COBI 150/150 mg once daily with rifabutin 150 mg every other day resulted in marked decreases in EVG and COBI C_{24h} and generally slight decreases in C_{max} and AUC_{24h}. There were no clinically relevant changes in rifabutin exposure, although exposure to the 25-*O*-desacetylrifabutin was increased 4- to 6-fold in the presence of EVG/COBI.

Information on dosing recommendations for ATV is available in Section 3.3.2.3, information on dosing recommendations for rosuvastatin is available in Section 3.3.2.6.25, and information on dosing recommendations for rifabutin is available in Section 3.3.2.6.13.

2.1.8.6. Ethinyl Estradiol/Norgestimate

GS-US-236-0106

Module 5.3.3.4/GS-US-236-0106-CSR

2.1.8.6.1.1. Objective

To investigate the effect of multiple doses of EVG/COBI/FTC/TDF 150/150/200/300 mg administered as a single-tablet regimen (STR) on the PK of ethinyl estradiol and norgestimate.

2.1.8.6.1.2. Subjects and Methods

This was a Phase 1, open-label, fixed-sequence study in 21 healthy female subjects to investigate the PK interaction between the EVG/COBI/FTC/TDF 150/150/200/300 mg STR and a representative oral contraceptive, Ortho Tri-Cyclen Lo (ethinyl estradiol 0.025 mg and norgestimate 0.180/0.215/0.250 mg). Subjects who had not taken Ortho Tri-Cyclen Lo or a generic equivalent for 1 full menstrual cycle were required to enroll into Part A, a lead in period consisting of dosing with Ortho Tri-Cyclen Lo for 1 full menstrual cycle. Otherwise, subjects could enroll directly into Part B, which consisted of two 28-day menstrual cycles. In Part B, subjects received the following treatments:

- Cycle 1: Ethinyl estradiol 0.025 mg/norgestimate 0.180/0.215/0.250 mg (Ortho Tri-Cyclen Lo) once daily in the morning on Days 1 to 28.
- Cycle 2: Ethinyl estradiol 0.025 mg/norgestimate 0.180/0.215/0.250 mg (Ortho Tri-Cyclen Lo) once daily in the morning on Days 29 to 56, and EVG/COBI/FTC/TDF 150/150/200/300 mg STR once daily in the morning on Days 40 to 49.

All treatments were administered under fed conditions within 5 minutes after a meal.

2.1.8.6.1.3. Results

2.1.8.6.1.3.1. COBI and EVG PK

The PK parameters of COBI and EVG after administration of the EVG/COBI/FTC/TDF STR in the presence of ethinyl estradiol/norgestimate are shown in Table 111.

Table 111: PK Parameters of COBI and EVG Following Coadministration of the EVG/COBI/FTC/TDF STR With Ethinyl Estradiol/Norgestimate (Study GS-US-236-0106)

Parameter	Mean (%CV)	
	EVG/COBI/FTC/TDF 150/150/200/300 mg + Ethinyl estradiol 0.025 mg/ Norgestimate 0.180/0.215/0.250 mg	**EVG/COBI/FTC/TDF 150/150/200/300 mg + Ethinyl estradiol 0.025 mg/ Norgestimate 0.180/0.215/0.250 mg**
N	15	15
C_{24h}, ng/mL[a]	25.6 (74.2)	415 (40.5)
C_{max}, ng/mL	1,560 (19.7)	2,695 (23.7)
AUC_{24h}, ng.h/mL[b]	10,716 (29.5)	26,918 (23.9)

qd=once daily.
[a] Reported as C_{τ}.
[b] Reported as AUC_{τ}.
Source: Module 5.3.3.4/GS-US-236-0106-CSR

2.1.8.6.1.3.2. Ethinyl Estradiol and Norelgestromin PK

The LS mean ratios for C_{max} and AUC_{24h} of ethinyl estradiol when ethinyl estradiol/norgestimate was coadministered with the EVG/COBI/FTC/TDF STR relative to administration of ethinyl estradiol/norgestimate alone were 94% and 75%, respectively (Table 112). For norelgestromin, the primary and pharmacologically active metabolite of norgestimate, the LS mean ratios for C_{max} and AUC_{24h} when ethinyl estradiol/norgestimate was coadministered with the

EVG/COBI/FTC/TDF STR relative to administration of ethinyl estradiol/norgestimate alone were 208% and 226%.

Table 112: PK Parameters of Ethinyl Estradiol and Norelgestromin Following Administration of Ethinyl Estradiol/Norgestimate in the Absence and Presence of the EVG/COBI/FTC/TDF STR (Study GS-US-236-0106)

Parameter	Mean (%CV)		Test/Reference Least Square Means Ratio, % (90% CI)
	Test	Reference	
	Ethinyl estradiol 0.025 mg/ Norgestimate 0.180/0.215/0.250 mg + EVG/COBI/FTC/TDF 150/150/200/300 mg	**Ethinyl estradiol 0.025 mg/ Norgestimate 0.180/0.215/0.250 mg**	
N	15	15	
C_{24h}, pg/mL[a]	13.7 (57.8)	25.8 (78.9)	56.48 (51.88; 61.49)
C_{max}, pg/mL	98.6 (27.8)	106 (30.7)	94.09 (85.54; 103.50)
AUC_{24h}, pg.h/mL[b]	775 (26.1)	1,051 (32.1)	74.97 (69.41; 80.98)
	Ethinyl estradiol 0.025 mg/ Norgestimate 0.180/0.215/0.250 mg + EVG/COBI/FTC/TDF 150/150/200/300 mg	**Ethinyl estradiol 0.025 mg/ Norgestimate 0.180/0.215/0.250 mg**	
N	15	15	
C_{24h}, pg/mL[a]	1,368 (24.7)	510 (23.1)	266.57 (243.06; 292.35)
C_{max}, pg/mL	4,461 (14.5)	2,147 (15.4)	207.98 (199.74; 216.57)
AUC_{24h}, pg.h/mL[b]	48,339 (17.7)	21,367 (17.1)	225.96 (215.13; 237.34)

qd=once daily.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.3.4/GS-US-236-0106-CSR

2.1.8.6.1.4. Pharmacodynamics

Following administration of ethinyl estradiol/norgestimate with the EVG/COBI/FTC/TDF STR compared with administration of ethinyl estradiol/norgestimate alone, the following PD changes between Day 0 and Day 21 were observed: serum progesterone concentrations were unchanged for both treatments, similar decreases in serum follicle-stimulating hormone concentrations were observed for both treatments, and a greater decrease in serum luteinizing hormone concentrations was observed when ethinyl estradiol/norgestimate was coadministered with the EVG/COBI/FTC/TDF STR relative to administration of ethinyl estradiol/norgestimate alone.

2.1.8.6.1.5. Conclusion

Coadministration of the EVG/COBI/FTC/TDF STR with ethinyl estradiol/norgestimate resulted in decreases in exposure to ethinyl estradiol and increases in exposure to norelgestromin. Serum progesterone and follicle-stimulating hormone concentrations were comparable with and without the EVG/COBI/FTC/TDF STR, while a greater decrease in serum luteinizing hormone concentrations was observed when ethinyl estradiol/norgestimate was coadministered with the EVG/COBI/FTC/TDF STR relative to administration of ethinyl estradiol/norgestimate alone.

Information on dosing recommendations is available in Section 3.3.2.6.17.

2.2. Human PD Studies

2.2.1. Healthy Subject PD and PK/PD for DRV

Not applicable.

2.2.2. Healthy Subject PD and PK/PD for COBI

Not applicable.

2.2.3. Thorough QT/QTc Study With DRV

TMC114-C153

Module 5.3.4.1/TMC114-C153-CRR

2.2.3.1. Objective

To assess the cardiac safety of DRV in the presence of rtv.

2.2.3.1.1.1. Subjects and Methods

This was a Phase 1, open-label, randomized, placebo- and active-controlled (moxifloxacin), 4-way crossover study to assess the cardiac safety of DRV (400-mg tablet formulation F001), together with rtv, in 40 healthy adults, with particular attention to the QT/QTcF interval duration and the influence of DRV/rtv on other electrocardiogram (ECG) parameters, such as QRS and PR intervals. Each subject received treatment in 4 sessions: DRV/rtv 1600/100 mg once daily for 7 days (Treatment A), DRV/rtv 800/100 mg twice daily for 7 days (Treatment B), moxifloxacin 400 mg once daily for 7 days (Treatment C), and placebo once daily for 7 days (Treatment D). Eleven 12-lead time-matched triplicate ECGs on Day #1 (pretreatment baseline), Day 1 (first dose), and Day 7 (last dose at steady-state) at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after the morning dose of each treatment period plus 1 additional 12-lead triplicate ECG after 24 hours on Day 2 and Day 8 were recorded. Subsequent sessions were separated by a washout period of 7 days. All treatments were administered under fed conditions.

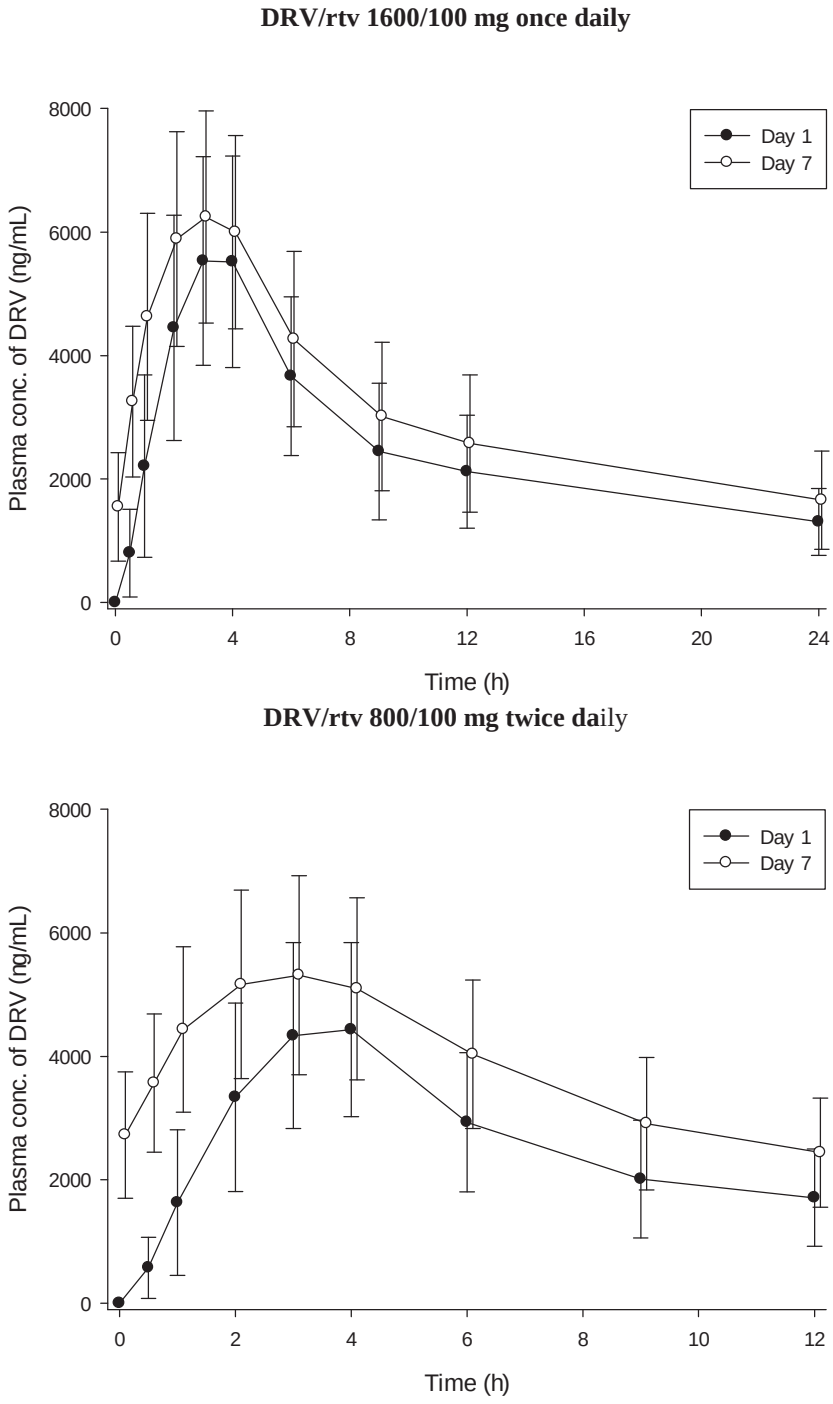
In addition to the measurement of PK parameters of DRV and rtv on Days 1 and 7, the plasma concentrations of AAG and the percentage of unbound DRV in plasma were measured on Day 1.

2.2.3.1.1.2. Results

2.2.3.1.1.2.1. DRV PK

The mean plasma concentration-time profiles for Treatments A and B are shown in Figure 3.

Figure 3 **Mean (SD) Plasma Concentration-Time Curve of DRV on Days 1 and 7 After Administration of DRV/rtv 1600/100 mg Once Daily (Treatment A, Upper Panel) or DRV/rtv 800/100 Twice Daily (Treatment B, Lower Panel) (Study TMC114-C153)**



Source: Module 5.3.4.1/TMC114-C153-CPK/DIS04

The PK of DRV in Treatments A and B on Days 1 and 7 are shown in Table 113.

For Treatments A and B, the mean C_{max} and AUC values of DRV on Days 1 and 7 indicated accumulation of DRV. With Treatment A (once daily dosing), the individual Day 7/Day 1

accumulation ratios ranged from 70% to 216% for C_{max} (geometric mean: 114%) and from 63% to 231% for AUC_{24h} (geometric mean: 126%). With Treatment B (twice daily dosing), the individual Day 7/Day 1 accumulation ratios ranged from 77% to 291% for C_{max} (geometric mean: 123%) and from 87% to 307% for AUC_{12h} (geometric mean: 152%).

Table 113: PK Parameters of DRV Following Administration of DRV/rtv Once or Twice Daily in Healthy Subjects for 1 and 7 Days (Study TMC114-C153)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment A DRV/rtv 1600/100 mg qd	Treatment B: DRV/rtv 800/100 mg bid
N	37	37
Day 1		
t_{max}, h	3.08 (2.05-4.08)	3.08 (2.00-6.05)
C_{0h}, ng/mL	0	0
C_{max}, ng/mL	5,914 (1,758)	4,740 (1,405)
AUC_{12h}, ng.h/mL	-	31,717 (11,113)
AUC_{24h}, ng.h/mL	60,328 (21,012)	-
Day 7		
t_{max}, h	3.05 (1.05-6.05)	3.05 (1.05-6.05)
C_{0h}, ng/mL	1,550 (879)	2,726 (1,024)
C_{min}, ng/mL	1,428 (780)	2,282 (849)
C_{max}, ng/mL	6,599 (1,754)	5,689 (1,533)
AUC_{12h}, ng.h/mL	-	46,511 (13,350)
AUC_{24h}, ng.h/mL	75,629 (25,615)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.4.1/TMC114-C153-CRR/Table 6

2.2.3.1.1.2.2. RTV PK

The PK of rtv in Treatments A and B on Days 1 and 7 are shown in Table 114.

For Treatments A and B, the mean C_{max} and AUC values of rtv on Days 1 and 7 indicated accumulation of rtv. With Treatment A (once daily dosing), the individual Day 7/Day 1 accumulation ratios ranged from 90% to 332% for C_{max} (geometric mean: 164%) and from 99% to 215% for AUC_{24h} (geometric mean: 151%). With Treatment B (twice daily dosing), the individual Day 7/Day 1 accumulation ratios ranged from 115% to 635% for C_{max} (geometric mean: 265%) and from 120% to 451% for AUC_{12h} (geometric mean: 249%).

Table 114: PK Parameters of rtv Following Administration of DRV/rtv in Healthy Subjects for 1 and 7 Days (Study TMC114-C153)

Parameter	Mean (SD); t_{max}: Median (Range)	
	Treatment A DRV/rtv 1600/100 mg qd	**Treatment B: DRV/rtv 800/100 mg bid**
N	37	37
Day 1		
t_{max}, h	4.05 (1.05-6.07)	4.05 (1.07-9.00)
C_{0h}, ng/mL	0	0
C_{max}, ng/mL	516 (258)	508 (303)
AUC_{12h}, ng.h/mL	-	3,119 (1,475)
AUC_{24h}, ng.h/mL	4,471 (2,618)	-
Day 7		
t_{max}, h	4.05 (1.05-6.05)	4.05 (1.07-6.05)
C_{0h}, ng/mL	38.0 (18.8)	303 (185)
C_{min}, ng/mL	35.3 (18.2)	213 (126)
C_{max}, ng/mL	813 (400)	1,272 (538)
AUC_{12h}, ng.h/mL	-	7,649 (3,051)
AUC_{24h}, ng.h/mL	6,186 (2,581)	-

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.4.1/TMC114-C153-CRR/Table 7

2.2.3.1.1.3. Moxifloxacin PK

The PK of moxifloxacin in Treatments A and B on Days 1 and 7 are shown in Table 115. These PK data were comparable to those reported in the US Package Insert for Avelox given at the same dose.[1]

Table 115: PK Parameters of Moxifloxacin Following Administration of Moxifloxacin in Healthy Subjects for 1 and 7 Days (Study TMC114-C153)

Parameter	Mean (SD); t_{max}: Median (Range)
	Treatment C Moxifloxacin 400 mg qd
N	38
Day 1	
t_{max}, h	2.08 (0.57-6.05)
C_{0h}, ng/mL	0
C_{max}, ng/mL	3,453 (729)
AUC_{24h}, ng.h/mL	37,345 (8,145)
Day 7	
t_{max}, h	2.05 (0.55-6.07)
C_{0h}, ng/mL	975 (364)
C_{min}, ng/mL	979 (350)
C_{max}, ng/mL	4,295 (1,075)
AUC_{24h}, ng.h/mL	53,662 (15,411)

N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.4.1/TMC114-C153-CRR/Table 8

2.2.3.1.1.4. PK/PD Relationship for DRV

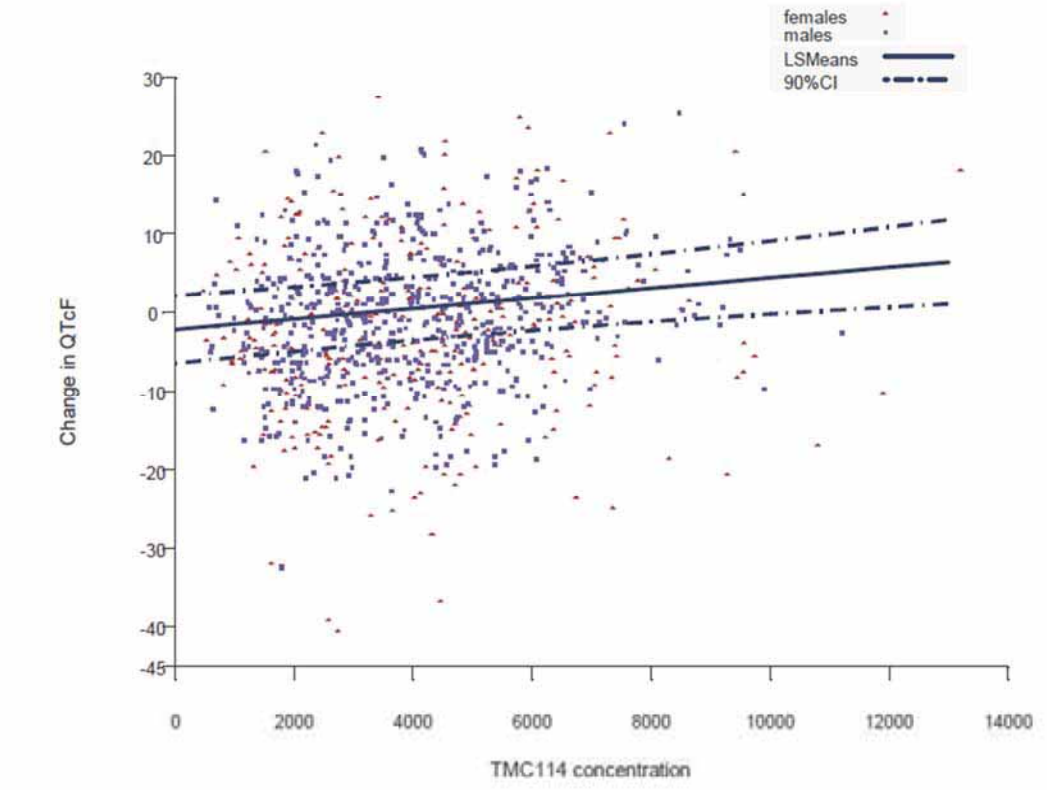
The DRV treatments at the doses evaluated in this study (1600/100 mg once daily and 800/100 mg twice daily) were associated with small prolongations in QTc interval when compared with QTc changes observed in the placebo group. The 2-sided 90% CIs of the time-matched mean changes versus placebo control showed that the upper bounds of both DRV/rtv

groups for the overall population did not exceed 10 ms following single or multiple doses of DRV/rtv (refer to Module 5.3.4.1/TMC114-C153-CRR/Section 4.3.4.1 and Module 2.7.4 for further details).

A linear mixed model was developed to estimate the relationship between QTcF and plasma concentrations of DRV. To account for study design aspects and sex differences, a longitudinal model was applied including the following parameters: subject as a random effect, and treatment sequence, time-dependent baseline QTcF, sex, time, treatment, the interaction between time and treatment, the interaction between sex and treatment, and concentration as fixed effects. A linear slope (power=1) provided the best model for the first-degree fractional (refer to Module 5.3.4.1/TMC114-C153-CRR/Section 4.3.4.3 for details).

The observed and predicted time-matched changes in QTcF versus DRV concentration along with the 90% 2-sided CI (with different symbols used to discriminate male and female subjects for the observed values) are shown in Figure 4.

Figure 4: Changes in QTcF Interval Versus DRV Concentration by Sex (Day 7) (Study TMC114-153)



Source: Module 5.3.4.1/TMC114-C153-CRR/Figure 13

These data show that the variability in the observed values for female subjects was larger than that for male subjects. An additional analysis was performed to investigate whether there was an interaction between sex and concentration by adding this interaction term to the model described above. This analysis resulted in a non-significant interaction between sex and concentration, with a p-value of 0.064 (refer to Module 5.3.4.1/TMC114-C153-CRR/Supporting Data Display 59),

and therefore, the sex interaction term was omitted from the final linear concentration-QTcF model. The slope for the concentration-QTcF relationship was estimated, and the estimate of the change in QTcF at the mean maximum concentration was derived. The estimated slope of QTcF versus plasma DRV concentration relationship is 0.000659 ms.mL/ng, with a 90% 2-sided CI of 0.000184 to 0.001135 ms.mL/ng. Although this CI excludes zero, the relationship between concentration and QTcF is shallow, in that for every 1,000 ng/mL increase in DRV concentration, a small additional shift in QTcF of 0.66 ms is predicted. At the mean maximum DRV concentration of 6,599 ng/mL observed in this study, the mean increase in QTcF is 2.2 ms, with a 90% 2-sided CI of –2.0 to 6.3 ms (refer to Module 5.3.4.1/TMC114-C153-CRR/Supporting Data Display 58).

2.2.3.1.1.5. Conclusion

DRV/rtv administered at 600/100 mg twice daily or 800/100 mg once daily would cause no relevant prolongation of the QT interval.

For further details, refer to Section 3.4.1.2.1.

2.2.4. Thorough QT/QTc Study With COBI

GS-US-216-0107

Module 5.3.4.1/GS-US-216-0107-CSR

2.2.4.1. Objective

To assess the effects of COBI on time-matched, baseline-adjusted, placebo-corrected QTcF.

2.2.4.1.1.1. Subjects and Methods

This was a Phase 1, open-label, randomized, placebo- and active-controlled (moxifloxacin), partially-blinded, 4-way crossover study to assess the cardiac safety of COBI (100- and 150-mg tablets) in 48 healthy adults. Subjects were randomized to 1 of 2 Williams squares, and then to 1 of 4 possible treatment sequences within each Williams square (6 subjects per treatment sequence). Treatments were separated by a 6-day washout period. Subjects received a single dose of the following treatments on Days 1, 8, 15, and 22 as follows:

- Treatment A: COBI 250 mg (1 COBI 150-mg active tablet, 1 COBI 100-mg active tablet, and 1 placebo 150-mg tablet).
- Treatment B: COBI 400 mg (2 COBI 150-mg active tablets, 1 COBI 100-mg active tablet).
- Treatment C: Placebo control (2 placebo 150-mg tablets, 1 placebo 100-mg tablet).
- Treatment D: Moxifloxacin 400 mg (1 moxifloxacin 400-mg tablet).

All treatments were administered under fed conditions within 5 minutes after a meal.

2.2.4.1.1.2. Results

2.2.4.1.1.2.1. COBI PK

Cobicistat exhibited nonlinear PK, with an approximately 2.1-fold increase in AUC_{∞} and a 1.8-fold increase in C_{max} following administration of COBI 400 mg relative to COBI 250 mg (Table 116). The absence of changes in COBI $t_{1/2,term}$ in the presence of lower CL/F and higher AUC_{∞} values with higher dose is indicative of an increase in COBI bioavailability at the 400 mg dose level relative to 250 mg. Exposure to COBI (AUC_{∞} and C_{max}) following administration of COBI 250 mg and 400 mg was higher than the steady-state exposure following administration of COBI 150 mg when administered once daily as a pharmacoenhancer (AUC_{24h} approximately 11,000 ng.h/mL; C_{max} approximately 1,500 ng/mL). Therefore, the exposures in this study are deemed adequate to cover predicted supratherapeutic exposures.

Table 116: PK Parameters of COBI Following Single-Dose Administration of 250 or 400 mg COBI (Study GS-US-216-0107)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)	
	Treatment A COBI 250 mg	Treatment B: COBI 400 mg
N	48	48
t_{max}, h	3.50 (3.00; 4.00)	4.00 (3.50; 4.50)
C_{max}, ng/mL	2,301 (22.7)	4,027 (18.3)
AUC_{∞}, ng.h/mL	20,178 (35.0)	41,660 (28.4)
$t_{1/2,term}$, h	4.46 (3.76; 5.01)	4.64 (4.11; 5.53)
CL/F, mL/h	14,056 (39.1)	10,462 (32.5)

Q=quartile.
Source: Module 5.3.4.1/GS-US-216-0107-CSR/Table 11

2.2.4.1.1.3. PK/PD Relationship for COBI

Evaluation of the baseline-adjusted mean differences between COBI 250 and 400 mg and placebo and their associated 2-sided 90% CIs demonstrated a lack of prolongation effect on the QTcF interval following COBI administration; the upper bounds of the 2-sided 90% CIs were +10 ms at all timepoints after dosing. The upper bounds of the 2-sided 90% CIs were also +10 ms for the COBI 250-mg and 400-mg doses at all timepoints for QT interval corrected for heart rate using population-specific correction factor and QT interval corrected for heart rate using subject-specific correction factor. An upper bound of the 2-sided 90% CI for QT interval corrected for heart rate using the Bazett formula was) 10 ms (10.1 ms) at a single timepoint (12 hours) with the COBI 400 mg dose. No subject had an absolute QTc interval >480 ms at any postdose assessment, or change from predose baseline QTc >60 ms using any of the correction factors following any of the treatments. The lower bound of the 2-sided 90% CI for the mean difference between the positive control and placebo was >5 ms at more than 1 timepoint after dosing, thereby establishing assay sensitivity

Results of PK/PD analysis of this study suggested a statistically significant, small, negative association between COBI plasma concentration and QTc interval that remained upon adjustment for sex. Based on the observed mean C_{max} for COBI (1,566 ng/mL) following administration of the EVG/COBI/FTC/TDF 150/150/200/300 mg STR, mean . . QTcF was

predicted to be #3.25 ms (–4.63 ms for females, –1.87 ms for males). At this COBI concentration, the nonlinear mixed-effect model-determined mean QT interval corrected for heart rate using an individual-specific correction factor (QTcM) change due to COBI, compared with placebo was predicted to be –5.87 ms for both females and males. Similarly, based on the COBI mean C_{max} (1,383 ng/mL) following coadministration of COBI 150 mg and ATV 300 mg, mean . . QTcF was predicted to be –2.7 ms (–4.05 ms for females, #1.28 ms for males). At this COBI concentration, the nonlinear mixed-effect model-determined mean QTcM change due to COBI was predicted to be –5.18 ms for both females and males.

2.2.4.1.1.4. Conclusion

Cobicistat exhibited nonlinear PK with respect to dose, which is consistent with mechanism-based inhibition of CYP3A. Exposure to COBI in this study was deemed adequate to cover predicted therapeutic and supratherapeutic exposures.

Results of this study demonstrated a lack of COBI prolongation effect on the QTcF interval in healthy adult volunteers (upper bounds of the 2-sided 90% CIs were <10 ms at all timepoints after dosing). Therefore, this study met the International Conference on Harmonisation (ICH) E14 definition of a negative “thorough QT/QTc study”.

For further details, refer to Section 3.4.1.2.1.

2.2.5. Patient PK and PD

2.2.5.1. PK and PD of COBI-boosted DRV Coadministered With Background Regimen (TDF/FTC) in ART-naïve and ART-experienced HIV-1 Infected Subjects (Study GS-US-216-0130)

GS-US-216-0130

Module 5.3.5.2/GS-US-216-0130-W24-CSR

2.2.5.1.1. Objective

To assess the safety, tolerability, and antiviral activity of DRV/COBI following multiple doses of DRV/COBI 800/150 mg once daily coadministered as single agents with 2 NRTIs in HIV-1 infected ART-naïve subjects and ART-experienced subjects with no DRV RAMs.

2.2.5.1.2. Subjects and Methods

This is an ongoing Phase 3b, open-label, single-arm, multicenter study to evaluate the safety and antiviral activity of a regimen of DRV and COBI plus 2 fully active NRTIs in HIV-1 infected, ART-naïve and ART-experienced adult subjects with no DRV RAMs. Darunavir was formulated as the commercial 400-mg tablet (F030) and COBI was formulated as the commercial 150-mg tablet.

A total of 314 subjects (296 ART-naïve, 18 ART-experienced) were enrolled to receive at least 48 weeks of combined therapy with DRV/COBI 800/150 mg once daily coadministered as single

agents plus 2 NRTIs determined based on resistance at screening; 313 of these subjects were treated. The primary analysis was performed at Week 24, when all subjects had either been treated for 24 weeks or had discontinued.

After 48 weeks of treatment, subjects were given the option to participate in the extension phase of the study to receive COBI and attend study visits every 12 weeks until COBI becomes commercially available or development is terminated by Gilead. Subjects who completed the Week-48 visit and did not wish to participate in the extension phase of the study were required to complete a follow-up visit 30 days after the Week-48 visit. The final analysis will be performed when all subjects have either completed the extension phase or have discontinued, and will be reported at a later date. The current summary includes only data obtained at the Week-24 analysis.

Sparse blood sampling was performed in all subjects as part of their safety laboratory blood draws at all study visits from Weeks 2 to 24. In addition, a PK substudy with intensive sampling was performed in a subset of subjects at any time between Week 2 and Week 8 to obtain full PK profiles of DRV and COBI.

Darunavir and COBI were both taken with food.

2.2.5.1.3. Results

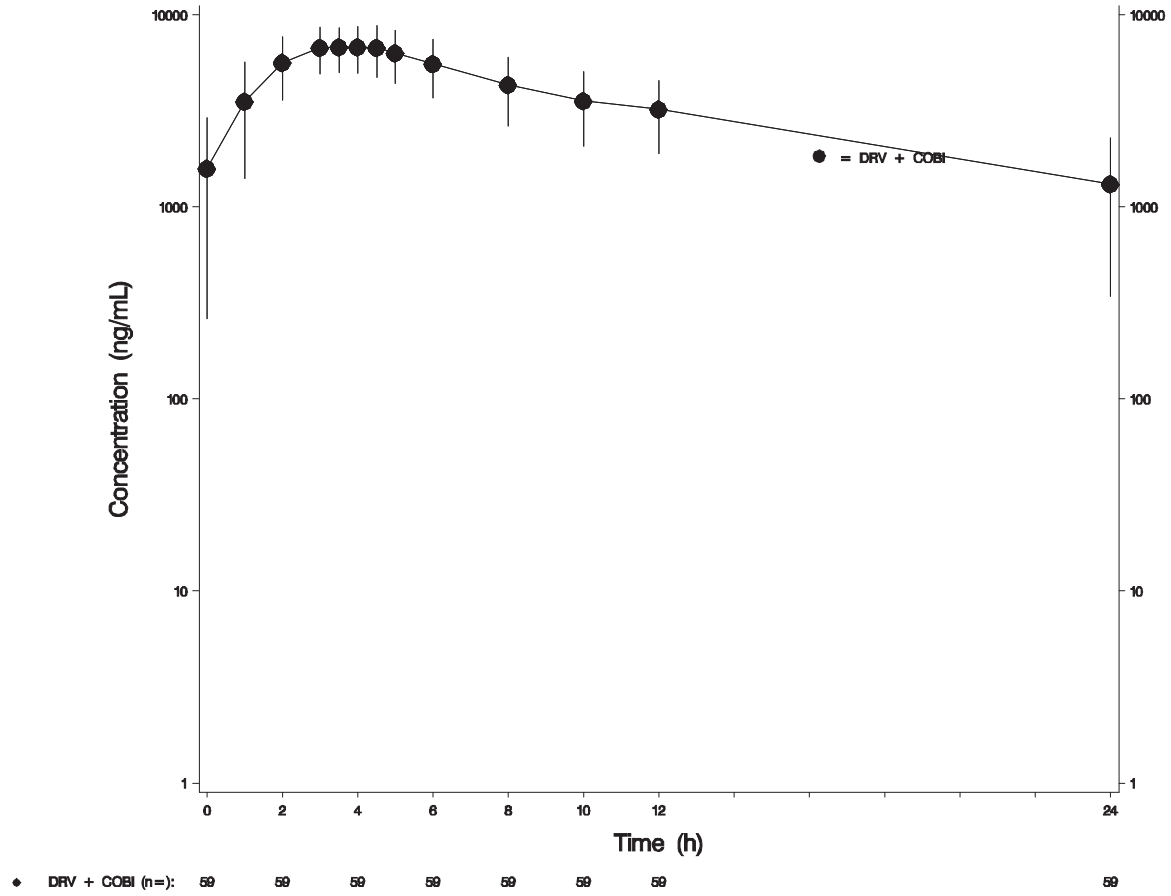
2.2.5.1.3.1. Population PK Analysis of DRV (Main Study)

The population PK analysis of DRV in study GS-US-216-0130 is described in a separate report (Module 5.3.3.5/GS-US-216-0130-W24-CSR-PopPK) and is summarized in Section 2.2.6.1.

2.2.5.1.3.2. Noncompartmental PK Analysis of DRV (PK Substudy)

In the PK substudy, following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in 60 subjects, maximum DRV concentrations were observed at 3.5 hours postdose (Figure 5).

Figure 5: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0130 Substudy)



Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Figure 10-1

The mean PK values for DRV following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents are summarized in Table 117. These PK values were generally higher than historical values in ART-naïve HIV-1 infected subjects (Section 3.1.3.3).

Table 117: Noncompartmental PK Parameters of DRV Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0130 Substudy)

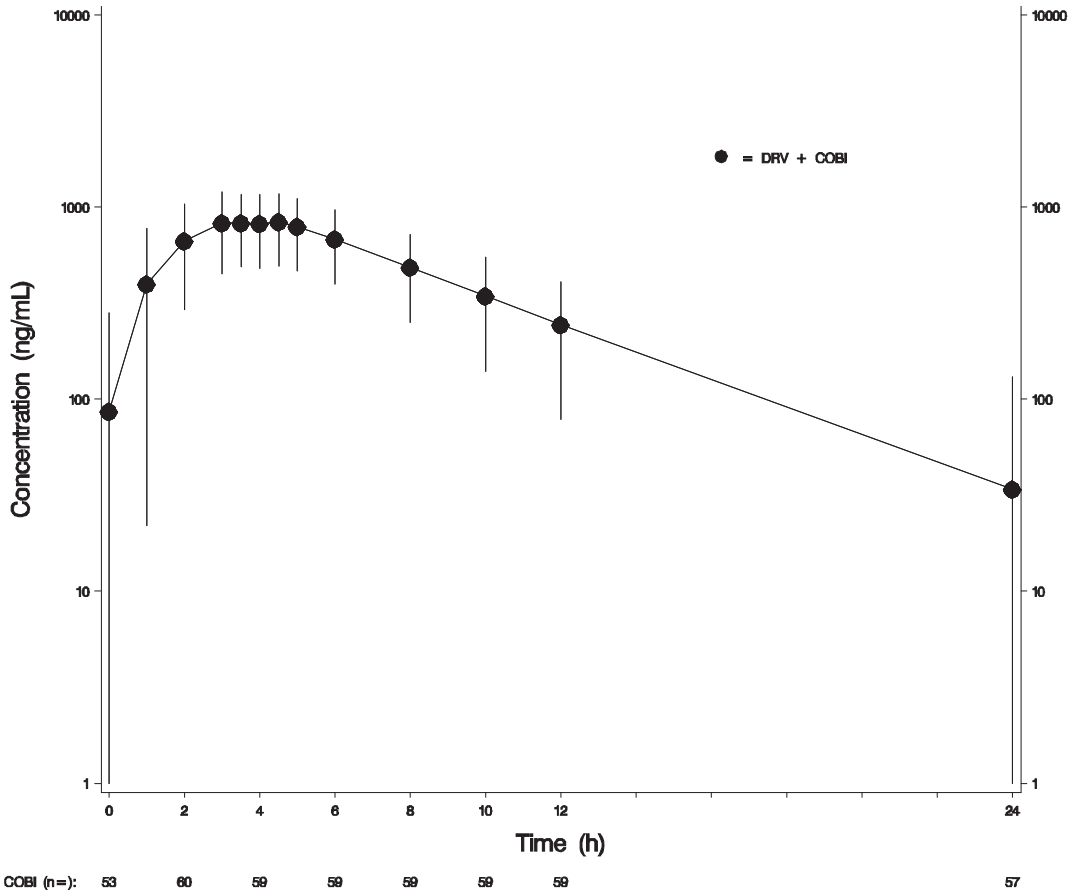
Parameter	Mean (SD); t_{max}: Median (Range)
N	59
t_{max}, h	3.5 (1.0-6.0)
C_{0h}, ng/mL	1,560 (1,328)
C_{max}, ng/mL	7,663 (1,920)
C_{24h}, ng/mL[a]	1,311 (969)
AUC_{24h}, ng.h/mL[b]	81,646 (26,322)
$t_{1/2,term}$, h	10.8 (10.0)

N=maximum number of subjects with data.
[a] Reported as C_τ.
[b] Reported as AUC_τ.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-1, Table 6.2.1.3, and Table 6.3.1.1

2.2.5.1.3.2.1. Noncompartmental PK Analysis of COBI (PK Substudy)

In the PK substudy, following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in 60 subjects, maximum COBI concentrations were observed 3.5 hours postdose (Figure 6).

Figure 6: Mean (SD) Plasma Concentration-Time Profiles of COBI Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0130 Substudy)



Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Figure 10-2

The mean PK values for COBI following multiple-dose administration of DRV/COBI 800/150 mg are summarized in Table 118. The PK values for COBI were modestly lower than those observed in the study GS-US-216-0115 in healthy subjects (mean [SD] AUC_{24h}: 10,370 [2,150] ng.h/mL; C_{max}: 1,376 [268] ng/mL) (Module 2.7.1/Section 2.1.1), but comparable with those observed in HIV-1 infected subjects treated with the EVG/COBI/FTC/TDF STR, which contains 150 mg COBI (mean [SD] AUC_{24h}: 8,300 [3,800] ng.h/mL; C_{max}: 1,100 [400] ng/mL).[47]

Table 118: Noncompartmental PK Parameters of COBI Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0130 Substudy)

Parameter	Mean (SD); t_{max}: Median (Range)
N	60
t_{max}, h	3.5 (0.9-6.0)
C_{0h}, ng/mL	76 (186)
C_{max}, ng/mL	991 (331)
C_{24h}, ng/mL[a]	33 (95)
AUC_{24h}, ng.h/mL[b]	7,596 (3,657)
$t_{½,term}$, h	3.8 (3.5)

N=maximum number of subjects with data.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-2, Table 6.2.2.3, and Table 6.3.2.1

2.2.5.1.3.2.2. Noncompartmental PK Analysis of FTC (PK Substudy)

The mean PK values for FTC following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents are summarized in Table 119 and were similar to historical data (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 10.1.3.2).

Table 119: Noncompartmental PK Parameters of FTC Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0130 Substudy)

Parameter	Mean (SD); t_{max}: Median (Range)
N	59
t_{max}, h	2.0 (1.0-5.0)
C_{0h}, ng/mL	147 (171)
C_{max}, ng/mL	1,862 (491)
C_{24h}, ng/mL[a]	113 (101)
AUC_{24h}, ng.h/mL[b]	11,793 (3,490)
$t_{1/2,term}$, h	7.3 (1.1)

N=maximum number of subjects with data.
[a] Reported as C_t.
[b] Reported as AUC_t.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-3, Table 6.2.4.3, and Table 6.3.4.1

2.2.5.1.3.2.3. Noncompartmental PK Analysis of Tenofovir (PK Substudy)

The mean PK values for tenofovir following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents are summarized in Table 120, and were similar to historical data following administration of TDF in combination with boosted PIs or the FDC of EVG/COBI/FTC/TDF (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 10.1.4.2).

Table 120: Noncompartmental PK Analysis of Tenofovir Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0130 Substudy)

Parameter	Mean (SD); t_{max}: Median (Range)
N	59
t_{max}, h	2.0 (0.7-4.7)
C_{0h}, ng/mL	84 (45)
C_{max}, ng/mL	382 (118)
C_{24h}, ng/mL[a]	78 (33)
AUC_{24h}, ng.h/mL[b]	3,613 (1,203)
$t_{1/2,term}$, h	13.7 (3.6)

N=maximum number of subjects with data.
[a] Reported as C_τ.
[b] Reported as AUC_τ.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-4, Table 6.2.3.3, and Table 6.3.3.1

2.2.5.1.3.3. Pharmacodynamics

The primary endpoint of this study was the onset of any treatment-emergent grade 3 or grade 4 AEs through Week 24. Sixteen of the 295 subjects (5.4%) in the ART-naïve group experienced grade 3 (14 subjects; 4.7%) or grade 4 (2 subjects; 0.7%) AEs. Two of the 18 subjects (11.1%) in the ART-experienced group experienced grade 3 AEs (none of which occurred in more than 1 subject), and none of the subjects had a grade 4 AE. Further details are available in Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.2.1.

The percentage of subjects with virologic success at Week 24 (plasma viral load of <50 HIV-1 RNA copies/mL) using the FDA-defined snapshot analysis algorithm was assessed. In the ART-naïve group, virologic success was achieved by 83.7% of subjects (247 of 295 subjects), virologic failure occurred in 9.8% of subjects (29 of 295 subjects), and 6.4% of subjects (19 of 295 subjects) had no virologic data for the Week 24 window. In the ART-experienced group (N=18), virologic success was achieved in 61.1% of subjects (11 of 18 subjects) and virologic failure occurred in 38.9% of subjects (7 of 18 subjects). Further details are available in Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 9.1.1.

2.2.5.1.3.4. PK/PD Relationships

Exposure-response relationships for virologic response and safety were assessed in a separate report and are summarized in Section 2.2.7.1.

2.2.5.1.4. Conclusion

- Plasma exposures of DRV were generally comparable to or higher than historical data from HIV-1 infected subjects (Sections 3.1.3.3).
- Plasma exposures of COBI were modestly lower than historical data from healthy subjects, but comparable with historical data from HIV-1 infected subjects (Module 2.7.1/Section 2.1.1 and STRIBILD® Prescribing Information[47]).
- DRV/COBI 800/150 mg once daily coadministered as single agents together with 2 NRTIs, was effective at suppressing the plasma viral load to <50 HIV-1 RNA copies/mL through

24 weeks in the ART-naïve and ART-experienced groups; the virologic response rate was lower in the ART-experienced group.

- DRV/COBI coadministered as single agents was generally well tolerated in the ART-naïve and ART-experienced groups.

2.2.5.2. Efficacy, Safety, and Tolerability of DRV/rtv Versus LPV/rtv in ART-naïve HIV-1 Infected Subjects (Week 48 Primary Efficacy Analysis) (Study TMC114-C211)

TMC114-C211-W48

Module 5.3.5.1/TMC114-C211-W48-CRR

2.2.5.2.1. Objective

To demonstrate the noninferiority in virologic response (confirmed plasma viral load of <50 HIV-1 RNA copies/mL) with DRV/rtv versus LPV/rtv at 48 weeks when administered in a fixed background regimen consisting of TDF and FTC.

2.2.5.2.2. Subjects and Methods

This was a Phase 3, randomized, controlled (LPV/rtv), open-label study to determine the efficacy, safety, and tolerability of DRV, administered as the 400-mg tablet formulation F021, together with rtv, and other ARV drugs over a 192-week treatment period. A total of 691 ART-naïve HIV-1 infected subjects with viral load ≥5,000 HIV-1 RNA copies/mL were randomized, and 689 subjects were treated.

At baseline, subjects started their ARV therapy, consisting of a PI (randomized in a 1:1 ratio to DRV/rtv 800/100 mg once daily or LPV/rtv 800/200 mg total daily dose) combined with a fixed background regimen consisting of TDF/FTC at a dose of 300/200 mg once daily.

In addition to efficacy and safety analyses, the PK of DRV were analyzed using rich sampling in a substudy and sparse sampling in the main study (population analysis), and PK/PD relationships were analyzed using the population approach.

The study included a screening period of approximately 14 to 28 days, and a 192-week treatment period followed by a 4-week follow-up period. Subjects meeting the per-protocol-defined criteria for virologic failure (DRV/rtv or LPV/rtv group), or who experienced a grade 4 AE or confirmed grade 4 (or specific grade 3) laboratory abnormality considered at least possibly related to DRV/rtv or LPV/rtv treatment, could enter the 96-week rollover phase of the study. The current summary describes the results of the primary efficacy analysis at 48 weeks.

DRV/rtv was to be taken within 30 minutes after completion of a meal. Whenever possible, TDF/FTC and DRV/rtv or LPV/rtv were to be taken at the same time. However, the usual prescribed dosing schedule had to be respected.

2.2.5.2.3. Results

2.2.5.2.3.1. Population PK Analysis of DRV (Main Study)

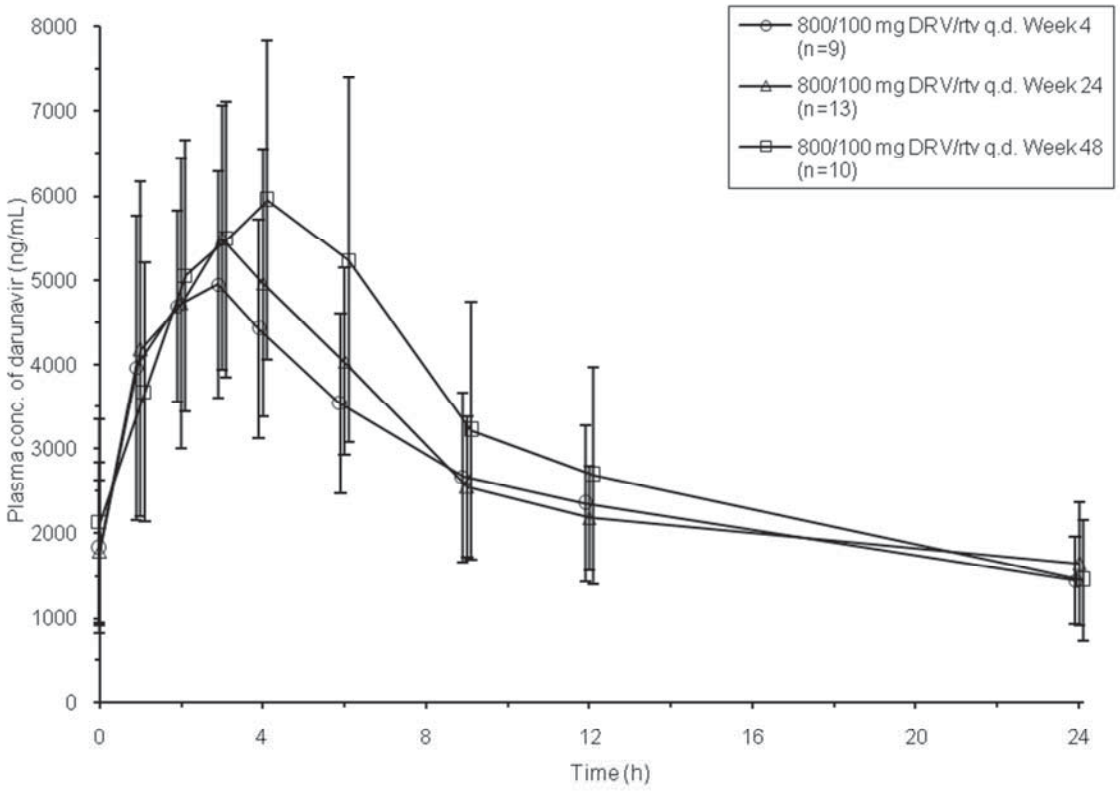
The population PK analysis of DRV in study TMC114-C211-W48 is described in a separate report (Module 5.3.3.5/TMC114-C935-CPOP) and is summarized in Section 2.2.6.2.

2.2.5.2.3.2. Noncompartmental PK Analysis of DRV (PK Substudy)

In the PK substudy, PK parameters were obtained for DRV and rtv after 4, 24, and 48 weeks of treatment. At each of these timepoints, subjects participated in a 24-hour PK sampling period in addition to the assessments required for the main study.

The mean plasma concentration-time curves of DRV at Weeks 4, 24, and 48 are shown in Figure 7.

Figure 7: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Administration of DRV/rtv 800/100 mg Once Daily for 4, 24, and 48 Weeks With a Fixed Background Regimen in ART-naïve HIV-1 Infected Subjects (TMC114-C211 PK Substudy)



Source: Module 5.3.5.1/TMC114-C211sub-CPK/Figure 1

The mean PK values for DRV were comparable between Weeks 4 and 24 (Table 121). At Week 48, the mean C_{max} and AUC_{24h} were somewhat higher compared to Weeks 4 and 24, but the individual values were in the same range at all 3 timepoints (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 4.7.2.5.1). The values for C_{min} were also

comparable across Weeks 4, 24, and 48. The median t_{max} was slightly prolonged at Week 48, with a larger ISV. The mean C_{0h} values were comparable between Weeks 4, 24, and 48, indicating steady-state and the absence of time-dependent PK during this period.

Table 121: Noncompartmental PK Parameters of DRV Following Administration of DRV/rtv 800/100 mg Once Daily for 4, 24, and 48 Weeks With a Fixed Background Regimen in ART-naïve HIV-1 Infected Subjects (TMC114-C211 PK Substudy)

	Mean (SD); t_{max}: Median (Range)		
Parameter	**Week 4**	**Week 24**	**Week 48**
N	9	13	10
t_{max}, h	3.00 (1.00-4.10)	3.00 (0.92-4.02)	3.50 (0.80-6.00)
C_{0h}, ng/mL	1,826 (1,003)	1,786 (838)	2,133 (1,220)
C_{min}, ng/mL	1,189 (410)	1,419 (671)	1,352 (688)
C_{max}, ng/mL	5,471 (1,320)	5,804 (1,558)	6,756 (1,683)
$C_{ss,av}$, ng/mL [a]	2,675 (758)	2,808 (767)	3,156 (1,100)
AUC_{24h}, ng.h/mL [b]	64,230 (18,210)	66,950 (18,610)	75,620 (26,440)
FI, %	167 (48.7)	161 (39.4)	185 (60.8)

N=maximum number of subjects with data.
Source: Module 5.3.5.1/TMC114-C211-W48-CRR/Table 79

2.2.5.2.3.2.1. Noncompartmental PK Analysis of rtv (PK Substudy)

The mean C_{min}, C_{max}, and AUC_{24h} of rtv were within the same range at Weeks 4, 24, and 48 (Table 122).

Table 122: Noncompartmental PK Parameters of rtv Following Administration of DRV/rtv 800/100 mg Once Daily for 4, 24, and 48 Weeks With a Fixed Background Regimen in ART-Naïve HIV-1 Infected Subjects (TMC114-C211 PK Substudy)

	Mean (SD); t_{max}: Median (Range)		
Parameter	**Week 4**	**Week 24**	**Week 48**
N	9	13	10
t_{max}, h	4.00 (0.00-6.00)	4.00 (1.00-6.08)	4.00 (1.98-6.00)
C_{0h}, ng/mL	141 (156)	111 (120)	94.4 (49.8)
C_{min}, ng/mL	84.1 (71.4)	78.0 (68.5)	51.0 (17.0)
C_{max}, ng/mL	603 (320)	556 (240)	685 (343)
$C_{ss,av}$, ng/mL [a]	245 (131)	223 (106)	247 (101)
AUC_{24h}, ng.h/mL [b]	5,891 (3,152)	5,331 (2,560)	5,933 (2,443)
FI, %	217 (45.5)	222 (47.7)	249 (71.5)

N=maximum number of subjects with data.
Source: Module 5.3.5.1/TMC114-C211-W48-CRR/Table 79

2.2.5.2.3.3. Pharmacodynamics

The primary efficacy variable was virologic response at Week 48, defined as the percentage of subjects with confirmed plasma viral load <50 HIV-1 RNA copies/mL (time to loss of virologic response [TLOVR]). The efficacy results of this study demonstrated noninferiority in virologic response with DRV/rtv 800/100 mg once daily when compared to a daily dose of LPV/rtv 800/200 mg (both in combination with a fixed background regimen of TDF/FTC). This result was supported by the results of the secondary virologic parameters (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 4.2).

2.2.5.2.3.4. PK/PD Relationships

Pharmacokinetic/PD relationships based on observed data were evaluated for the relationship between PK parameters and antiviral activity, and between PK and safety parameters and are described in detail in Section 2.2.7.2.

2.2.5.2.4. Conclusion

- Noninferiority of DRV/rtv versus LPV/rtv in virologic response, defined as a confirmed plasma viral load of <50 HIV-1 RNA copies/mL, was demonstrated at Week 48 (primary efficacy parameter). Similar trends were seen for the secondary virologic parameters.
- In general, the DRV PK parameters were comparable between Weeks 4 and 24; at Week 48, the mean C_{max} and AUC_{24h} were somewhat higher compared with Weeks 4 and 24, but individual values were within the same range at all 3 timepoints.
- The mean C_{min} and C_{0h} were comparable between Weeks 4, 24, and 48, indicating steady-state and the absence of time-dependent PK during this period.

2.2.5.3. Efficacy and Safety of DRV/rtv (800/100 mg) Once Daily Versus DRV/rtv (600/100 mg) Twice Daily in ART-experienced HIV-1 Infected Subjects With no DRV RAMs (Week 48 Analysis) (Study TMC114-C229)

TMC114-C229-W48

Module 5.3.5.1/TMC114-C229-W48-CRR

2.2.5.3.1. Objective

To demonstrate the noninferiority in virologic response with DRV/rtv 800/100 mg once daily versus 600/100 mg twice daily in early ART-experienced subjects with a noninferiority margin (delta) of 12%, when administered in combination with an individually selected optimized background regimen.

2.2.5.3.2. Subjects and Methods

This was a Phase 3, randomized, open-label study to compare efficacy, safety, and tolerability of DRV (tablet formulation F030 or F032), coadministered with rtv, as 800/100 mg once daily versus 600/100 mg twice daily over a 48-week treatment period. A total of 599 HIV-1 infected subjects who were early treatment-experienced (with screening genotype results showing no DRV RAMs) and had a viral load of >1,000 HIV-1 RNA copies/mL were randomized, and 590 subjects were treated. At baseline, subjects changed their screening regimen. An optimized background regimen was initiated, consisting of ≥2 NRTIs selected by the investigator. Additionally, subjects were randomized at baseline in a 1:1 ratio to receive a new PI regimen (along with the selected optimized background regimen) consisting of either DRV/rtv 800/100 mg once daily or DRV/rtv 600/100 mg twice daily.

The primary objective of the study was to demonstrate noninferiority in virologic response (defined as a confirmed plasma viral load of <50 HIV-1 RNA copies/mL [TLOVR algorithm])

with DRV/rtv 800/100 mg once daily versus DRV/rtv 600/100 mg twice daily at 48 weeks, when administered in combination with an optimized background regimen.

The study included a 4-week screening period and a 48-week treatment period, followed by a 4-week follow-up period. Randomization was stratified for screening viral load (≤50,000 and >50,000 HIV-1 RNA copies/mL). In regions where DRV is not yet commercially available or not yet reimbursed by the public and/or private health system, subjects who completed the 48 weeks of treatment with DRV/rtv, and who continued to benefit from this treatment, had the opportunity to continue DRV/rtv 600/100 mg twice daily in the extension phase of this study, where they have access to DRV/rtv until DRV is commercially available, reimbursed, or can be accessed from another source (eg, access program, government program).

The PK of DRV and rtv were analyzed using sparse sampling at Weeks 4 and 24 (population analysis). Pharmacokinetic/PD relationships were analyzed using the population approach.

DRV/rtv was to be taken within 30 minutes after completion of a meal.

2.2.5.3.3. Results

2.2.5.3.3.1. Population PK Analysis of DRV (Main Study)

The population PK analysis of DRV in study TMC114-C229-W48 is described in a separate report (Module 5.3.3.5/TMC114-C947-CPK) and is summarized in Section 2.2.6.3.

2.2.5.3.3.2. Pharmacodynamics

The primary analysis demonstrated noninferiority in confirmed virologic response (plasma viral load <50 HIV-1 RNA copies/mL at Week 48 [TLOVR]) with DRV/rtv 800/100 mg once daily when compared with DRV/rtv 600/100 mg twice daily, both in combination with an optimized background regimen. The virologic response rate was 72.1% with DRV/rtv once daily and 70.9% with DRV/rtv twice daily. The results of the secondary efficacy analyses were supportive of this finding for the primary analysis. Further details are available in Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.2.

2.2.5.3.3.3. PK/PD Relationships

Pharmacokinetic/PD relationships were analyzed by treatment group and by pooled treatment groups (ie, across both treatment groups), with the main focus being on the pooled analysis. Pharmacokinetic/PD relationships are described in detail in Section 2.2.7.3.

2.2.5.3.4. Conclusion

Virologic response (plasma viral load <50 HIV-1 RNA copies/mL at Week 48 [TLOVR], the primary efficacy parameter) with DRV/rtv 800/100 mg once daily (72.1%) was noninferior to the response with DRV/rtv 600/100 mg twice daily (70.9%) in ART-experienced HIV-1 infected adults with no DRV RAMs.

2.2.5.4. Integrated Analysis of DRV and rtv PK of 2 Dose-Finding Phase 2b Studies (TMC114-C202 and TMC114-C213) in ART-experienced HIV-1 Infected Subjects

TMC114-C926-CPKPD

Module 5.3.4.2/TMC114-C926-CPKPD

2.2.5.4.1. Objective

To summarize the PK of DRV and rtv from the Phase 2b studies TMC114-C202 and TMC114-C213.

2.2.5.4.2. Subjects and Methods

Studies TMC114-C202 and TMC114-C213 were both Phase 2b, randomized, controlled, partially blinded studies to evaluate the dose-response relationship of efficacy between different DRV/rtv treatment groups (DRV/rtv 400/100 mg once or twice daily, 800/100 mg once daily, and 600/100 mg twice daily [DRV tablet formulations F001 and F002]) after 24 weeks of treatment in HIV-1 infected subjects who were 3-class experienced and were receiving a stable PI-containing regimen. In addition, the safety, tolerability and the durability of efficacy of DRV, formulated as an oral tablet, and coadministered with rtv over a 96-week treatment period, were evaluated and compared with a control arm. The PK of DRV and rtv were assessed from rich sampling in PK substudies and from sparse sampling in the main studies.

Both studies were similar in design and differed only in the following:

- Study TMC114-C202 incorporated a 2-week phase at the start of treatment in which subjects were treated with functional monotherapy, where they substituted only the PIs used at screening for 1 of 4 DRV/rtv treatment groups, but stayed on the background NRTIs with or without enfuvirtide. Two weeks after the baseline timepoint, the background NRTIs with or without enfuvirtide in the background regimen used at screening were replaced by the investigator-selected optimized background regimen.
- In study TMC114-C213, subjects with hepatitis co-infection could be enrolled.

In study TMC114-C202, 278 subjects were included in this primary Week 24 analysis, and in study TMC114-C213, 318 subjects were included in this primary Week 24 analysis.

2.2.5.4.3. Results

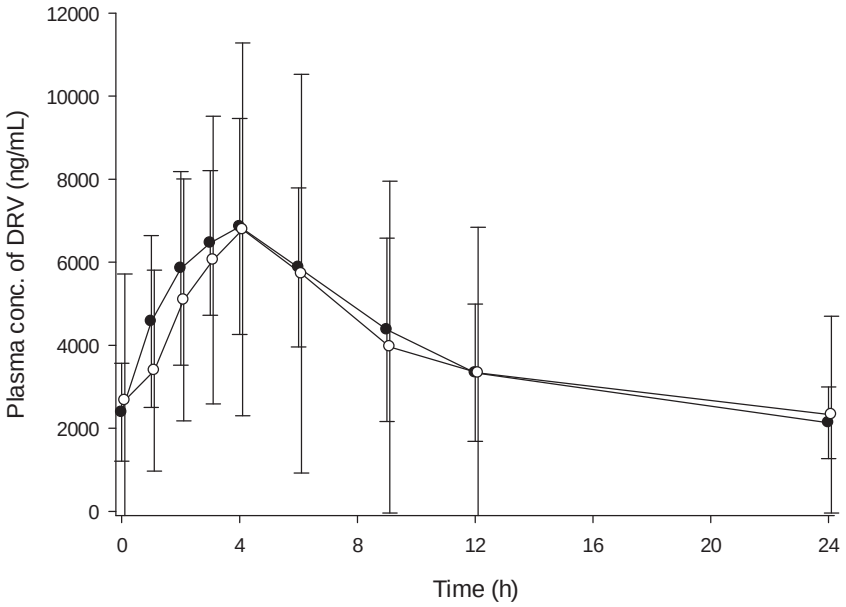
2.2.5.4.3.1. Population PK Analysis of DRV (Main Study)

The population PK analyses of DRV from both studies are summarized in Section 2.2.6.4.

2.2.5.4.3.2. Noncompartmental PK Analysis of DRV (PK Substudy)

In the PK substudies, PK parameters were obtained for DRV and rtv after 4 and 24 weeks of treatment. The mean plasma concentration-time curves of DRV following administration of DRV/rtv 800/100 mg once daily, for both studies combined, are shown in Figure 8.

Figure 8: Mean (SD) Plasma Concentration-Time Profiles of DRV Following Administration of DRV/rtv 800/100 mg Once Daily at Week 4 and Week 24 in ART-experienced HIV-1 Infected Subjects in Studies TMC114-C202 and TMC114-C213 (TMC114-C926-CPKPD)



Source: Module 5.3.4.2/TMC114-C926-CPKPD/Supporting Data Display 3

The mean PK values for DRV at 4 and 24 weeks are summarized in Table 123. Apart from at Week 4 in the twice daily groups of study TMC114-C213, DRV exposure (AUC) increased with dose for the once daily and twice daily regimens. The median t_{max} ranged from 2 to 4 hours.

Table 123: Noncompartmental PK Parameters of DRV Following Administration of DRV/rtv Once Daily for 4 and 24 Weeks in ART-experienced HIV-1 Infected Subjects in Studies TMC114-C202 and TMC114-C213 (TMC114-C926-CPKPD)

	Mean (SD); t_{max}: Median (Range)			
Parameter	**DRV/rtv 400/100 mg qd**	**DRV/rtv 800/100 mg qd**	**DRV/rtv 400/100 mg bid**	**DRV/rtv 600/100 mg bid**
Week 4				
N	10	9	15	8
t_{max}, h	2.0 (1.0-4.0)	4.0 (1.0-6.0)	3.0 (1.0-6.0)	3.0 (0.9-4.0)
C_{0h}, ng/mL	1,027 (455)	2,385 (1,178)	3,683 (1,581)	4,010 (1,635)
C_{min}, ng/mL	987 (444)	1,898 (945)	2,748 (1,369)	2,904 (1,516)
C_{max}, ng/mL	5,252 (1,609)	7,534 (2,209)	5,731 (1,836)	6,890 (1,729)
AUC_{12h}, ng.h/mL	-	-	50,714 (12,632)	54,243 (22,362)
AUC_{24h}, ng.h/mL	58,032 (21,429)	93,220 (34,677)	-	-
$C_{ss,av}$, ng/mL	2,418 (893)	3,884 (1,445)	4,226 (1,053)	4,520 (1,864)
FI, %	180 (45.7)	153 (30.9)	76.1 (25.9)	96.0 (29.7)
Week 24				
N	11	14	15	9
t_{max}, h	3.0 (1.0-4.0)	4.0 (2.0-6.0)	3.0 (1.0-12.0)	3.0 (1.0-4.1)
C_{0h}, ng/mL	1,199 (890)	2,667 (3,048)	2,567 (994)	4,086 (1,642)
C_{min}, ng/mL	1,083 (864)	1,956 (2,131)	2,202 (820)	3,386 (1,547)
C_{max}, ng/mL	4,748 (1,853)	7,091 (4,400)	5,309 (1,695)	6,468 (1,697)
AUC_{12h}, ng.h/mL	-	-	44,042 (15,583)	51,951 (13,246)
AUC_{24h}, ng.h/mL	56,894 (24,268)	91,485 (81,305)	-	-
$C_{ss,av}$, ng/mL	2,371 (1,011)	3,812 (3,388)	3,670 (1,299)	4,329 (1,104)
FI, %	163 (49.6)	157 (53.8)	81.4 (21.5)	74.3 (23.4)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.4.2/TMC114-C926-CPKPD/Table 9

2.2.5.4.3.2.1. Noncompartmental PK Analysis of rtv (PK Substudy)

The mean PK values for rtv at 4 and 24 weeks are summarized in Table 124.

Table 124: Noncompartmental PK Parameters of rtv Following Administration of DRV/rtv Once Daily for 4 and 24 Weeks in ART-experienced HIV-1 Infected Subjects in Study TMC114-C202 and TMC114-C213 (TMC114-C926-CPKPD)

	Mean (SD); t_{max}: Median (Range)			
Parameter	**DRV/rtv 400/100 mg qd**	**DRV/rtv 800/100 mg qd**	**DRV/rtv 400/100 mg bid**	**DRV/rtv 600/100 mg bid**
Week 4				
N	3	2	6	2
t_{max}, h	12 (3.1-12)	4.0 (4.0-4.0)	3.0 (1.0-6.0)	6.0 (6.0-6.1)
C_{min}, ng/mL	106 (82.4)	57.3 (6.01)	278 (133)	462 (19.8)
C_{max}, ng/mL	588 (285)	533 (142)	1,012 (648)	1,098 (272)
AUC_{12h}, ng.h/mL	-	-	7,118 (4,139)	9,304 (877)
AUC_{24h}, ng.h/mL	7,465 (4,701)	5,032 (282)	-	-
$C_{ss,av}$, ng/mL	311 (196)	210 (11.7)	593 (345)	775 (73.1)
FI, %	172 (69.4)	225 (52.3)	116 (22.2)	80.6 (30.0)
Week 24				
N	1	2	3	2
t_{max}, h	4.0	5.0 (1.0-9.1)	4.0 (4.0-4.1)	5.0 (4.1-6.0)
C_{min}, ng/mL	31.0	151 (137)	218 (15.3)	423 (379)
C_{max}, ng/mL	328	819 (284)	716 (99)	964 (660)
AUC_{12h}, ng.h/mL	-	-	5,143 (444)	8,705 (5,808)
AUC_{24h}, ng.h/mL	3,174	9,832 (6,211)	-	-
$C_{ss,av}$, ng/mL	132	410 (259)	429 (37.0)	725 (484)
FI, %	225	190 (83.8)	115 (16.9)	79 (14.2)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.4.2/TMC114-C926-CPKPD/Table 10

2.2.5.4.3.3. Pharmacodynamics

In studies TMC114-C202 and TMC114-C213, and therefore also for the integrated data from these studies, all selected dosages of DRV coadministered with 100 mg ritonavir exhibited a statistically superior ARV efficacy when compared with individually optimized ARV regimens used in the control group (optimized background regimen + selected PIs) (refer to Module 5.3.4.2/TMC114-C926-CPKPD/Section 4.4).

2.2.5.4.3.4. PK/PD Relationships

Pharmacokinetic/PD relationships based on observed data were evaluated for the relationship between PK parameters and antiviral activity, and between PK and safety parameters and are described in detail in Section 2.2.7.4.

2.2.5.4.4. Conclusion

- Apart from at Week 4 in the twice daily groups of study TMC114-C213, DRV exposure (AUC) increased with dose for the once daily and twice daily regimens.
- All DRV/rtv treatment regimens had superior ARV efficacy compared with the control treatment regimen.

2.2.6. Patient Population PK Analyses

2.2.6.1. Population PK Analysis at Week 24 Following Treatment With DRV/COBI in ART-naïve and ART-experienced HIV-1 Infected Subjects (Study GS-US-216-0130)

GS-US-216-0130

Module 5.3.3.5/GS-US-216-0130-W24-PopPK

2.2.6.1.1. Objective

Based upon data obtained from plasma sampling in study GS-US-216-0130 (Section 2.2.5.1) objectives were:

- To describe DRV plasma concentration-time data by updating a previously developed population PK model.
- To identify and quantify covariate effects on DRV PK.
- To evaluate the final population PK model for DRV using simulation techniques.
- To determine and summarize the individual empirical Bayesian PK parameter estimates for DRV C_{0h}, AUC_{τ}, $C_{ss,av}$, and CL/F at Week 24.

2.2.6.1.2. Methods

Based on a previously developed population PK model for DRV, an updated model was developed using a subset of richly sampled PK data collected in study GS-US-216-0130 (ie, the PK substudy). Model parameters were then re-estimated using the rich sampled data available from the Week 24 dataset. All subjects had sparse sampling data for DRV at Week 24, and some subjects had sparse sampling data beyond Week 24. The final model was then used together with those sparse and rich sampled data for the Bayesian feedback analysis to estimate the individual PK parameters (AUC_{24h} and C_{0h}) of DRV. A total of 53 subjects were included in the initial model build dataset, with 55 subjects included in the parameter re-estimation dataset. All subjects with available PK data (298 subjects) were included in the Week-24 Bayesian feedback analysis dataset.

The model build and Bayesian feedback analysis were performed using mixed-effects modeling methods, as implemented in NONMEM (version VII level 2.0). Models were fitted to untransformed data using the first-order conditional estimation method in NONMEM with the INTERACTION option. For the empirical Bayes estimation, MAXEVAL was set to 0.

2.2.6.1.3. Results

2.2.6.1.3.1. Model Building

The best model to describe the PK of DRV was a 2-compartment disposition model with a sequential zero-order-first-order absorption. The effects of total daily dose and AAG on CL/F were retained from the original model. The relative bioavailability term was corrected for the commercial formulation (compared to the tablet used in previous clinical studies), and was fixed

to a value of 1.18, as determined in the previously developed model. This allowed CL/F and central volume of distribution (V_c/F) to be directly compared with previous estimates.

Intersubject variability terms were included on the disposition parameters CL/F, V_c/F, and intercompartmental clearance (CL_p/F), with an ISV term also included on the zero-order absorption duration parameter D1. The ISV term on the peripheral volume of distribution (V_p/F) was fixed to 55.7 %CV, a value previously determined for DRV. The median prediction error for the model was 2.61%, and the median absolute prediction error was 7.43%.

The model was therefore considered acceptable for determination of individual DRV exposure metrics in the Bayesian feedback analysis. Parameter estimates for the final model are shown in Table 125.

Table 125: Final Population PK Model Parameter Estimates of DRV Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents in Study GS-US-216-0130

Parameter		Parameter Estimate	Parameter SE (%CV)	ISV Estimate (%CV)	ISV SE (%CV)
CL_{INT}/F (L/h)	θ_1	51.6	3.4	24.9	18.3
Effect of TDD on CL_{INT}/F	θ_2	0.388 [a]	-	-	-
Effect of AAG on CL_{INT}/F (dL/mg)	θ_3	0.030 [a]	-	-	-
V_c/F (L)	θ_4	35.6	19.9	15.6	210
CL_p/F (L/h)	θ_5	24.0	19.4	51.0	34.3
V_p/F (L)	θ_6	90.0	10.4	55.7 FIXED	-
KA (/h)	θ_7	0.393	18.5	-	-
F_{REL}	θ_8	1.18 [a]	-	-	-
D1(h)	θ_9	1.49 [b]	11.1	88.4	27.4
RUV (%CV)	-	18.2	20.5	-	-

CL_{INT} /F=intrinsic clearance; D1=zero-order duration of input; F_{REL}=relative bioavailability; KA=absorption rate constant; RUV=residual unexplained variability; TDD=total daily dose.

[a] Parameter fixed.

[b] Estimate shown has been converted out of logit domain.

Source: Module 5.3.3.5/GS-US-216-0130-W24-PopPK/Table 15

No significant covariate was identified so that the final model was the same as the base model.

2.2.6.1.3.2. Bayesian Feedback

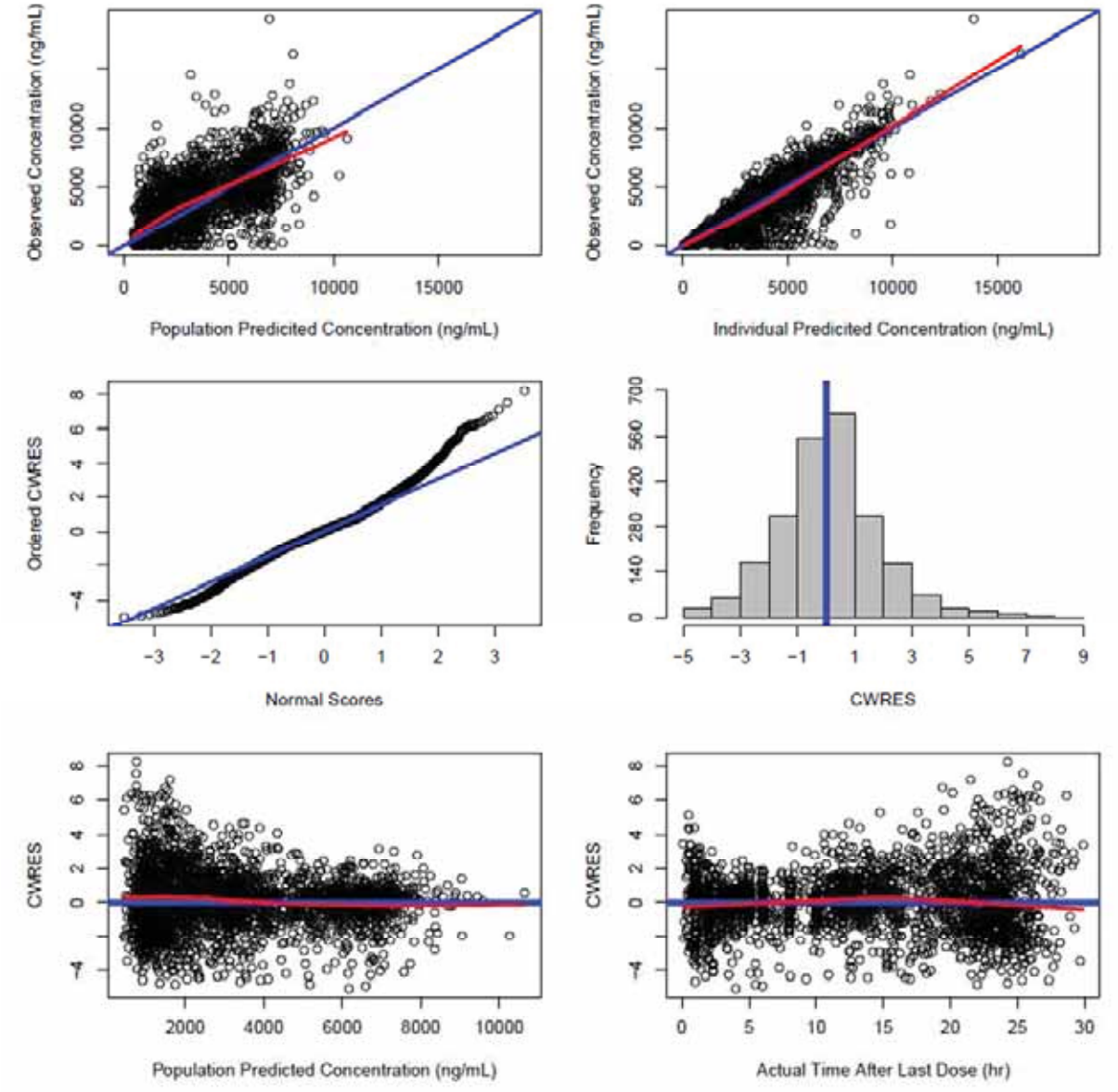
There were a total of 2,364 PK samples available for the Bayesian feedback analysis. The mean (range) number of PK samples per subject was 7.9 (1 to 19).

The final model was fitted to the Week-24 Bayesian feedback dataset with parameters fixed to those obtained during the estimation process. Plots of observed versus population predicted plasma concentrations and observed versus individual predicted plasma concentrations of DRV for the Bayesian feedback at Week 24 were similar to the plots for the final model and showed no obvious bias (Figure 9). However, the distribution of observations around the line of unity when compared to individual predicted concentrations was wider for the final model, suggesting that the model was less precise when applied to this dataset. The conditional weighted residuals

were evenly distributed, with no skewness. A visual predictive check showed that the model adequately described the data (Figure 10).

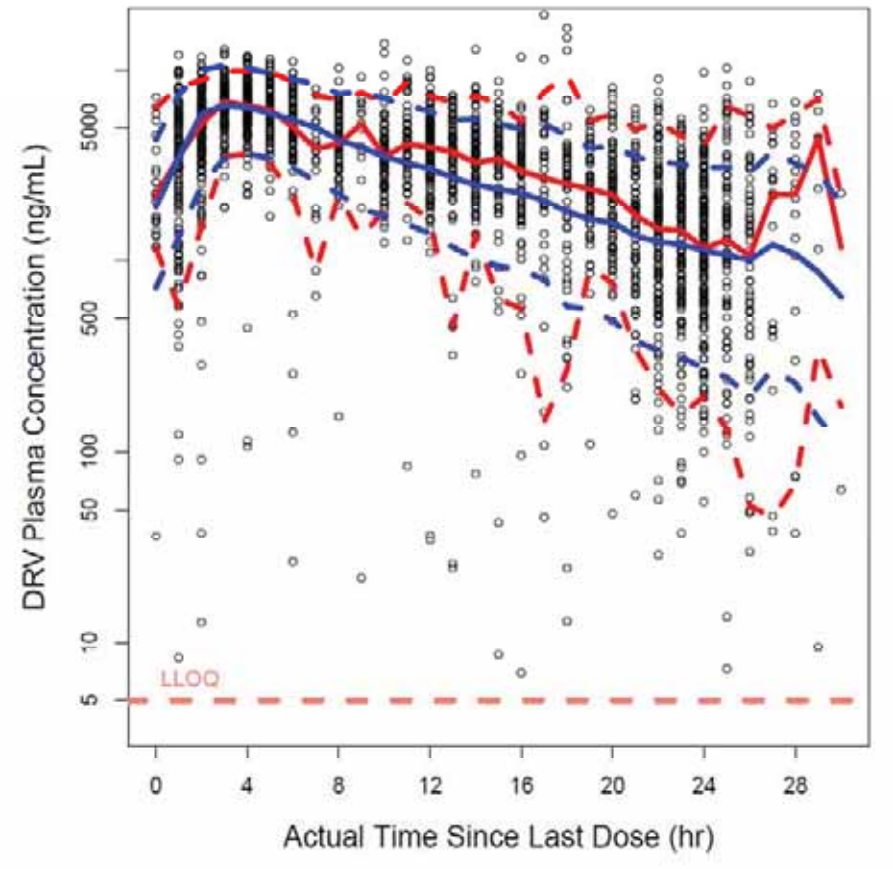
The median prediction error and median absolute prediction error for the model when fitted to the Bayesian feedback dataset were #1.83% and 17.3%, respectively. This indicated that the model was suitable for determination of individual DRV exposure metrics.

Figure 9 Goodness of Fit Plots for the Updated Population PK Model of Study GS-US-216-0130 at Week 24



CWRES=conditional weighted residual.
The blue solid line in the top panel represents the line of unity with the solid red line representing a smoother of the data.
Source: Module 5.3.3.5/GS-US-216-0130-W24-PopPK/Figure 15

Figure 10 Visual Predictive Check for the Bayesian Feedback at Week 24



Black circles=observed data; lower and upper red dashed lines=5th and 95th percentiles for the observed data; red solid line=50th percentile for the observed data; lower and upper blue dashed lines=5th and 95th percentiles for the simulated data; blue solid line=50th percentile for the simulated data; dashed horizontal pink line=lower limit of quantification.
Source: Module 5.3.3.5/GS-US-216-0130-W24-PopPK/Figure 17

The population PK parameter estimates for DRV are summarized in Table 126.

Table 126: Population PK Parameter Estimates for DRV Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (Study GS-US-216-0130)

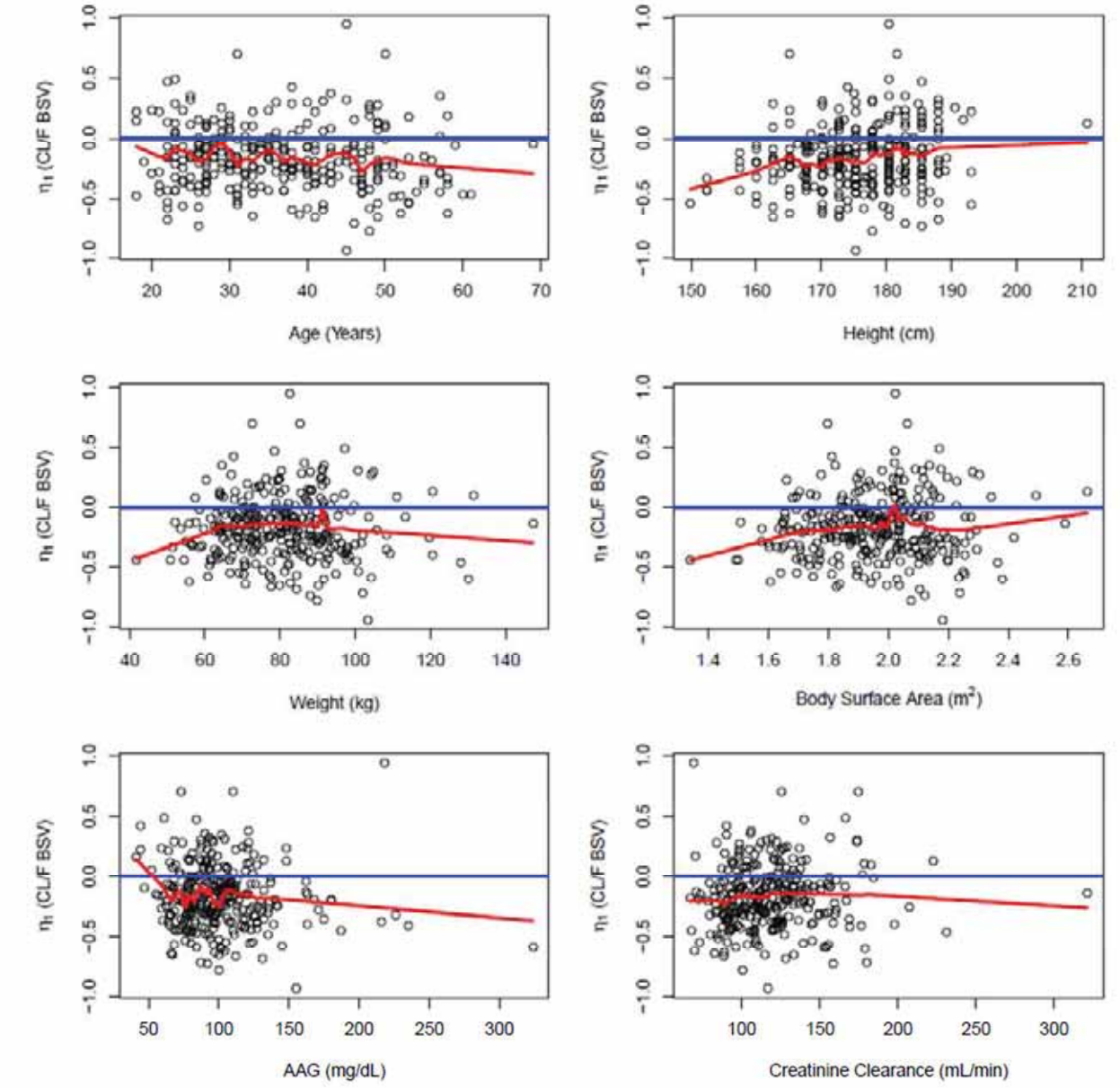
Parameter	Mean (SD); Median (Range)
N	298
C_{0h}, ng/mL	2,043 (1,257)
	1,875 (70-6,890)
AUC_{24h}, ng.h/mL	100,152 (32,042)
	96,900 (34,500-224,000)

N=maximum number of subjects with data.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-5

Further covariates that were assessed for their potential to explain variability in the PK of DRV included age, height, weight, body surface area, body mass index, creatinine clearance, sex, and race. Graphical analyses between individual parameters and these covariates suggested that age and sex may explain some of the variability in CL/F, although no significant covariate could be

identified during the model building process (Figure 11). Similar findings were also observed for V_p/F (Module 5.3.3.5/GS-US-216-0130-W24-PopPK/Figure 36).

Figure 11 Relationship Between ETA on CL/F and Continuous Covariates



BSV=between subject variability (synonymous with ISV).
The blue solid line represents the line of unity, and the red solid line represents the trend of the data.
Source: Module 5.3.3.5/GS-US-216-0130-W24-PopPK/Figure 34

2.2.6.1.4. Conclusion

- The PK of DRV can be described by a 2-compartment model with a zero-order-first-order input.

- Graphical analyses between individual parameters and these covariates suggested that age and sex may explain some of the variability in CL/F and V_p/F, although no significant covariate could be identified during the model building process.
- The individual PK parameters and exposure metrics for DRV were successfully determined with good precision and no bias.

2.2.6.2. Population PK Analysis at Week 48 Following Treatment With DRV/rtv Versus LPV/rtv in ART-naïve HIV-1 Infected Subjects (Study TMC114-C211)

TMC114-C935-CPOP

Module 5.3.3.5/TMC114-C935-CPOP

2.2.6.2.1. Objective

To determine individual PK model parameters of DRV and rtv in subjects who participated in study TMC114-C211 (Section 2.2.5.2) using Bayes' estimation based on previously developed population PK models.

2.2.6.2.2. Methods

Empirical Bayesian estimates of DRV exposure for data from subjects participating in study TMC114-C211 were derived using a population PK model taking into account AAG levels and total daily dose of DRV. The data used in the current analysis were obtained from 335 subjects that were treated with DRV 800 mg once daily together with rtv 100 mg once daily.

The model used in the feedback was a 2-compartmental model with first-order absorption of DRV given as a 400-mg tablet (formulation F021) under fed conditions in combination with a low dose of rtv. Apparent oral clearance was modeled to be dependent on total daily DRV dose and AAG concentrations, with a decreasing apparent total clearance of DRV with higher concentrations of AAG.

Empirical Bayes estimation was performed using mixed-effects modeling methods, as implemented in NONMEM (version V, using the MAXEVAL=0 option in the $ESTIMATION record).

2.2.6.2.3. Results

2.2.6.2.3.1. Model Building

A previously developed 2-compartmental PK model with first-order absorption was used for the empirical Bayes' estimation of PK parameters. Parameter estimates for the original model are shown in Table 127.

Table 127: PK Model Parameter Estimates of DRV from the Original Population PK Model

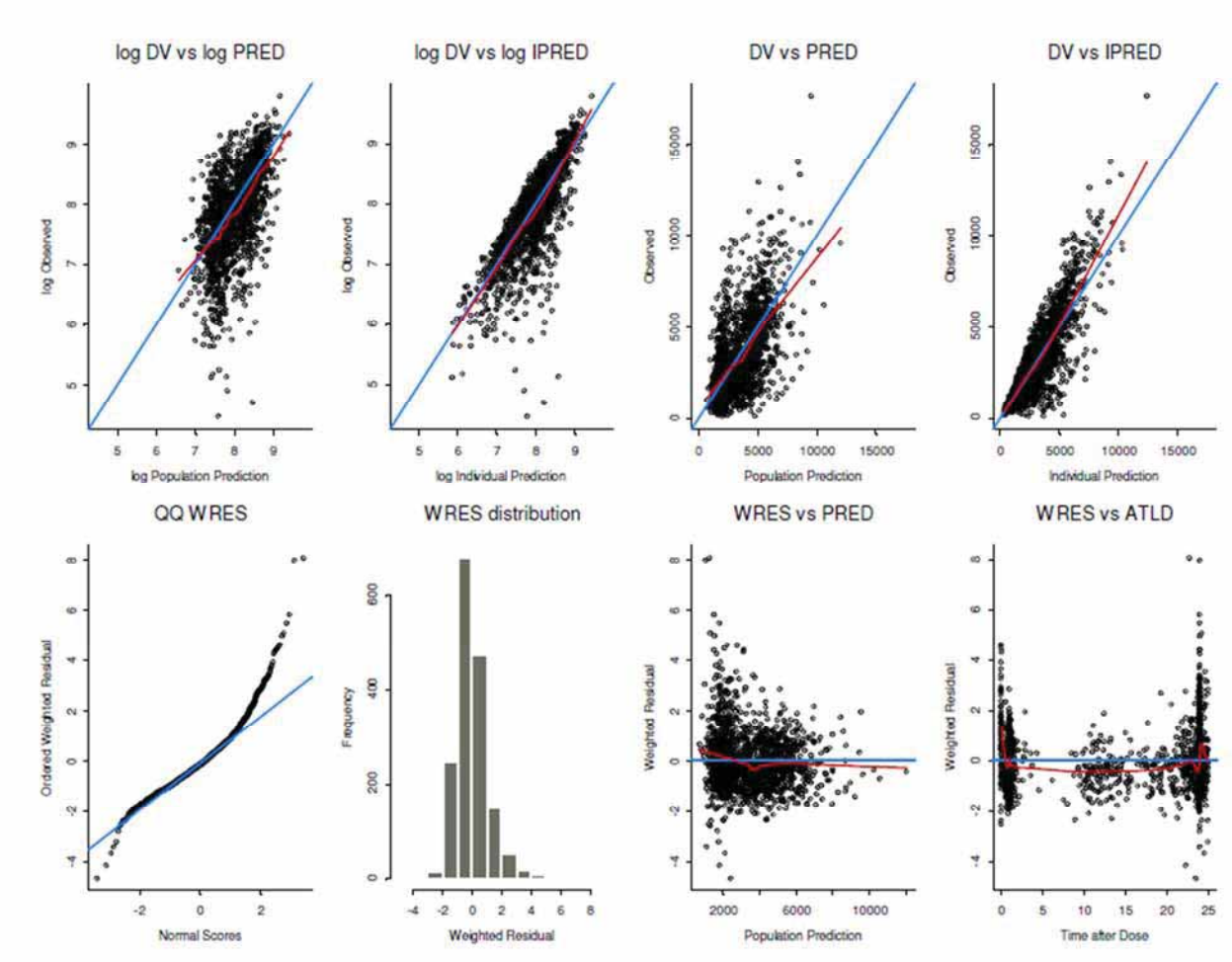
Parameter	Parameter Estimate	Parameter SE (%CV)	ISV Estimate (%CV)	ISV SE (%CV)
CL_{INT}/F (L/h)	41.9	13	26	8
Effect of TDD on CL_{INT}/F	0.388	8.8	-	-
Effect of AAG (dL/mg)	0.030	18	-	-
V_c/F (L)	122	8.2	88 [a]	23
CL_p/F (L/h)	15.0	11	65	30
V_p/F (L)	84.3	11	56	36
KA (/h)	0.455	8.1	74 [a]	17
F_{REL}	1.18	1.6	-	-
Residual Error	0.122	4.2	-	-

CL_{INT} /F=intrinsic clearance; F_{REL}=relative bioavailability; KA=absorption rate constant; TDD=total daily dose.
[a] Correlation between variance estimates of apparent central volume and absorption rate constant estimated at 0.61.
Source: Module 5.3.3.5/TMC114-C935-CPOP/Table 5

2.2.6.2.3.2. Bayesian Feedback

The goodness of fit plots for the empirical Bayes' estimates are shown in Figure 12. Individual parameters and concentrations were well estimated. The population predictions had a slight bias when comparing the plots for DRV concentration versus population predictions. An overprediction of the concentrations is present, as can be seen from inspection of the weighted residuals. This bias is not evident in the plots for the individual predictions, which is as expected, because the model will adjust the individual parameter estimates so that a good individual fit can be obtained. The cause of this bias could not easily be ascertained using the current study data.

Figure 12 Goodness of Fit Plots for the Empirical Bayes' Estimates for DRV



DV=DRV concentration; WRES=Weighted residual.
Red lines=observed trend; blue lines=expected trend.
Source: Module 5.3.3.5/TMC114-C935-CPOP/Figure 6

The population PK parameter estimates for DRV are summarized in Table 128. The C_{0h} exceeded the predefined value of 55 ng/mL (based on the EC_{50} value for wild-type HIV-1 strains when corrected for protein binding) in all subjects.

Table 128: Population PK Parameter Estimates for DRV Following Administration of DRV/rtv at a Dose of 800/100 mg Once Daily With a Fixed Background Regimen in ART-Naïve HIV 1 Infected Subjects (Study TMC114-C211)

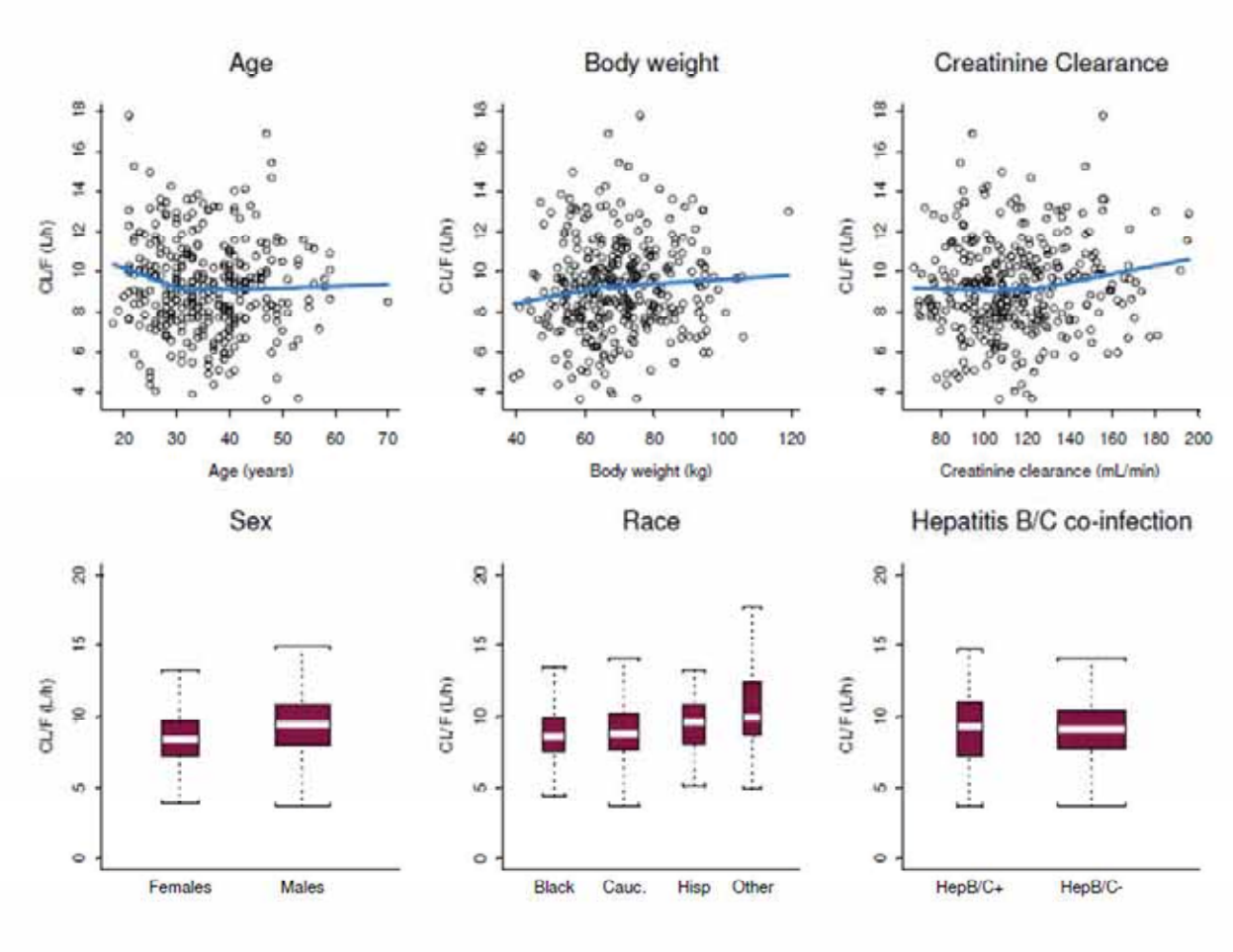
Parameter	Median (Range)
N	335
C_{0h}, ng/mL	2,041 (368-7,242)
AUC_{24h}, ng.h/mL	87,854 (45,000-219,240)

N=maximum number of subjects with data.
Source: Module 5.3.5.1/TMC114-C211-W48-CRR/Table 78

Descriptive analysis showed that age, weight, and hepatitis B and/or C virus co-infection status did not appear to influence the DRV PK (Figure 13 and refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 4.7.1). Higher baseline AAG levels were associated with higher values for

DRV AUC_{24h} and C_{0h}. Female subjects had an approximately 1.10-fold (N=102) higher exposure compared with males (N=233). There was an approximately 13% lower exposure in Asian subjects (N=44) compared to Caucasian subjects (N=135). These findings were supported by analysis of covariance (ANCOVA) (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Supporting Data Display PK/PD.3). These differences in exposure were relatively small compared to the overall variability and were not considered clinically relevant. The relationship between CL/F and creatinine clearance was not considered clinically relevant.

Figure 13 Relationship Between Median DRV CL/F and Covariates



The blue solid line represents the line of unity, and the red solid line represents the trend of the data.
Source: Module 5.3.3.5/TMC114-C935-CPOP/Figure 8

2.2.6.2.4. Conclusion

- Individual parameters and concentrations were well estimated. There was a small bias in population predictions, indicating a model parameter may have a different value in the current study.
- DRV trough concentrations exceeded the predefined value of 55 ng/mL (the EC_{50} for wild-type HIV-1 strains when corrected for protein binding) in all subjects.

- Graphical analysis of the relationship between CL/F and the covariates age, body weight, sex, creatinine clearance, race, and hepatitis co-infection status revealed no clinically relevant covariate.

2.2.6.3. Population PK Analysis at Week 48 Following Treatment With DRV/rtv Versus LPV/rtv in ART-experienced HIV-1 Infected Subjects With no DRV RAMs (Study TMC114-C229)

TMC114-C947-CPK

Module 5.3.3.5/TMC114-C947-CPK

2.2.6.3.1. Objective

To determine individual PK model parameters of DRV and rtv in subjects who participated in study TMC114-C229 (Section 2.2.5.3) using Bayes' estimation based on previously developed population PK models.

2.2.6.3.2. Methods

In study TMC114-C229 in ART-experienced HIV-1 infected subjects, in which DRV/rtv was administered at a dose of 800/100 mg once daily or 600/100 mg twice daily, sparse sampling for the determination of plasma concentrations of DRV was performed at Weeks 4 and 48.

Empirical Bayesian estimates of DRV exposure for data from subjects participating in study TMC114-C229 were derived using previously developed population PK models. The DRV model used was a 2-compartmental model with first-order absorption where CL/F was dependent upon free drug concentrations, which in turn were dependent upon AAG concentrations and the affinity of DRV for AAG. A correction factor to account for dose non-linearity in CL/F was also included in the model. The rtv model used in the analysis was a 1-compartmental model with a combined zero-first order input following a lag time together with first-order elimination. The model included 2 subpopulations to describe the partition between subjects that had a lag time and those that had no lag time.

Empirical Bayes estimation was performed using mixed-effects modeling methods, as implemented in NONMEM (using the MAXEVAL=0 option in the $ESTIMATION record).

2.2.6.3.3. Results

2.2.6.3.3.1. Model Building

A previously developed 2-compartmental PK model with first-order absorption was used for the empirical Bayes' estimation of DRV PK parameters and is summarized in Section 2.2.6.2.3.1, with parameter estimates shown in Table 127. Parameter estimates for the rtv model are shown in Table 129.

Table 129: PK Model Parameter Estimates of rtv From the Original Population PK Model

Parameter	Parameter Estimate	Parameter SE (%CV)	ISV Estimate (%CV)	ISV SE (%CV)	IOV SE Estimate (%CV)	IOV SE (%CV)
PLAG	#0.45	FIXED	-	-	-	-
CL/F (L/h)	22.7	3.9	41.0	16	24.8	17
V/F (L)	181	5.1	38.2	21	23.0	39
D1 (h)	1.47	3.8	-	-	-	-
KA (/h)	1.29	19	57.7	126	178	22
ALAG (L/h)	2.14	4.3	39.4	35	26.9	46
F1	-	-	-	-	37.6	25
WT on CL/F	1.15	21	-	-	-	-
WT pm V/F	1.07	23	-	-	-	-

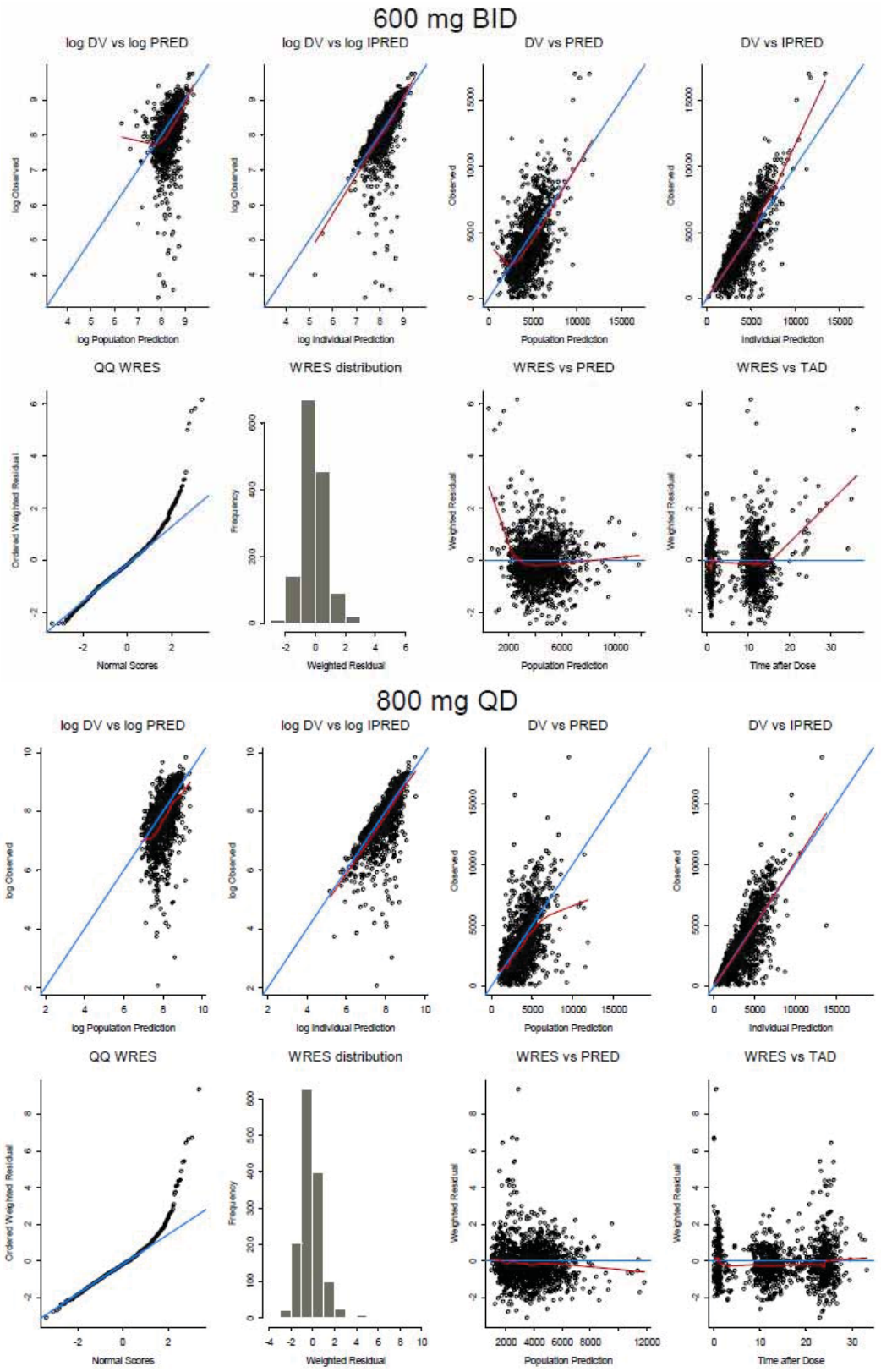
ALAG=lag time of the absorption; D1=duration of zero order input; F1=bioavailability; IOV=inter-occasion variability; KA=absorption rate constant; PLAG=mixing parameter for bimodal distribution on ALAG; V/F=apparent volume of distribution.
Source: Module 5.3.3.5/TMC114-C947-CPK/Table 5

2.2.6.3.3.2. Bayesian Feedback

The goodness of fit plots for the empirical Bayes' estimates when DRV was administered as 800 mg once daily or 600 mg twice daily (together with 100 mg rtv once or twice daily) are shown in Figure 14. The plots for the DRV 600 mg twice daily analysis suggest a slight bias for the individual predicted concentrations, which are under-predicted at high concentrations and somewhat over-predicted at low concentrations, and also for typical predicted concentrations. For DRV 800 mg once daily, the plots suggest almost no bias in individual predicted concentrations and a slight over-prediction for typical predicted concentrations. The weighted residuals were normally distributed.

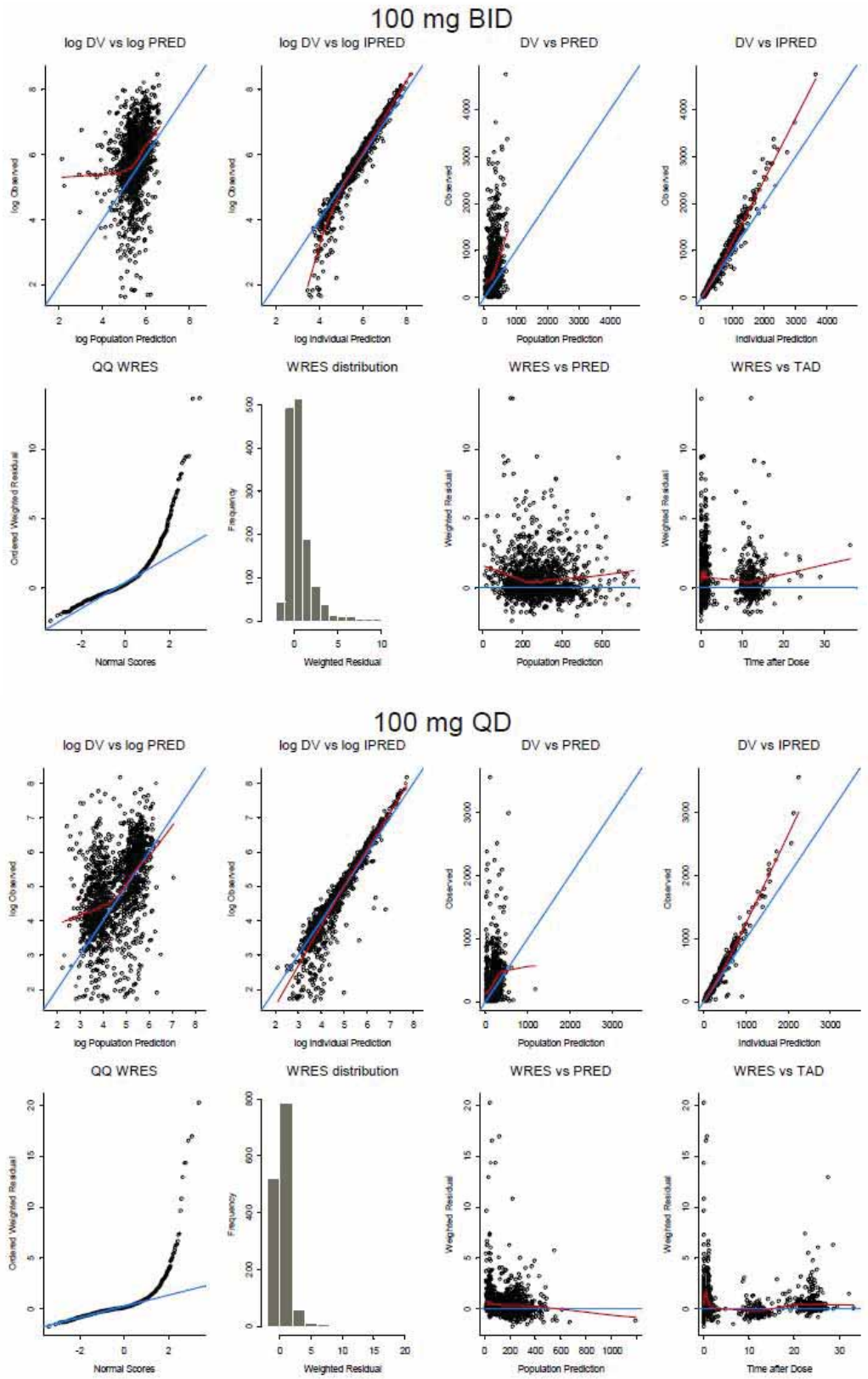
The goodness of fit plots for the empirical Bayes' estimates when rtv was administered as 100 mg once daily or twice daily are shown in Figure 15. All plots showed bias and the weighted residuals were skewed and not normally distributed. These results were due to the overall bias in the predictions as a result of differing PK data between the model development and study TMC114-C229 datasets (C_{max} was greater in study C229).

Figure 14 Goodness of Fit Plots for the Empirical Bayes' Estimation for DRV



WRES=weighted residual.
Red lines=observed trend; blue lines=expected trend.
Source: Module 5.3.3.5/TMC114-C947-CPK/Figure 5 and Figure 6

Figure 15 Goodness of Fit Plots for the Empirical Bayes' Estimation for rtv



WRES=weighted residual.
Red lines=observed trend; blue lines=expected trend.
Source: Module 5.3.3.5/T TMC114-C947-CPK/Figure 9 and Figure 10

2.2.6.3.3.2.1. DRV PK Estimates

The population PK parameter estimates for DRV are summarized in Table 130. Dosing with DRV/rtv once daily resulted in lower C_{0h} and AUC_{24h} values compared with dosing with DRV/rtv twice daily. Despite the lower DRV trough and lower overall exposure with DRV/rtv 800/100 mg once daily, comparable efficacy to the DRV/rtv 600/100 mg twice daily treatment group was observed (see Section 2.2.5.3.3.2), confirming that adequate DRV exposures were achieved following DRV/rtv once daily dosing. The C_{0h} exceeded the predefined value of 55 ng/mL (based on the EC_{50} value for wild-type HIV-1 strains when corrected for protein binding) in all subjects.

Table 130: Population PK Parameter Estimates for DRV Following Administration of DRV/rtv at a Dose of 800/100 mg Once Daily or 600/100 mg Twice Daily in ART-Experienced HIV 1 Infected Subjects (Study TMC114-C229)

	Median (Range)	
Parameter	**DRV/rtv 800/100 mg qd**	**DRV/rtv 600/100 mg bid**
N	280	278
C_{0h}, ng/mL	1,896 (184-7,881)	3,197 (250-11,865)
AUC_{24h}, ng.h/mL	87,788 (45,456-23,6920)	109,401 (48,934-323,820)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.5.1/TMC114-C229-W48-CRR/Table 84 and Table 85

Descriptive analyses of the DRV PK parameters by subgroups revealed the following with respect to DRV AUC_{24h} (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.7.1.1 and Module 5.3.3.5/TMC114-C947-CPK/Section 6.1.3):

- *Plasma AAG level at baseline*: For DRV/rtv once daily and twice daily, DRV exposure was approximately 38% higher in subjects with a baseline AAG level of >1.11 g/L than in subjects with a baseline AAG level of ≤0.80 g/L. Thus, higher plasma concentrations of AAG at baseline were associated with higher exposures to DRV.
- *Hepatitis co-infection status*: No apparent effect on DRV exposure.
- *Sex:* There was a trend towards higher DRV exposure in females (approximately 1.13-fold with DRV/rtv once daily and approximately 1.04-fold with DRV/rtv twice daily) compared with males.
- *Age*: No apparent effect on DRV exposure.
- *Race*: There was a trend towards lower DRV exposure in Asian subjects (approximately 15% with DRV/rtv once daily and twice daily) compared with Caucasian subjects.
- *Region*: There was a trend towards lower DRV exposure in subjects from the Asian region (approximately 20% with DRV/rtv once daily and approximately 16% with DRV/rtv twice daily) compared with subjects from North America. There was also a trend towards higher exposure in subjects from the African region (approximately 17% with DRV/rtv once daily and approximately 23% with DRV/rtv twice daily) compared with subjects from North America.
- *Weight*: No apparent effect on DRV exposure.
- *Creatinine clearance*: No apparent effect on DRV exposure.

The small differences in DRV exposure in these subgroups were not considered to be clinically relevant. The findings of these descriptive analyses were supported by ANCOVAs. In all subgroup analyses, similar trends to those observed for DRV AUC_{24h} were also observed for DRV C_{0h}.

2.2.6.3.3.2.2. RTV PK Estimates

The Bayesian estimates of the rtv PK parameters following treatment with DRV/rtv 800/100 mg once daily or DRV/rtv 600/100 mg twice daily are summarized in Table 131. The C_{0h} and AUC_{24h} values for rtv were lower following dosing with DRV/rtv once daily compared with dosing with DRV/rtv twice daily. Despite the lower rtv exposure with DRV/rtv 800/100 mg once daily, adequate rtv exposure was achieved in this treatment group to achieve comparable efficacy to the DRV/rtv 600/100 mg twice daily group (see Section 2.2.5.3.3.2).

Table 131: Population PK Parameter Estimates for rtv Following Administration of DRV/rtv at a Dose of 800/100 mg Once Daily or 600/100 mg Twice Daily in ART-Experienced HIV 1 Infected Subjects (Study TMC114-C229)

	Mean (SD); Median (Range)	
Parameter	**DRV/rtv 800/100 mg qd**	**DRV/rtv 600/100 mg bid**
N	280	278
C_{0h}, ng/mL	59 (6-1,049)	307 (41-1,657)
AUC_{24h}, ng.h/mL	5,776 (1,801-39,027)	12,588 (3,404-44,762)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.5.1/TMC114-C229-W48-CRR/Table 86

Descriptive analyses of the rtv PK parameters by subgroups revealed the following with respect to AUC_{24h} (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.7.1.2 Module 5.3.3.5/TMC114-C947-CPK/Section 6.2.1):

- *Plasma AAG level at baseline*: No apparent effect on rtv exposure.
- *Hepatitis co-infection status*: No apparent effect on rtv exposure.
- *Sex:* There was a trend towards higher rtv exposure in females (approximately 27% with DRV/rtv once daily and approximately 19% with DRV/rtv twice daily) compared with males.
- *Age*: No apparent effect on rtv exposure.
- *Race*: There was a trend towards higher rtv exposure in Asian subjects (approximately 23% with DRV/rtv once daily and approximately 32% with DRV/rtv twice daily) compared with Caucasian subjects.
- *Region*: There was a trend towards higher rtv exposure in subjects from the Asian region (approximately 23% with DRV/rtv once daily and approximately 36% with DRV/rtv twice daily) compared with subjects from North America. There was also a trend towards higher rtv exposure in subjects from the African region (approximately 10% with DRV/rtv once daily and approximately 36% with DRV/rtv twice daily) compared with subjects from North America.
- *Weight*: Higher weight was associated with lower rtv exposure, with a difference of approximately 44% between the highest and lowest weight categories.

- *Creatinine clearance*: No clinically relevant effect on rtv exposure.

The differences in rtv exposure in these subgroups are not considered to be clinically relevant. The findings of these descriptive analyses were supported by ANCOVAs. In all subgroup analyses, similar trends to those observed for rtv AUC_{24h} were also observed for rtv C_{0h}.

2.2.6.3.4. Conclusion

- Dosing with DRV/rtv 800/100 mg once daily resulted in lower C_{0h} and AUC_{24h} values for DRV and rtv compared with dosing with DRV/rtv 600/100 mg twice daily, but the comparable efficacy with DRV/rtv once daily and DRV/rtv twice daily confirmed that adequate DRV and rtv exposures were achieved with DRV/rtv once daily dosing.
- Sex, age, race, region, body weight, hepatitis B and/or C co-infection, and AAG plasma concentrations at baseline had no relevant effects on the PK of DRV or rtv.

2.2.6.4. Integrated Population PK Analysis of DRV at Week 24 Following Treatment With DRV/rtv in ART-experienced HIV-1 Infected Subjects in Studies TMC114-C202 and TMC114-C213 (TMC114-C926-CPKPD)

TMC114-C926-CPKPD

Module 5.3.4.2/TMC114-C926-CPKPD

2.2.6.4.1. Objective

To summarize the PK of DRV and rtv from the Phase 2b studies TMC114-C202 and TMC114-C213 (Section 2.2.5.4) using population PK modeling.

2.2.6.4.2. Methods

In studies TMC114-C202 and TMC114-C213 in ART-experienced HIV-1 infected subjects, in which DRV/rtv was administered at once and twice daily dosing regimens (400/100 mg once or twice daily, 800/100 mg once daily, 600/100 mg twice daily), sparse sampling for the determination of DRV plasma concentrations was performed in all subjects randomized to one of the DRV/rtv treatment groups. The planned timepoints for collection of blood samples were at baseline and at Weeks 2, 4, 8, 12, 24, 48, 72, and 96 (or at withdrawal). Exposure parameters were obtained using population PK modeling of sparse samples obtained up to Week 24 in study TMC114-C213 and up to Week 48 (some subjects) in study TMC114-C202.

Descriptive statistics and multivariate ANCOVA models were used to investigate the impact of the covariates of dosing regimen, region, sex, race, primary PI virus mutations, concomitant use of TDF, co-infection with hepatitis, body weight, and baseline concentration of AAG on the PK of DRV.

2.2.6.4.3. Results

2.2.6.4.3.1. Model Building

A 2-compartmental PK model with sequential zero- and first-order absorption without a lag time was developed based on data from 7 relevant single- and multiple-dose studies using DRV

formulation F001 (studies TMC114-C202, TMC114-C213, TMC114-C129, TMC114-C137, TMC114-C138, TMC114-154, and TMC114-C156).

2.2.6.4.3.1.1. DRV PK Estimates

The population PK parameter estimates for DRV are summarized in Table 132. The estimates from sparse sampling were in the same range and consistent with those observed in the PK substudies of studies TMC114-C202 and TMC114-C213 for the different dosing regimens (Section 2.2.5.4). Exposure to DRV generally increased with increasing daily doses of DRV. The AUC_{24h} and C_{0h} values for DRV appeared to increase less than dose proportionally for the once daily and twice daily treatment regimens.

Table 132: Population PK Parameter Estimates for DRV Following Administration of DRV/rtv Once Daily for 4 and 24 Weeks in ART-experienced HIV-1 Infected Subjects in Study TMC114-C202 and TMC114-C213

	Mean (SD); Median (Range)			
Parameter	**DRV/rtv 400/100 mg qd**	**DRV/rtv 800/100 mg qd**	**DRV/rtv 400/100 mg bid**	**DRV/rtv 600/100 mg bid**
N	118	118	113	119
C_{0h}, ng/mL	1,342 (755)	1,963 (1,003)	3,008 (1,048)	3,578 (1,151)
	1,258	1,840	2,806	3,539
	(140-5,380)	(256-5,868)	(646-6,391)	(1,255-7,368)
AUC_{12h}, ng.h/mL	-	-	49,839 (13,653)	62,349 (16,143)
			47,796	61,668
			(18,515- 98,593)	(33,857-106,490)
AUC_{24h}, ng.h/mL	58,201 (22,597)	92,670 (33,711)	99,678 (27,306)	124,697 (32,285)
	56,576	89,845	95,592	123,336
	(13,035-163,950)	(25,828-214,040)	(37,030-197,186)	(67,714-212,980)

bid=twice daily; N=maximum number of subjects with data; qd=once daily.
[a] AUC_{24h} for the twice daily regimens was calculated by multiplying the AUC_{12h} by 2.
Source: Module 5.3.4.2/TMC114-C926-CPKPD/Table 16

In subgroup analyses, race, number of primary PI virus mutations, concomitant use of TDF, region (North America, South America, Europe/Australia), and body weight did not appear to affect DRV exposure, but the number of subjects in some subgroups (eg, race) was too small to allow definite conclusions. An effect of sex on DRV exposure was primarily noted in the 400/100 mg once daily group in (refer to Module 5.3.4.2/TMC114-C926-CPKPD/Section 4.3.2.1.2). Additionally, a trend for higher DRV exposure for subjects with higher baseline AAG plasma concentrations was observed.

2.2.6.4.4. Conclusion

Estimates for DRV exposure from sparse sampling increased less than dose proportionally and were consistent with the PK values observed in the PK substudies of studies TMC114-C202 and TMC114-C213.

2.2.7. Patient PK/PD Analyses

2.2.7.1. PK/PD Analyses of DRV at Week 24 in Study GS-US-216-0130

GS-US-216-0130

Module 5.3.4.2/GS-US-216-0130-CPK-W24

2.2.7.1.1. Objective

To assess PK/PD relationships for virologic response and safety in HIV-1 infected subjects from study GS-US-216-0130 (Section 2.2.5.1) following 24 weeks of treatment with DRV/COBI 800/150 mg once daily coadministered as single agents, and to develop a GAM relating virologic response to DRV exposure.

2.2.7.1.2. Methods

The PK/PD relationship between DRV exposure and virologic response was assessed by comparing DRV exposure (AUC_{24h} or C_{0h} divided into quartiles) in ART-naïve or ART-experienced HIV-1 infected subjects with changes in viral load or with virologic success (plasma viral load of <50 HIV-1 RNA copies/mL, observed case). A GAM analysis for Week-24 virologic response by DRV AUC_{24h} or C_{0h}, fitted as a smoothed spline with 2 degrees of freedom, was also performed.

The PK/PD relationship between DRV exposure (AUC_{24h} or C_{0h}) and safety was evaluated using descriptive statistics, per subgroup defined as whether or not a subject experienced an AE of rash, diarrhea, vomiting, and nausea; whether or not a subject experienced an AE leading to permanent discontinuation of study drug; and by worst laboratory abnormality (according to the DAIDS grading scale) for selected laboratory parameters: AST, ALT, ALP, total cholesterol, LDL, HDL, triglycerides, glucose, amylase, or lipase.

2.2.7.1.3. Results

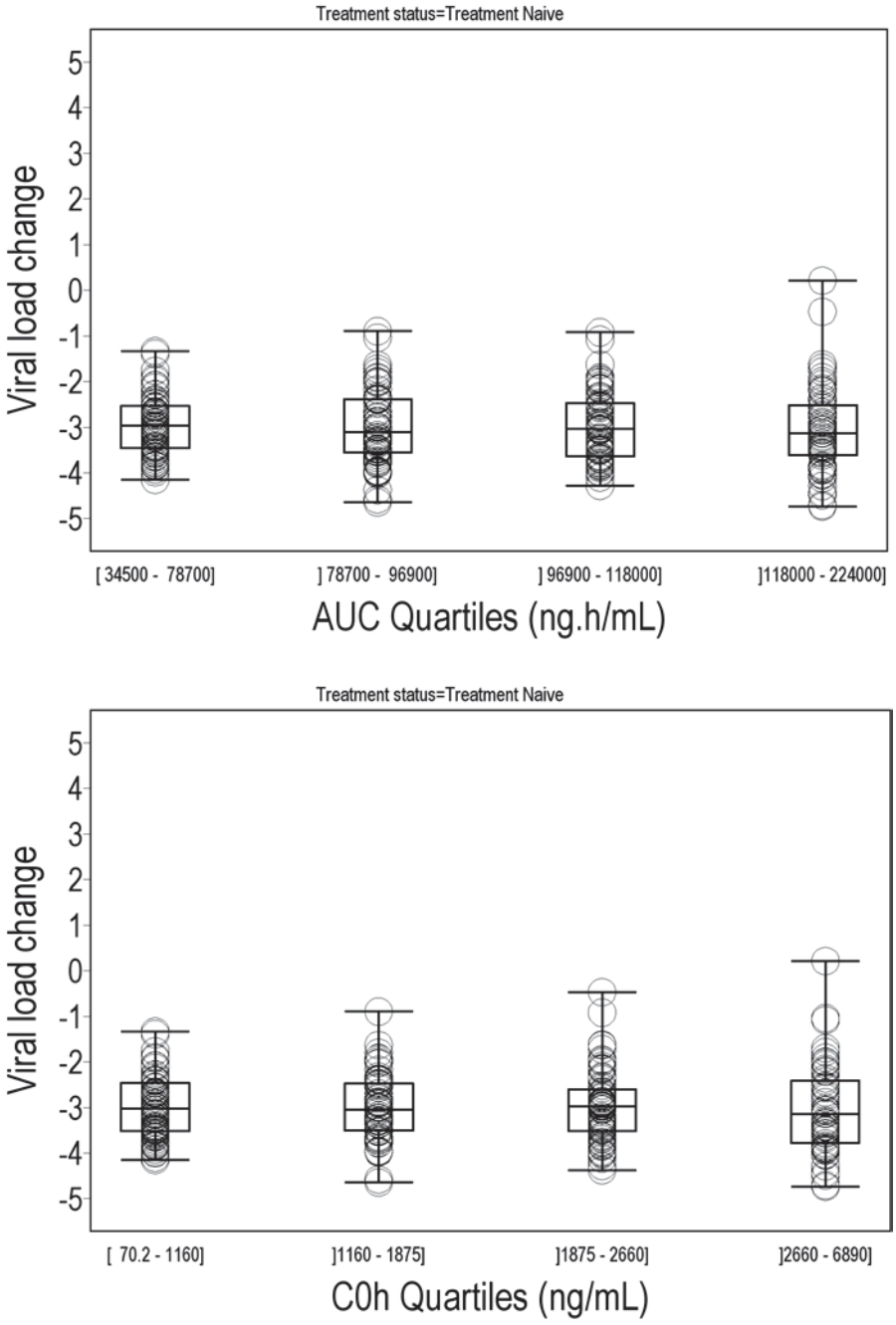
2.2.7.1.3.1. PK/PD Relationships for Antiviral Activity

2.2.7.1.3.1.1. ART-naïve Subjects

For subjects in the ART-naïve group, there was no apparent relationship between the change in log_{10} viral load from baseline at Week 24 and DRV exposure (Figure 16). Virologic success (plasma viral load of <50 HIV-1 RNA copies/mL) was comparable across the first to third DRV exposure quartiles (93.8% to 97.2% for AUC_{24h} and 93.7% to 97.3% for C_{0h}) and was modestly lower in the fourth (ie, highest) DRV exposure quartile (86.2% for AUC_{24h} and 86.4% for C_{0h}) (Module 5.3.4.2/GS-US-216-0130-CPK-W24/Table 2).

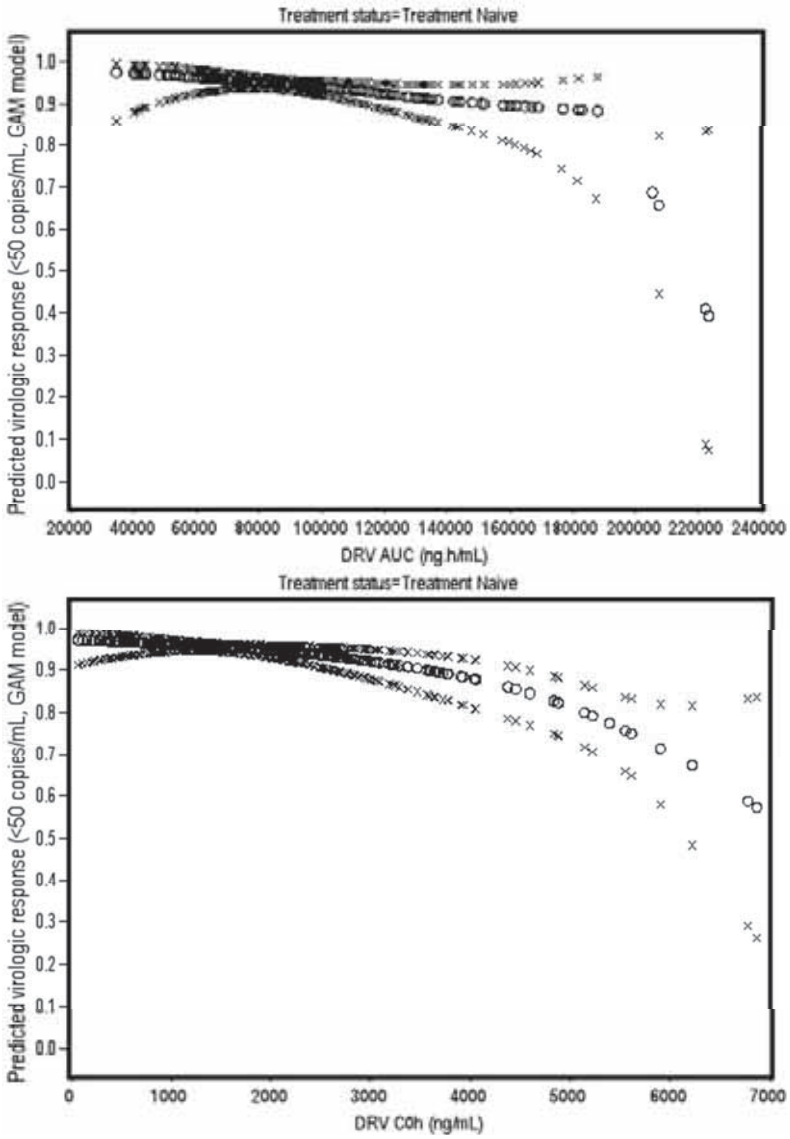
A GAM analysis was used to generate predictions of a smoothed spline for virologic response, defined as a plasma viral load of <50 HIV-1 RNA copies/mL at Week 24, and DRV AUC_{24h} or C_{0h} in ART-naïve subjects (Figure 17). Inverse relationships were observed among ART-naïve subjects for both DRV AUC_{24h} and C_{0h}.

Figure 16 **Change in Viral Load (Log_{10} HIV-1 RNA Copies/mL) From Baseline at Week 24 by Quartiles of DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in ART-naïve HIV-1 Infected Subjects (Study GS-US-216-0130)**



Boxplots and whiskers represent maximum, Q3, Q2 (median), Q1, and minimum values.
Source: Module 5.3.4.2/GS-US-216-0130-CPK-W24/Figure 3 and Figure 4

Figure 17 Predicted Virologic Response (Plasma Viral Load of <50 HIV-1 RNA Copies/mL, Smoothed Spline Fit From a Univariate GAM Model) at Week 24 by DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in ART-naïve HIV-1 Infected Subjects (Study GS-US-216-0130)



Note: Circles indicate predicted response, and crosses indicate upper and lower 95% confidence limits on the predictions.
Source: Module 5.3.4.2/GS-US-216-0130-CPK-W24/Figure 7 and Figure 8

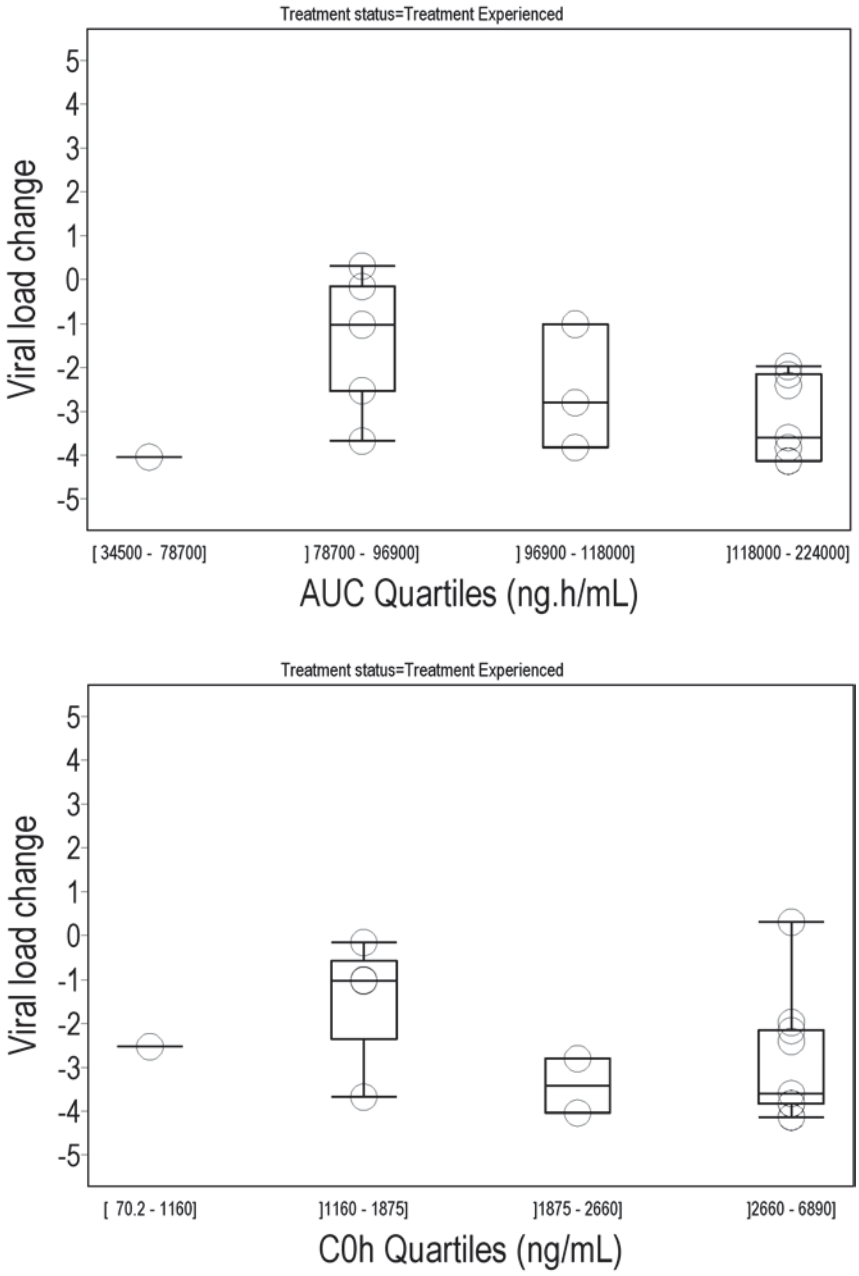
2.2.7.1.3.1.2. ART-experienced Subjects

For subjects in the ART-experienced group, change in $\log_{10}$ viral load from baseline at Week 24 appeared greater in subjects within the 2 highest quartiles compared with the second lowest quartile (Figure 18). There was a trend towards higher virologic success with higher exposures, but these data should be interpreted with caution due to the small sample size (N=18).

A GAM analysis was used to generate predictions of a smoothed spline for virologic response, defined as a plasma viral load of <50 HIV-1 RNA copies/mL at Week 24, and DRV AUC_{24h} or

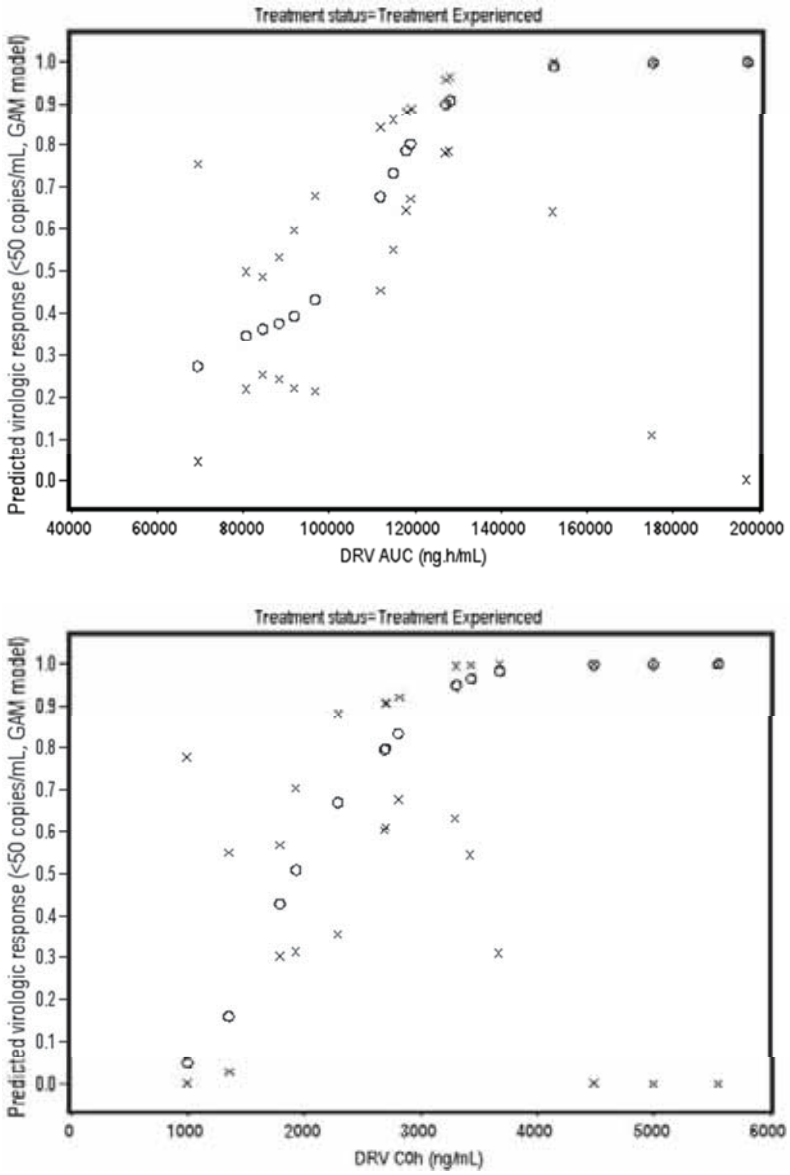
C_{0h} in ART-experienced subjects (Figure 19). Trends for positive relationships between DRV PK parameters and virologic response were observed, but interpretation of this result is limited by the small sample size.

Figure 18 Change in Viral Load (Log_{10} HIV-1 RNA Copies/mL) From Baseline at Week 24 by Quartiles of DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in ART-experienced HIV-1 Infected Subjects (Study GS-US-216-0130)



Boxplots and whiskers represent maximum, Q3, Q2 (median), Q1, and minimum values.
Source: Module 5.3.4.2/GS-US-216-0130-CPK-W24/Figure 5 and Figure 6

Figure 19 Predicted Virologic Response (Plasma Viral Load of <50 HIV-1 RNA Copies/mL, Smoothed Spline Fit From a Univariate GAM) at Week 24 by DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in ART-experienced HIV-1 Infected Subjects (Study GS-US-216-0130)



Note: Circles indicate predicted response, and crosses indicate upper and lower 95% confidence limits on the predictions.
Source: Module 5.3.4.2/GS-US-216-0130-CPK-W24/Figure 9 and Figure 10

2.2.7.1.3.2. PK/PD Relationships for Safety

No apparent exposure-response relationships were observed between DRV AUC_{24h} or C_{0h} and the occurrence of rash, diarrhea, nausea, or vomiting, or between DRV AUC_{24h} and the worst toxicity grade in ALP, ALT, AST, amylase, lipase, glucose, total cholesterol, LDL, HDL, or triglycerides (Module 5.3.4.2/GS-US-216-0130-CPK-W24/Section 3). Higher DRV AUC_{24h} or

C_{0h} were observed in subjects with grade 3 cholesterol and grade 4 lipase changes, but this analysis was limited by small sample sizes (N=4 and 3, respectively).

2.2.7.1.4. Conclusion

- No apparent relationships between DRV exposure and change in log_{10} viral load from baseline or virologic success at Week 24 were observed for ART-naïve subjects.
- In ART-experienced subjects, the change in log_{10} viral load from baseline at Week 24 and virologic success appeared to be greater in subjects with higher DRV exposures, but no firm conclusion can be drawn given the small sample size.
- A GAM analysis indicated an inverse relationship between DRV exposure and virologic response in ART-naïve subjects, but a positive relationship between DRV exposure and virologic response in ART-experienced subjects (although the ART-experienced result is limited by the small sample size).
- Overall, no apparent exposure-response relationships between DRV exposure and safety parameters were observed; a trend for increased lipids with increased DRV exposures was seen, but no conclusions can be drawn given the small sample size.

2.2.7.2. PK/PD Analyses of DRV at Week 48 in Study TMC114-C211

TMC114-C211-W48

Module 5.3.5.1/TMC114-C211-W48-CRR and Module 5.3.4.2/TMC114-C0000009-CPK

2.2.7.2.1. Objective

To assess PK/PD relationships based on observed data from study TMC114-C211 (Section 2.2.5.2).

2.2.7.2.2. Methods

Analyses for the relationships between DRV PK and the change in log_{10} viral load from baseline at Week 48 were performed according to the statistical analysis plan (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 3.6.9). Log_{10} viral load and virologic response were both analyzed by DRV exposure quartiles for ART-naïve subjects from study TMC114-C211. The PK/PD relationship between DRV exposure and safety was evaluated using descriptive statistics of exposure for subjects who did or did not present the following AEs of interest: rash-related cardiac-related, gastrointestinal-related, liver-related, lipid-related, and glucose-related; and AEs from the SOCs psychiatric disorders and nervous system disorders.

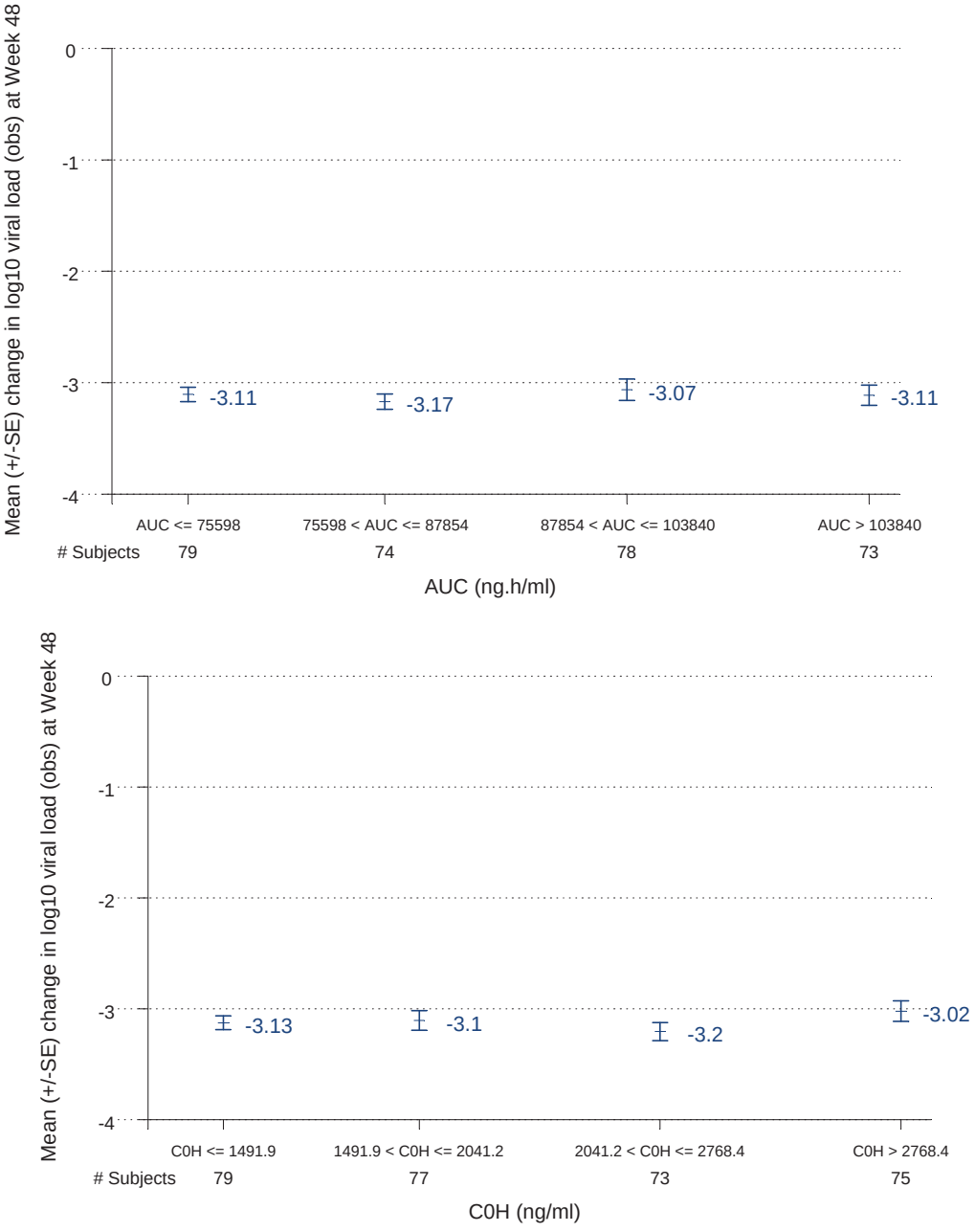
A univariate GAM analysis exploring the relationship between Week-48 virologic response and DRV C_{0h} was also performed.

2.2.7.2.3. Results

2.2.7.2.3.1. PK/PD Relationships for Antiviral Activity

No apparent relationship between DRV PK and change in log_{10} vial load from baseline at Week 48 (observed case analysis) was observed (Figure 20).

Figure 20 **Change (Observed) in Viral Load (Log_{10} HIV-1 RNA Copies/mL) From Baseline at Week 48 by Quartiles of DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/rtv 800/100 mg Once Daily + Background Regimen in ART-naïve HIV-1 Infected Subjects (Study TMC114-C211)**



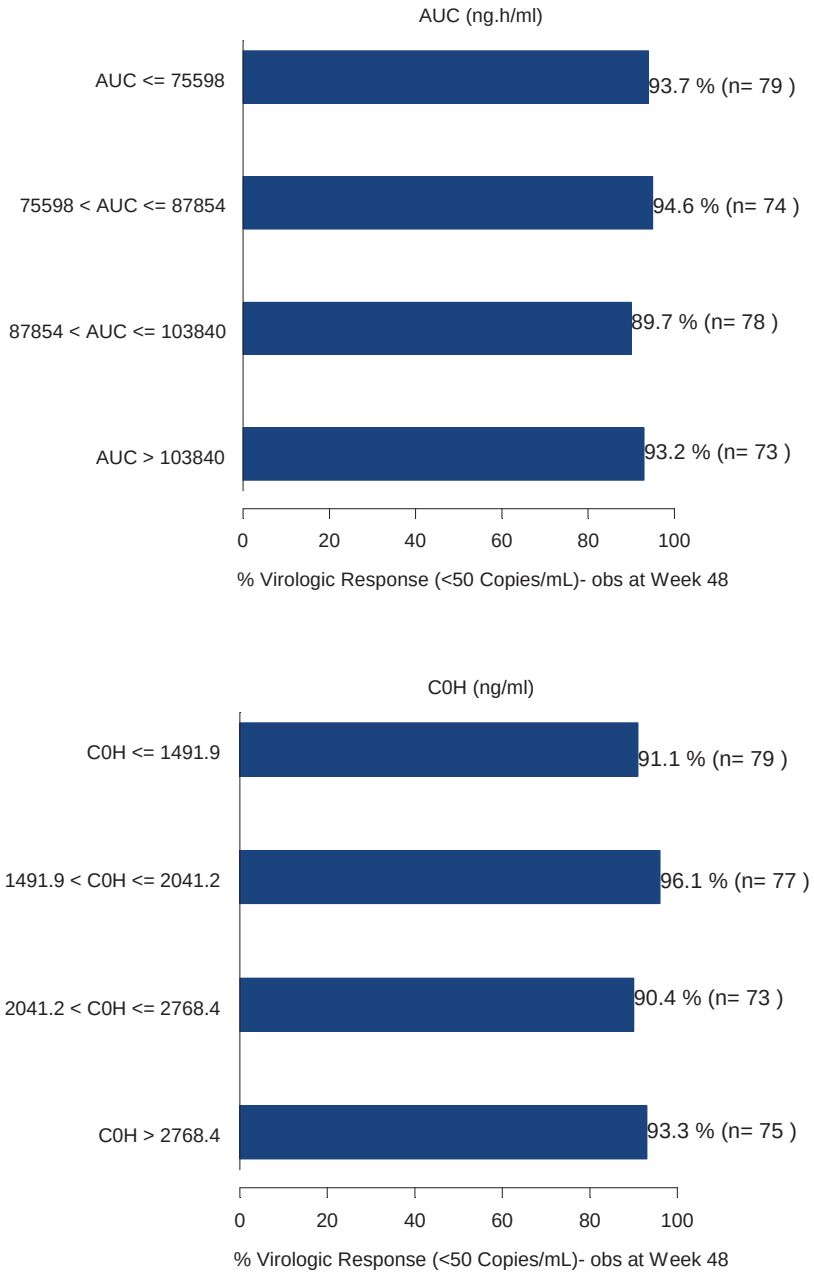
Source: Module 5.3.5.1/TMC114-C211-W48-CRR/Figure 35

Analyses for the relationships between DRV PK and the 3 definitions of virologic response (viral load <50 and <400 HIV-1 RNA copies/mL, and viral load decrease from baseline of ≥2.0 log_{10}) at Week 48 revealed no relevant relationship between AUC_{24h} or C_{0h} values and virologic response (observed case analysis) (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 4.8.1.2). Graphic presentations of the PK/PD relationship between AUC_{24h} and C_{0h},

and virologic response defined as plasma viral load <50 HIV-1 RNA copies/mL (observed case analysis) at Week 48 by quartile ranges of the PK parameters are shown in Figure 21.

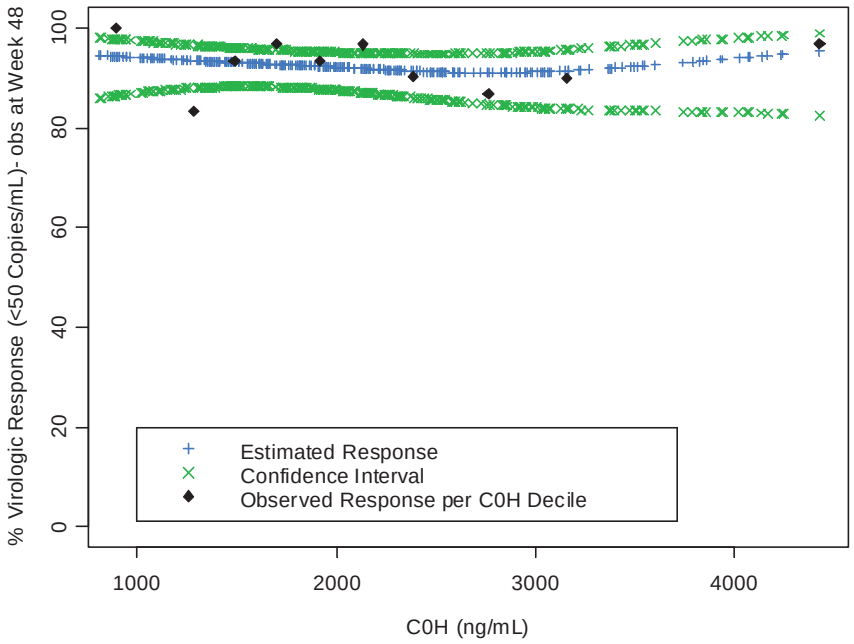
A GAM analysis, exploring the relationship between DRV C_{0h} and virologic response in study TMC114-C211, showed no indication that lower values within the observed DRV C_{0h} range lead to lower estimated virologic response (Figure 22). The mean predicted virologic response was 92.8% in the total population (Module 5.3.4.2/TMC114-C0000009-CPK/Section 3.1).

Figure 21: Confirmed Virologic Response as Week 48 (Viral Load <50 HIV-1 RNA Copies/mL, Observed Case Analysis) by Quartile Ranges of DRV AUC (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/rtv 800/100 mg Once Daily + Background Regimen in ART-naïve HIV-1 Infected Subjects (Study TMC114-C211)



Source: Module 5.3.5.1/TMC114-C211-W48-CRR/Figure 36

Figure 22 Observed and Predicted Virologic Response (Plasma Viral Load of <50 HIV-1 RNA Copies/mL at Week 48) Using a GAM Analysis of Study TMC114-C211 to Predict Virologic Response Using DRV C_{0h}



Source: Module 5.3.4.2/TMC114-C0000009-CPK/Figure 28

2.2.7.2.3.2. PK/PD Relationships for Safety

No apparent relationships were observed between the AUC_{24h} and C_{0h} of DRV and the occurrence of AEs of interest, including rash-, cardiac-, gastrointestinal-, liver-, lipid-, and glucose-related AEs, or AEs in the SOCs of nervous system disorders and psychiatric disorders (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 4.8.2).

2.2.7.2.4. Conclusion

- There was no relevant relationship between DRV PK and the change in $\log_{10}$ viral load from baseline or any of the definitions of virologic response at Week 48.
- There was no relevant relationship between exposure to DRV and the occurrence of AEs of interest.

2.2.7.3. PK/PD Analyses of DRV at Week 48 in Study TMC114-C229

Module 5.3.5.1/TMC114-C229-W48-CRR and Module 5.3.4.2/TMC114-C0000009-CPK

2.2.7.3.1. Objective

To assess PK/PD relationships based on observed data from study TMC114-C229 (Section 2.2.5.3).

2.2.7.3.2. Methods

Relationships were evaluated between the DRV PK parameters AUC_{24h} and C_{0h} and the following efficacy parameters: change in log_{10} viral load at Week 48 and virologic response, defined as viral load <50 copies/mL at Week 48, for ART-experienced subjects from study TMC114-C229. Log_{10} viral load and virologic response were both analyzed by DRV exposure quartiles. The PK/PD relationship between DRV exposure and safety was evaluated using descriptive statistics of exposure for subjects who did or did not present the following AEs of interest: rash-, cardiac-, gastrointestinal-, liver-, lipid-, and glucose-related; and AEs from the SOCs psychiatric disorders and nervous system disorders.

A univariate GAM analysis exploring the relationship between Week-48 virologic response and DRV C_{0h} was also performed.

2.2.7.3.3. Results

2.2.7.3.3.1. PK/PD Relationships for Antiviral Activity

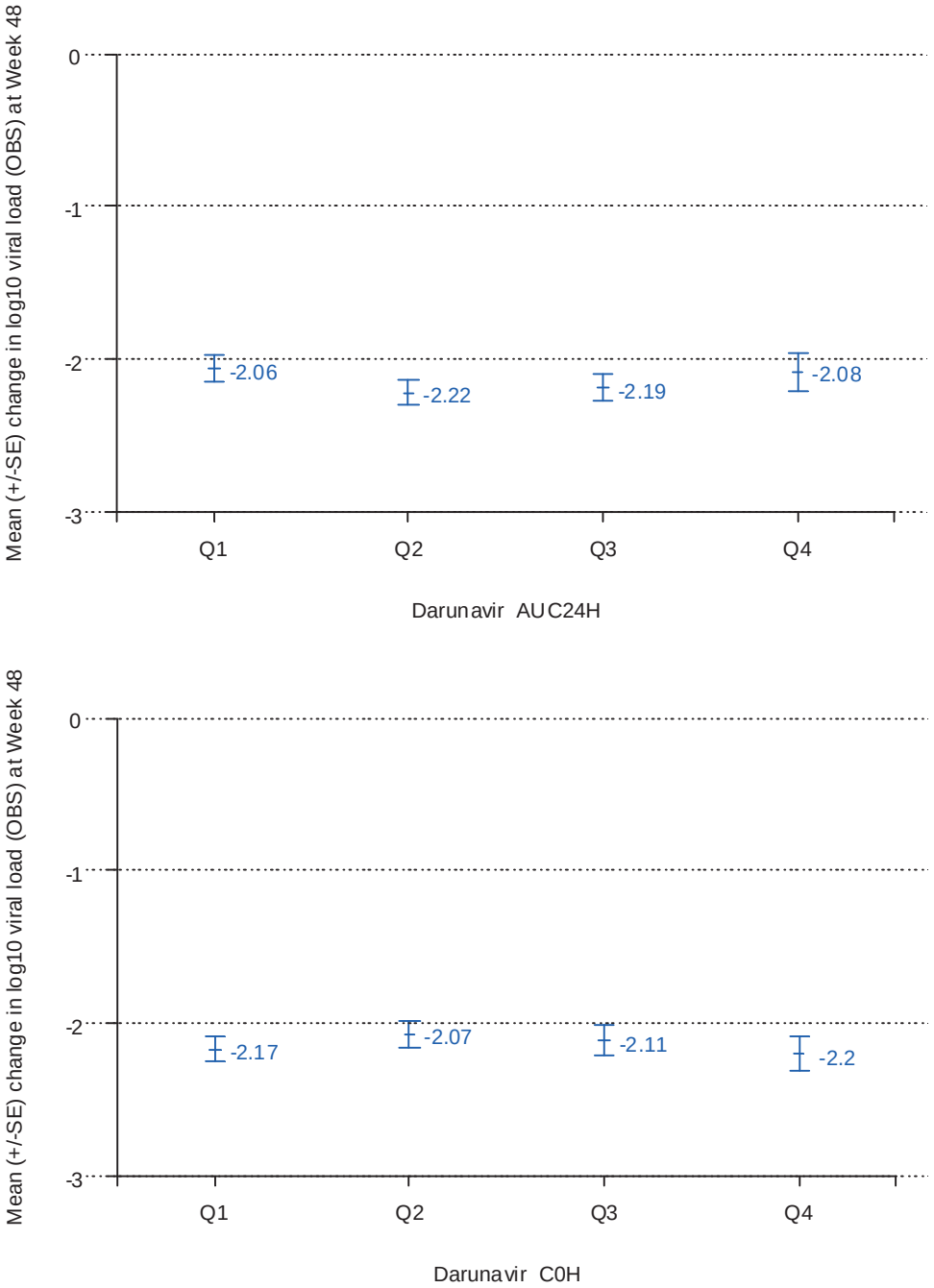
Change in Plasma Viral Load: Analysis by Treatment Group

A graphical analysis indicated that there was no relevant relationship between DRV C_{0h} and the decrease in log_{10} viral load from baseline at Week 48 in either treatment group (DRV/rtv 800/100 mg once daily versus 600/100 mg twice daily) (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.8.1.1). The decrease in log_{10} viral load from baseline in the DRV/rtv once daily group tended to be smaller in subjects with higher AUC_{24h} values, while no relevant relationship between AUC_{24h} and the change in log_{10} viral load was observed in the DRV/rtv twice daily group. An ANCOVA (Observed Case) confirmed the findings of the graphical analysis.

Change in Plasma Viral Load: Analysis of Pooled Treatment Groups

The graphic analysis of the pooled treatment groups showed no relevant relationship between DRV C_{0h} or AUC_{24h} and the change in log_{10} viral load from baseline at Week 48 (Figure 23).

Figure 23 **Change (Observed) in Viral Load (Log_{10} HIV-1 RNA Copies/mL) From Baseline at Week 48 by Quartiles of DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/rtv at a Dose of 800/100 mg Once Daily or 600/100 mg Twice Daily in ART-experienced HIV-1 Infected Subjects (Study TMC114-C229)**



Source: Module 5.3.5.1/TMC114-C229-W48-CRR/Figure 34

ANCOVAs (Observed Case, including the number of susceptible NRTIs in the optimized background regimen as factor, and baseline AAG, baseline log_{10} viral load, and log_{10} AUC_{24h} or log_{10} C_{0h} as covariates) showed a statistically significant effect of DRV AUC_{24h} on the change in log_{10} viral load from baseline at Week 48 (inverse relationship, with greater DRV AUC_{24h} being associated with a somewhat smaller change in log_{10} viral load from baseline) (refer to

Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.8.1.1). The effect of DRV C_{0h} was not statistically significant. The same ANCOVAs also showed that baseline log_{10} viral load and the number of susceptible NRTIs in the optimized background regimen were predictors of response, as was observed in the efficacy analyses (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.2.4.1). In these ANCOVAs, baseline AAG did not appear to account for the observed inverse relationship, as the effect was not statistically significant in the models. The trend towards an inverse relationship between DRV AUC_{24h} and the change in log_{10} viral load from baseline at Week 48 is not considered to be clinically relevant. The reason for this inverse relationship is currently unknown.

Virologic Response: Analysis by Treatment Group

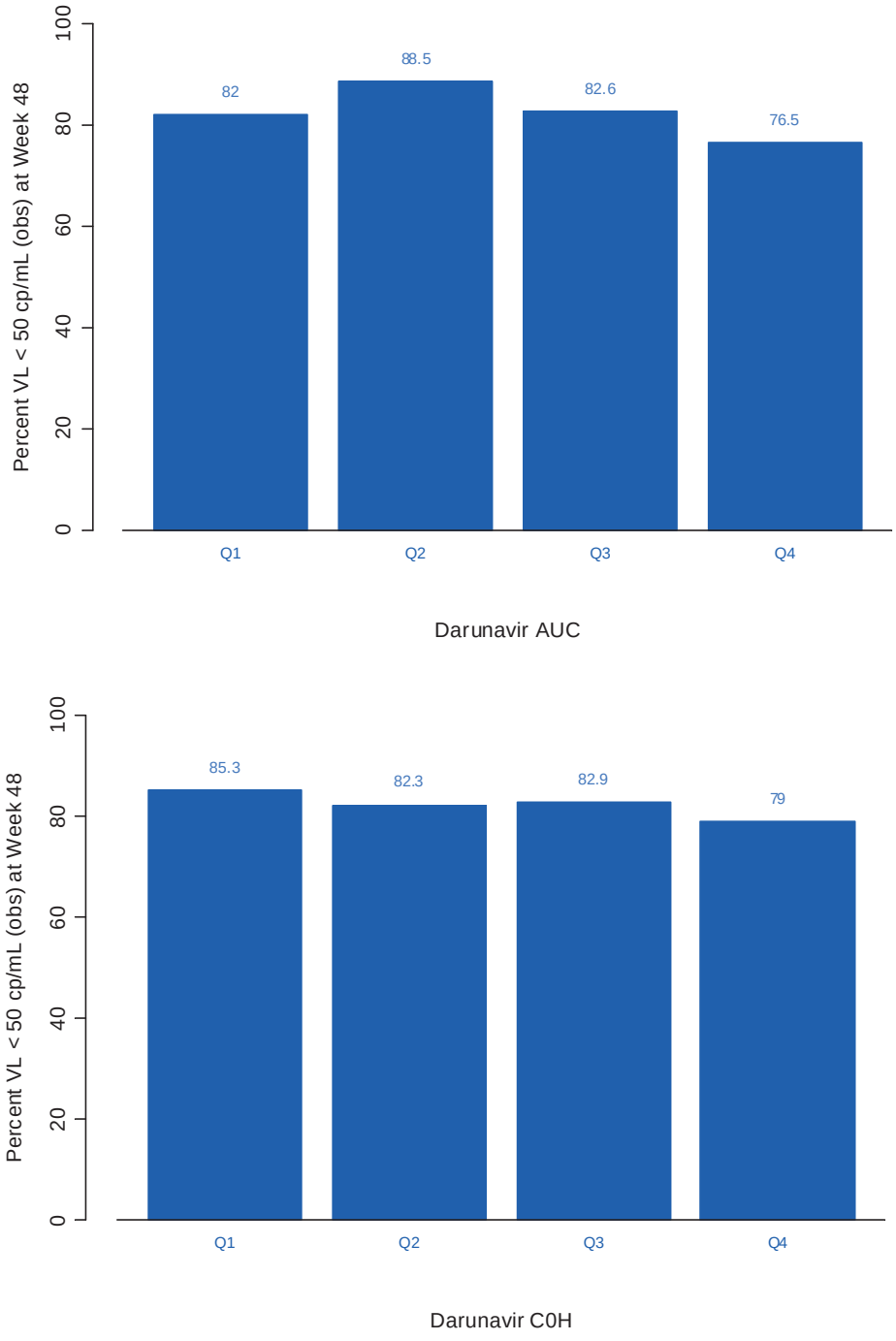
A graphical analysis indicated that there was no consistent relationship between DRV C_{0h} and virologic response, defined as plasma viral load <50 HIV-1 RNA copies/mL at Week 48, in either treatment group, although with DRV/rtv once daily, the virologic response was lower in the highest quartile of C_{0h} values relative to the other C_{0h} quartiles (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.8.1.2). Virologic response at Week 48 in the DRV/rtv once daily group tended to be smaller in subjects with higher AUC_{24h} values. No relevant relationship between AUC_{24h} and virologic response at Week 48 was observed in the DRV/rtv twice daily group. A regression analysis (Observed Case) confirmed the findings of the graphical analysis.

Virologic Response: Analysis of Pooled Treatment Groups

The graphical analysis of the pooled treatment groups showed no relevant relationship between DRV C_{0h} or AUC_{24h} and virologic response defined as plasma viral load <50 HIV-1 RNA copies/mL at Week 48 (Figure 24).

Regression analyses (Observed Case, including the number of susceptible NRTIs in the optimized background regimen as a factor, and baseline AAG, baseline log_{10} viral load, and log_{10} AUC_{24h} or log_{10} C_{0h} as covariates) revealed no relevant relationships between the DRV PK and virologic response defined as viral load <50 HIV-1 RNA copies/mL at Week 48 (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.8.1.2). The effects between DRV AUC_{24h} and C_{0h} versus virologic response were not statistically significant. The same regression analyses also showed that baseline log_{10} viral load and number of susceptible NRTIs were predictors of response. Baseline AAG was not found to be a significant predictor of response. These findings were consistent with the findings from the PK/PD analyses for the change in log_{10} viral load.

Figure 24: Virologic Response, Defined as Viral Load <50 HIV-1 RNA Copies/mL, at Week 48 (Observed Case) by Quartile Ranges of DRV AUC (Upper Panel) and C_{0h} (Lower Panel) Following Administration of DRV/rtv at a Dose of 800/100 mg Once Daily or 600/100 mg Twice Daily in ART-experienced HIV-1 Infected Subjects (Study TMC114-C229)

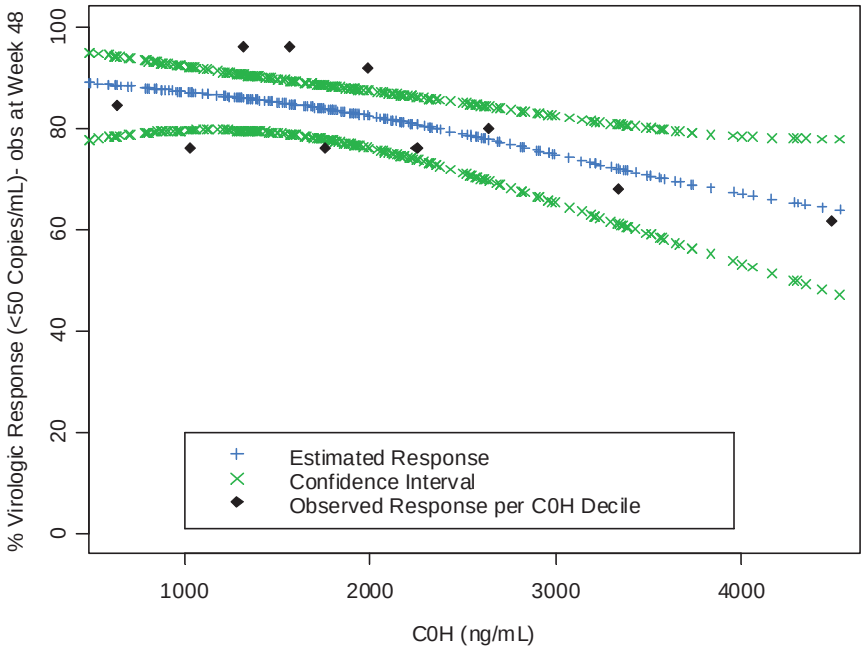


Source: Module 5.3.5.1/TMC114-C229-W48-CRR/Figure 35

A GAM analysis, similar to the one described for study TMC114-C211 (Section 2.2.7.2), showed an inverse relationship between DRV C_{0h} and virologic response in the ART-experienced HIV-1 infected population of study TMC114-C229 (Figure 25); virologic response was somewhat lower in the highest 2 deciles of the observed DRV C_{0h} range,

suggesting a counterintuitive relationship (Module 5.3.4.2/TMC114-C0000009-CPK/Section 3.2). However, in the first 8 deciles (DRV C_{0h} values up to 2,961 ng/mL) there was no clear relationship between DRV C_{0h} and virologic response at the observed rate. Of note, the variability of the estimate is higher in the last 2 deciles. The mean predicted response was 80.6% in the total population.

Figure 25 Observed and Predicted Virologic Response (Plasma Viral Load of <50 HIV-1 RNA Copies/mL at Week 48) Using a GAM Analysis of Study TMC114-C229 to Predict Virologic Response Using DRV C_{0h}



Source: Module 5.3.4.2/TMC114-C0000009-CPK/Figure 31

2.2.7.3.3.2. PK/PD Relationships for Safety

Within both treatment groups, no apparent relationships were observed between the PK parameters for DRV or rtv and the occurrence of AEs leading to permanent discontinuation of the study drug; or between DRV or rtv PK and rash-, cardiac-, gastrointestinal-, liver-, lipid- and glucose-related AEs; or AEs in the SOCs of nervous system disorders or psychiatric disorders system; or laboratory lipid abnormalities (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.8.2).

In addition, a pooled analysis for DRV and rtv exposure in the 2 treatment groups versus gastrointestinal-related AEs and maximum changes in lipid parameters showed no relevant relationships between DRV or rtv exposure and these safety parameters (refer to Module 5.3.5.1/TMC114-C229-W48-CRR/Section 4.8.2).

2.2.7.3.4. Conclusion

- There was no relevant relationship between DRV C_{0h} or AUC_{24h} and the change in $\log_{10}$ viral load from baseline or virologic response at Week 48.

- Baseline log_{10} viral load and the number of susceptible NRTIs in the optimized background regimen were significant predictors of antiviral activity; baseline AAG was not found to be a significant predictor of response.
- There was no relevant relationship between the exposure (C_{0h} or AUC_{24h}) to DRV or rtv and the occurrence of AEs of interest.
- Virologic response was somewhat lower in the highest 2 deciles of the observed DRV C_{0h} range, suggesting a counterintuitive relationship. However, in the first 8 deciles, there was no clear relationship between DRV C_{0h} and virologic response at the observed rate, and variability was high in the last 2 deciles.

2.2.7.4. Integrated PK/PD Analysis of DRV from the Phase 2b Studies TMC114-C202 and TMC114-C213 (TMC114-C926-CPKPD)

TMC114-C926-CPKPD

Module 5.3.4.2/TMC114-C926-CPKPD

2.2.7.4.1. Objective

To assess PK/PD relationships based on observed data from the Phase 2b studies TMC114-C202 and TMC114-C213 (Section 2.2.5.4).

2.2.7.4.2. Methods

TMC114-C202 and TMC114-C213 were Phase 2b, randomized, controlled, partially blinded studies in ART-experienced HIV-1 infected subjects to evaluate the dose-response relationship of efficacy between different DRV/rtv treatment groups (DRV/rtv 400/100 mg once daily, 800/100 mg once daily, and 600/100 mg once daily) after 24 weeks of treatment.

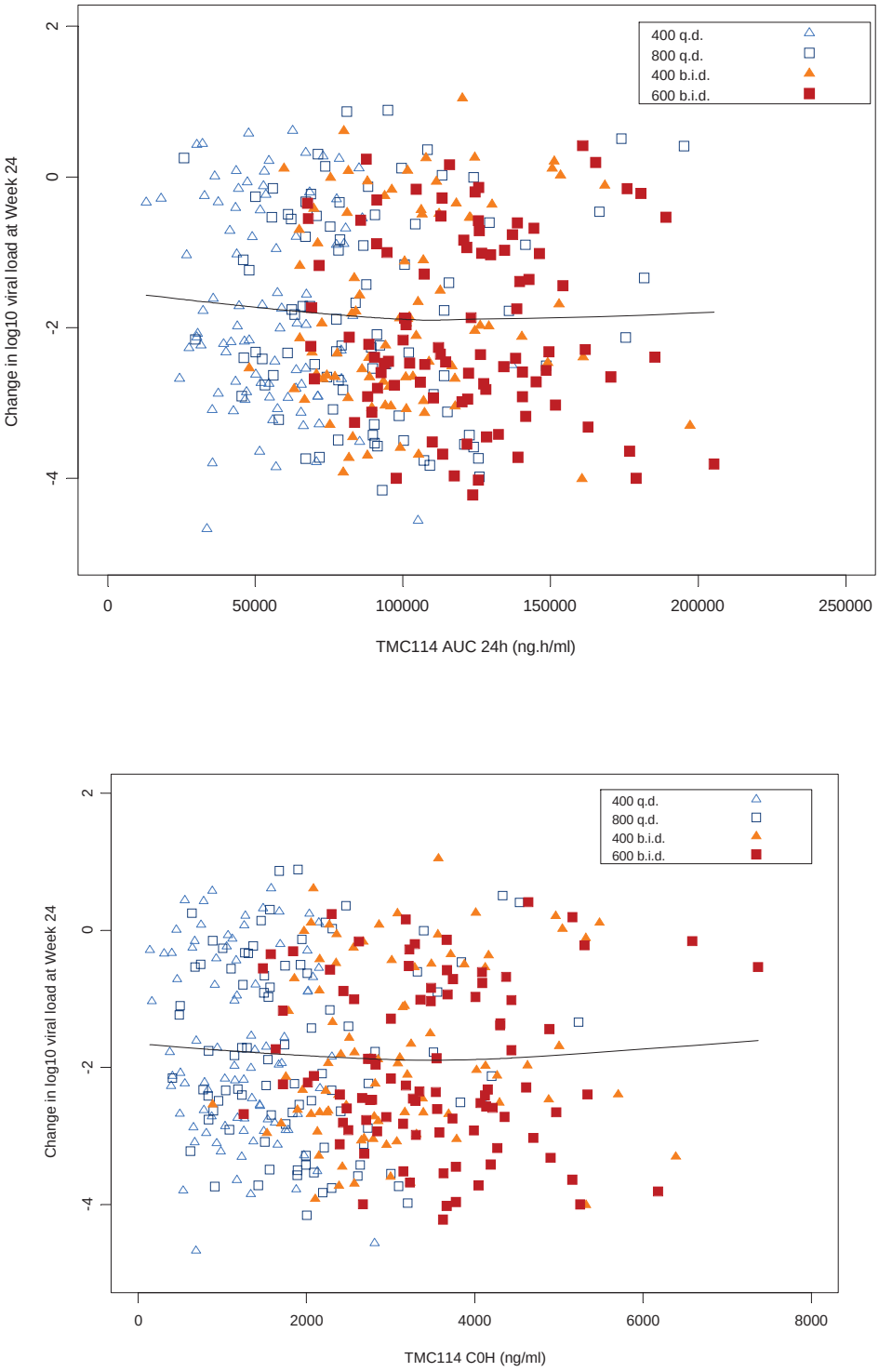
Pharmacokinetic/PD relationships based on observed data were evaluated for the relationship between PK parameters and efficacy, between inhibitory quotient and virologic response, and between PK and safety parameters. For the PK/PD analysis of the integrated data, the PD parameters were analyzed by using either the observed data or by imputation methods, such as non-completer=failure or by TLOVR.

2.2.7.4.3. Results

2.2.7.4.3.1. PK/PD Relationships for Antiviral Activity

The relationship between DRV PK and change in log_{10} viral load from baseline at Week 24 is shown in Figure 26.

Figure 26 Individual Changes in Log_{10} Viral Load From Baseline at Week 24 Versus DRV AUC_{24h} (Upper Panel) and C_{0h} (Lower Panel), With Lowess Smoothed Spline



Source: Module 5.3.4.2/TMC114-C926-CPKPD/Figure 21 and Figure 22

ANCOVA models were performed to investigate the relationship between the change in log_{10} viral load and PK parameters (log_{10} AUC_{24h} and log_{10} C_{0h}), including the covariates baseline log_{10} viral load, number of sensitive NRTIs in the optimized background regimen, DRV log_{10} fold change (in EC_{50} values) at baseline, and use of enfuvirtide in the optimized background regimen (Table 133). The response parameters that were tested included change in log_{10} viral load at Weeks 2 and 24, as well as time-averaged difference at Week 24.

Darunavir log_{10} AUC_{24h} was statistically significantly associated with changes in viral load from baseline at Week 24 (p=0.036) and time-averaged difference at Week 24 (p=0.046), but not with changes in viral load from baseline at Week 2. Darunavir log_{10} fold change at baseline, baseline viral load, number of sensitive NRTIs, and use of enfuvirtide in the optimized background regimen were stronger predictors of response in all analyses (all p<0.01). Darunavir log_{10} C_{0h} was statistically significantly associated with change in viral load from baseline at Weeks 2 (p=0.049) and 24 (p=0.015), as well as with time-averaged difference at Week 24 (p=0.020). Darunavir log_{10} fold change at baseline, baseline viral load, and use of enfuvirtide in the optimized background regimen were stronger predictors of response in all analyses (p<0.01), as well as the number of sensitive NRTIs in the optimized background regimen (eg, p=0.006 for DAVG at Week 24) (refer to Module 5.3.4.2/TMC114-C926/Section 4.5.1.2).

Table 133: Significance Values From the Statistical Analysis of the Relationship Between Population PK Parameters and Viral Load for the Integrated Analysis of Studies TMC114-C202 and TMC114-C213

Response Parameter	AUC_{24h}	C_{0h}	Baseline Viral Load	Number of Sensitive NRTIs	Use of ENF in OBR	DRV FC
Change in Viral Load Week 2	0.054	0.049	<0.001	<0.001	<0.001	<0.001
Change in Viral Load Week 24	0.036	0.015	<0.001	0.004	<0.001	<0.001
DAVG Week 24	0.046	0.020	<0.001	0.006	<0.001	<0.001

DAVG=time-averaged difference; ENF=enfuvirtide; FC=fold change; OBR=optimized background regimen.
Source: Module 5.3.4.2/TMC114-C926-CPKPD/Table 21

To investigate the relationship between response parameters of viral activity and the PK parameters log_{10} AUC_{24h} and log_{10} C_{0h}, logistic regression models were applied using the same covariates and timepoints as mentioned above for the ANCOVA model (Module 5.3.4.2/TMC114-C926/Section 4.5.1.2). The following response parameters of efficacy were tested: viral load <50 and <400 HIV-1 RNA copies/mL and change of at least 0.5 and 1.0 log_{10} viral load from baseline, at Weeks 2 and 24. Exposure to DRV (AUC_{24h} and C_{0h}) was statistically significantly associated with all response parameters at Week 24 and with some of the response parameters at Week 2. However, in general these relationships were not as strongly correlated as other parameters such as DRV fold change at baseline, number of sensitive NRTIs, and use of enfuvirtide in the optimized background regimen, which were stronger predictors of response in all analyses.

An association between DRV log_{10} AUC_{24h} and C_{0h} and viral load decrease at Week 24 in the ANCOVA analysis indicates estimates (standard error [SE]) of #0.646 (0.307) and #0.521

(0.214), respectively (refer to Module 5.3.4.2/TMC114-C926/Supporting Data Display 11). These estimates indicate that, over the dose range studied, an increase in AUC_{24h} or C_{0h} by 10-fold would be associated with a decrease in viral load of 0.646 and 0.521 log_{10} HIV-1 RNA copies/mL at Week 24, respectively. This calculation assumes linearity of the PK/PD relationship and is based on data generated over the daily dose range of 400 to 1,200 mg.

In addition, the relationships between DRV exposure and change in viral load at Week 24 were examined for different ranges of DRV fold change at baseline (Module 5.3.4.2/TMC114-C926-CPKPD/Section 4.5.1.2). This analysis showed that the relationship between exposure and response indicated in the ANCOVA model was primarily due to subjects whose baseline DRV fold change was 4 to ≤40. Contrary to the theory that response to therapy may be improved in subjects with higher DRV fold change by an increase in DRV plasma concentrations, there was no clear relationship between exposure and response in subjects whose DRV fold change values were >40. Similarly, there was no clear relationship between exposure and response in subjects with DRV fold change values ≤4.

2.2.7.4.3.2. PK/PD Relationships for Safety

No apparent relationship was observed between the PK of DRV and the occurrence of AEs of interest. Additionally, no apparent relationships were observed between the PK of DRV and the maximum changes in laboratory and ECG parameters tested (Module 5.3.4.2/TMC114-C926/Section 4.5.3.2). No associations were found between exposure to DRV and changes in liver function test values or lipids. In the analysis by dose group, lipid-related events were more commonly reported with the DRV/rtv twice daily regimens than with the once daily regimens. Ritonavir concentrations were also higher with the twice daily regimens than with the once daily regimens; therefore, this relationship between dosing regimen and lipid-related events may have been influenced by the increased rtv concentrations with the twice daily regimens.

2.2.7.4.4. Conclusion

- The relationship observed between DRV exposure and response was primarily due to subjects whose baseline DRV fold change (in EC_{50} values) was 4 to ≤40. There was no clear relationship between exposure and response in subjects whose DRV fold-change values were >40, which was contrary to the theory that response to therapy may be improved in subjects with a higher DRV fold change by an increase in DRV plasma concentrations.
- For all 4 dosing regimens, there was no apparent relationship between DRV exposure and maximum changes in laboratory safety parameters, vital signs, or ECG parameters.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

3.1. PK Characteristics of DRV and COBI

3.1.1. General ADME Characteristics of DRV

3.1.1.1. Absorption of DRV

3.1.1.1.1. In Vitro Absorption of DRV

The in vitro transport characteristics of DRV have not been investigated in the context of the current submission for the DRV/COBI FDC.

In support of the marketing authorization of DRV, human Caco-2 cells were used as an in vitro model to investigate the bi-directional transepithelial transport characteristics of ^{14}C-DRV (Section 1.2.1.4), which indicated that DRV can be classified as a compound with intermediate to high absorptive permeability. It was concluded that DRV would exhibit sufficient membrane permeability to obtain adequate intestinal absorption. The ratio of secretory/absorptive transport decreased with DRV concentration, indicative of efflux (eg, P-gp). This was further supported by a drug-drug interaction study indicating that digoxin (a P-gp substrate) exposure was increased when digoxin was coadministered with DRV/rtv (Section 2.1.7.2.2).

3.1.1.1.2. Bioavailability of DRV

An overview table of all bioavailability parameters for DRV across biopharmaceutic and clinical pharmacology studies in which DRV and COBI were coadministered in the current submission is provided in Appendix 2.

The absolute bioavailability of DRV was investigated in support of the marketing authorization of DRV. When tablet formulations of DRV (F014 [400-mg] and F015 [200-mg] used for a 600 mg dose) were coadministered with rtv 100 mg under fed conditions, the absolute bioavailability of DRV was 82%, compared with 37% when DRV was given without rtv (TMC114-C114/Section 4.2.4.3[9]).

Relative bioavailability studies (GS-US-216-0115, TMC114IFD1001, and TMC114IFD1003) have been conducted to compare the systemic exposure to DRV following the administration of various DRV/COBI 800/150-mg FDC tablet formulations, DRV/COBI 800/150 mg coadministered as single agents, and DRV/rtv 800/100 mg coadministered as single agents (Section 3.1.3 and refer to Module 2.7.1/Section 2). The effect of food on the bioavailability of DRV with the intended commercial DRV/COBI FDC tablet formulation (G006) and DRV/COBI coadministered as single agents was investigated in study TMC114IFD1003 (Section 3.3.1), and the effect of 4 different types of food or fasted conditions on the bioavailability of DRV, when coadministered with rtv, was investigated in study TMC1114-C143 (Section 3.3.1).

3.1.1.2. Distribution of DRV

The in vitro plasma binding of DRV was investigated in studies TMC114-NC113 and TMC114-NC215; plasma protein binding was approximately 95% in plasma samples from healthy male

adults at a DRV concentration of 500 ng/mL (Section 1.2.1.1). Darunavir was mostly bound to AAG, and plasma protein binding was concentration dependent (Table 2).

3.1.1.3. Metabolism and Excretion of DRV

In vitro metabolism and clinical mass-balance studies were performed in support of the marketing authorization of DRV.

3.1.1.3.1. In Vitro Metabolism of DRV

A nonclinical study in human liver subcellular fractions and/or hepatocytes detected a relatively large number of metabolites for DRV (study TMC114-NC154; Section 1.2.1.2). Major metabolic pathways identified were aliphatic (M21, M23), aromatic (M24, M29), alicyclic hydroxylation (M12, M27, and M28), and carbamate hydrolysis (M19, which was then metabolized further via various pathways to M2, M6, M15, M1, M11, and M3). Minor pathways included glucuronidation (M18, M20, and M17), *N*-dealkylation (M14), and *N*-acetylation (M30). In a nonclinical study (TMC114-NC213) using samples from the clinical mass-balance study TMC114-C109, in the absence of rtv, biotransformation of DRV occurred through aliphatic and aromatic hydroxylation, carbamate hydrolysis, and glucuronidation (Section 1.2.1.2.1). The predominant metabolic pathway was carbamate hydrolysis, accounting for 13.2% of the dose. Aliphatic hydroxylation at the isobutyl moiety towards the tertiary alcohol function (9.8%) and aromatic hydroxylation at the aniline moiety (4.5%) were other major pathways. In the presence of rtv, the carbamate hydrolysis, isobutyl aliphatic hydroxylation, and aniline aromatic hydroxylation pathways were significantly inhibited, accounting for 0.67%, 2.26%, and 1.42% of the dose, respectively.

In human liver microsomes, the oxidative metabolism of DRV or ^{14}C-DRV was primarily catalyzed by CYP3A enzymes (studies TMC114-NC112 and TMC114-NC202; Section 1.2.1.2 and Section 1.2.1.2.1, respectively). All of the metabolites of DRV identified in human matrices showed activity that was at least 10-fold less than the activity of DRV against wild-type HIV.

A study of CYP interaction potential using CYP probe substrates found that DRV strongly inhibited CYP3A (inhibition constant=0.40 μM), indicating that drug-drug interactions due to CYP3A inhibition are likely (study TMC114-NC123; Section 1.2.1.3). A slight induction by DRV of CYP3A in human hepatocyte cultures was also observed.

3.1.1.3.2. Mass-Balance of DRV

In a clinical mass-balance study (TMC114-C109), the majority of ^{14}C-DRV-related radioactivity was excreted in feces (81.7% and 79.5% at 168 hours in the absence and presence of rtv, respectively); 12.2% and 13.9% of the radioactivity was recovered in urine in the absence and presence of rtv, respectively, including 1.2% and 7.7% as unchanged drug (Section 2.1.1). Darunavir was extensively metabolized in the absence of rtv (only 8% of the dose was excreted unchanged after 48 hours), while coadministration of rtv markedly reduced metabolism (48.8% of the dose excreted unchanged after 48 hours). Unchanged drug was mainly excreted in feces, both with and without rtv coadministration.

A mass-balance study of the DRV/COBI FDC has not been conducted.

3.1.2. General ADME Characteristics of COBI

3.1.2.1. Absorption of COBI

3.1.2.1.1. In Vitro Absorption of COBI

The in vitro transport characteristics of COBI have not been investigated in the context of the current submission for the DRV/COBI FDC.

When assessed alone, COBI displayed high forward permeability (7.61 x 10^{-6} cm/s), with little evidence for efflux (efflux ratio: 1.1) (Section 1.2.2.1). The efflux ratio in P-gp-transfected cells and BCRP-transfected cells was higher (16-fold and 1.9-fold, respectively) than in the corresponding wild-type cells, which suggests that COBI can act as a substrate for these transporters. However, given its high permeability, aqueous solubility, and local intestinal concentrations following oral dosing, the absorption potential of COBI is high.

3.1.2.1.2. Bioavailability of COBI

An overview table of all bioavailability parameters for COBI across biopharmaceutic and clinical pharmacology studies in which DRV and COBI were coadministered in the current submission is provided in Appendix 3.

The absolute bioavailability of COBI has not been evaluated. Cobicistat displays greater than dose-proportional increases in plasma exposure due to a combination of reduced systemic clearance and higher bioavailability via autoinhibition of its own metabolism by CYP3A, which is the desired PD effect. The bioavailability of COBI increases with dose following both single- and multiple-dose administration (before reaching a plateau at ≥150 to 200 mg), which is consistent with its metabolic autoinhibition properties and reduction in first-pass effect (Studies GS-US-216-0101, Section 2.1.4.1; GS-US-216-0113, Section 2.1.4.2), and results in a low CL/F (approximately 10% to 15% of hepatic blood flow). At doses greater than 150 to 200 mg, increases in COBI exposure following multiple-dose administration corresponded to proportional increases in plasma $t_{1/2,term}$ and reduction in CL/F, rather than to substantial changes in bioavailability. Accordingly, the bioavailability of COBI is considered to be high.

Cobicistat has 3 basic ionizable groups with pKa of 6.4, 2.5, and 1.8. The intrinsic aqueous solubility of COBI free base (0.075 mg/mL, pH approximately 7) is significantly enhanced under acidic conditions at pH 2 (70 mg/mL). Being a mechanism-based inhibitor of CYP3A, COBI exhibits both dose/concentration- and time-dependent inhibition of CYP3A; its ability to effectively boost CYP3A substrates is dependent on the concentrations that are achieved pre-systemically and/or systemically. Accordingly, clinical studies were conducted to examine the relative bioavailability and disposition of COBI (in combination with the HIV-integrase inhibitor and CYP3A substrate, EVG) when coadministered with acid-reducing agents (Studies GS-US-216-0120, Section 2.1.8.3; GS-US-216-0122, Section 2.1.8.4). Cobicistat absorption was unaffected upon staggered administration (12 hours apart) or coadministration with omeprazole or famotidine; the 90% CIs of the LS means ratios of COBI exposure

parameters were within 80.00% to 125.00% (Section 2.1.8.3 and Section 2.1.8.4), indicating that changes in gastric pH do not affect COBI PK or its pharmacoenhancing properties.

The effect of food on the bioavailability of COBI with the intended commercial DRV/COBI FDC tablet formulation (G006) and DRV/COBI coadministered as single agents was investigated in study TMC114IFD1003 (Section 3.3.1). The effect of different food types on the bioavailability of COBI when administered as the EVG/COBI/FTC/TDF STR was investigated in study GS-US-236-0105 (Section 3.3.1).

3.1.2.2. Distribution of COBI

The plasma protein binding of COBI in nonclinical species ranged from 90.9% to 97.7%, and was 97.3% in samples from clinical studies with healthy human subjects (on average 97% to 98%). Binding was concentration-independent. After an oral 150-mg dose of ^{14}C-COBI in healthy subjects, the blood-to-plasma ratio of ^{14}C-radioactivity was approximately 0.5 and was time-independent, indicating that COBI and its metabolites are excluded from the cellular components of the blood (GS-US-216-0111, Section 2.1.2). The distribution of COBI into compartments other than plasma (eg, cerebrospinal fluid or genital tract secretions) has not been clinically evaluated.

3.1.2.3. Metabolism and Excretion of COBI

3.1.2.3.1. In Vitro Metabolism of COBI

The metabolism of COBI is mediated primarily via oxidative processes. Preliminary identification of COBI metabolites was performed in vitro using human hepatocytes and in nonclinical and human hepatic microsomal fractions (Section 1.2.2.3). In all species apart from dog, COBI metabolism could be accounted for by the generation of 3 metabolites: M21, M31, and M26. Metabolite identification was performed with samples from in vivo studies with ^{14}C-COBI in nonclinical species and in humans. No direct conjugates of COBI were detected, and the 3 primary metabolites (M21, M26, and M31) were common to all species in vivo and in vitro.

The intended pharmacological effect of COBI is inhibition of human CYP3A enzyme activity. Assessment of CYP3A inhibitions in human hepatic microsomal fractions demonstrated that COBI is a potent mechanism-based inhibitor of human CYP3A (Section 1.2.2.4.1). COBI had relatively minimal off target inhibitory effects on other CYP isoforms in vitro and did not inhibit UGT1A1 in vitro.

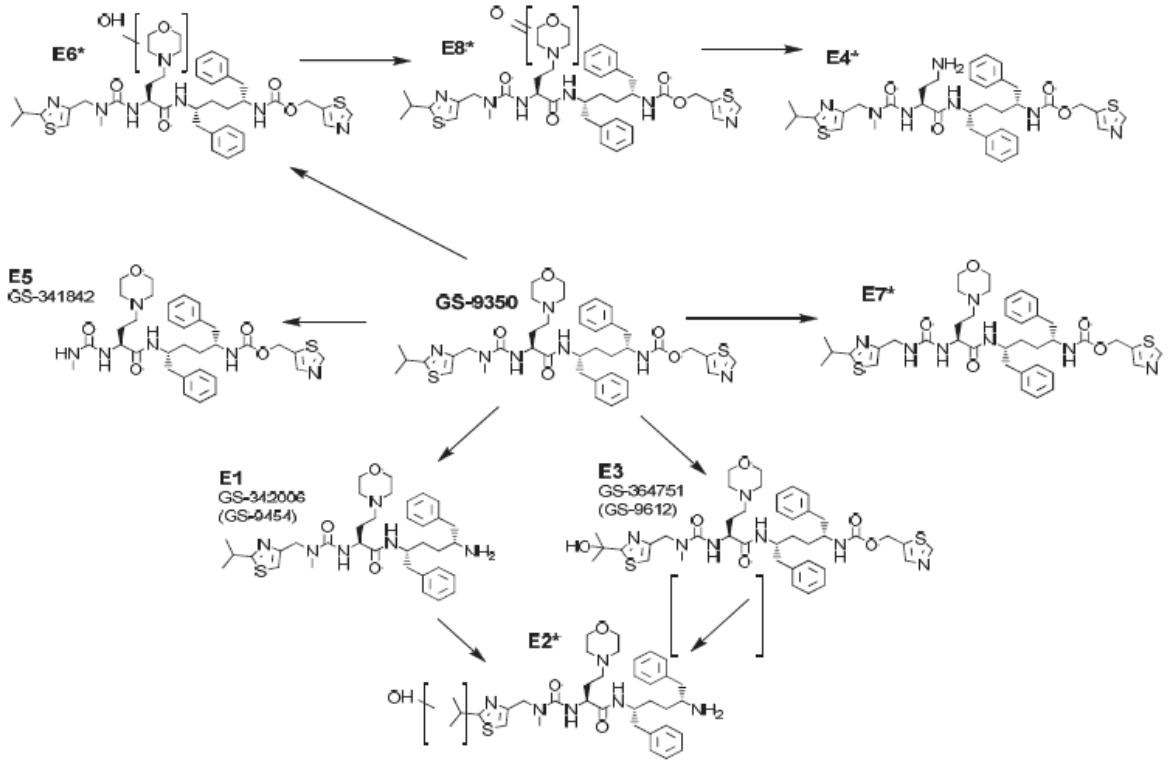
3.1.2.3.2. Mass-Balance of COBI

In a mass-balance, PK, and metabolite profile of COBI following administration of an oral dose of boosted ^{14}C-COBI in healthy subjects (Study GS-US-216-0111, Section 2.1.2), quantifiable levels of ^{14}C-radioactivity in whole blood and plasma were observed for up to 28 and 32 hours, respectively, following administration of ^{14}C-COBI. Following oral administration of ^{14}C-COBI, COBI was extensively metabolized, primarily via CYP3A- and/or CYP2D6-mediated oxidation, with no evidence of Phase 2 metabolism (Figure 27). The total combined recovery of

^{14}C-radioactivity in feces and urine was 94.4%, with most of the radioactive dose recovered from the feces (86.2%), consistent with the hepatobiliary excretion of COBI. The dose was primarily recovered as parent drug or metabolites M21 or M31; 8.2% of the administered dose was recovered in urine, primarily as unchanged parent drug, with low levels of metabolites M21 and M31. The predominant species circulating in plasma was COBI, which accounted for 98.6% of the total radioactivity over 24 hours. In some instances, at individual timepoints (, 2 timepoints), low levels of radioactive metabolite(s) were detected in pooled plasma samples; however, composite concentration-time profiles could not be drawn, precluding quantification of these metabolites.

In feces, COBI was the major species present (27%), followed by known oxidative metabolites, M31 (14%), which results from hydroxylation of isopropyl thiazole, and M21 (5.5%), which results from carbamate cleavage. All other metabolites detected in the feces were in trace amounts, with no values exceeding 3% of the administered dose. Renal excretion of COBI was a minor pathway for elimination (representing 6.31% of the total radioactive dose) and was comprised primarily of COBI. Metabolites M21 and M31 were present in very low amounts in urine.

Figure 27: Proposed Biotransformation Pathway of COBI in Humans



E1=M21; E3=M31; E5=M26.
E1, E3, and E5 were generated by humans, mice, rats, and dogs; E2, E4, E6, E7, and E8 were generated exclusively by dogs.
Source: Module 5.3.3.1/GS-US-216-0111/Figure 7-8; Module 4.2.2.4/AD-216-2038; AD-216-2074[30]

3.1.3. Noncompartmental PK of DRV

3.1.3.1. Single-Dose PK of DRV in Healthy Subjects

The noncompartmental PK of DRV in healthy subjects following single-dose administration of DRV/COBI 800/150 mg as the intended commercial FDC tablet (G006) or DRV/COBI 800/150 mg coadministered as single agents were assessed in study TMC114IFD1003 (Module 2.7.1/Section 2.2.1). Exposure to DRV with the DRV/COBI 800/150-mg FDC G006 tablet was bioequivalent to DRV/COBI 800/150 mg coadministered as single agents in this study (Table 134). Exposure to DRV was higher with the DRV/COBI FDC tablet compared with historical data for exposure to DRV following single-dose administration of DRV/rtv 800/100 mg coadministered as single agents in 2 studies (TMC114-C137 and TMC114-C181), and lower compared with historical data for exposure to DRV/rtv 800/100 mg coadministered as single agents in 2 other studies (TMC114-C182 and TMC114-C176). Ritonavir was dosed to steady-state (ie, for 3 days) in the historical studies, and this may have increased the PK variability of DRV because rtv is both an inhibitor and inducer of metabolism. The rate of absorption, however, was similar across all studies; median t_{max} ranged from 3.0 to 4.5 hours.

Table 134: Across-Study Comparison of PK Parameters of DRV in Healthy Subjects After Single-Dose Administration of DRV/COBI 800/150 mg as an FDC tablet, DRV/COBI 800/150 mg Coadministered as Single Agents, or DRV/rtv 800/100 mg Coadministered as Single Agents (Fed Conditions) (Studies TMC114IFD1003, TMC114-C137, TMC114-C181, TMC114-C182, and TMC114-C176)

	Mean (SD); t_{max}: Median (Range)				
	DRV/COBI FDC 800/150 mg	DRV/COBI Single Agents 800/150 mg		DRV/rtv Single Agents 800/100 mg	
Parameter	**TMC114IFD1003**	**TMC114IFD1003**	**TMC114IFD1003**	**TMC114-C137**	**TMC114-C181** [a]
DRV formulation	G006	G006	F030	TF036 (F001)	F030
N	40	18	38	7	18
t_{max}, h	4.0 (1.5-9.1)	4.5 (1.5-6.0)	4.0 (1.0-9.0)	4.0 (4.0-6.0)	4.0 (2.0-4.0)
C_{max}, ng/mL	6,773 (1,343)	7,053 (1,057)	6,979 (1,201)	4,113 (1,842)	5,612 (1,533)
AUC_{last}, ng.h/mL	78,942 (26,709) [a]	75,258 (21,632) [a]	81,483 (27,540) [a]	44,142 (22,041) [b]	64,600 (21,940) [b]
AUC_{∞}, ng.h/mL	78,811 (27,304)	76,165 (22,090)	79,836 (26,913)	-	-
$t_{1/2, term}$, h	6.7 (3.4)	6.6 (3.2)	5.5 (1.6)	-	-

	DRV/rtv Single Agents 800/100 mg			
Parameter	**TMC114-C182**	**TMC114-C182**	**TMC114-C176**	**TMC114-C176**
DRV formulation	F030	G002	F030	G002
N	16	16	43	44
t_{max}, h	3.0 (1.5-4.0)	3.5 (1.5-5.0)	3.0 (1.0-6.0)	3.0 (1.0-5.0)
C_{max}, ng/mL	7,790 (2,137)	6,993 (2,227)	7,031 (1669)	6,773 (1,668)
AUC_{last}, ng.h/mL	145,559 (59,296) [a]	136,472 (67,188) [a]	105,900 (32,530) [a]	105,100 (37,880) [a]
AUC_{∞}, ng.h/mL	150,873 (63,922)	138,093 (76,025)	109,700 (35,460)	109,600 (41,550)
$t_{1/2, term}$, h	14.2 (4.1)	14.0 (4.0)	13.5 (4.8)	14.0 (4.6)

N=maximum number of subjects with data.
[a] AUC_{72h}.
[b] AUC_{24h}.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 16 and Table 20; TMC114-C137-CRR/Table 8[10]; TMC114-C181-CRR/Table 6[12]; TMC114-C182-CSR/Table 6[15]; TMC114-C176-CSR[14]

3.1.3.2. Multiple-Dose PK of DRV in Healthy Subjects

The noncompartmental PK of DRV following multiple-dose administration of 2 different DRV/COBI 800/150-mg FDC tablet formulations (G003 and G004) and DRV/rtv 800/100 mg coadministered as single agents were assessed in 1 study in healthy subjects (TMC114IFD1001; Module 2.7.1/Section 2.2.1). Exposure (C_{max} and AUC_{24h}) to DRV following administration of DRV/COBI 800/150 mg once daily as the 2 candidate FDC tablet formulations was generally comparable to the exposure to DRV following coadministration of DRV/COBI 800/150 mg once daily as single agents or DRV/rtv 800/100 mg once daily as single agents in study GS-US-216-0115 (Module 2.7.1/Section 2.1.1) (Table 135). Darunavir exposure was also generally comparable to historical data for DRV exposure following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents. The rate of absorption of DRV was generally similar for the DRV/COBI FDC tablet formulations and DRV/rtv coadministered as single agents; median t_{max} ranged from 3.0 to 5.0 hours with the exception of study TMC278-C112 (t_{max} of 2.0 hours).

Table 135: Across-Study Comparison of PK Parameters of DRV in Healthy Subjects After Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily as an FDC tablet or as Single Agents or DRV/rtv 800/100 mg Once Daily as Single Agents (Fed Conditions) (Studies TMC114IFD1001, GS-US-216-0115, TMC114-C137, TMC114-C181, and TMC278-C112)

	Mean (SD); t_{max}: Median (Range)				
	DRV/COBI FDC 800/150 mg qd		DRV/COBI Single Agents 800/150 mg qd	DRV/rtv Single Agents 800/100 mg qd	
Parameter	Day 10 TMC114IFD1001	Day 10 TMC114IFD1001	Day 10 GS-US-216-0115 [a]	Day 10 GS-US-216-0115 [a]	Day 10 TMC114IFD1001
DRV formulation	G003	G004	F030	F030	F030
N	33	33	31	31	32
t_{max}, h	5.0 (2.5-6.0)	4.0 (1.5-5.0)	3.00 (2.72; 3.50)	3.00 (3.00; 4.00)	4.0 (1.5-5.0)
C_{0h}, ng/mL	1,504 (1,114)	1,478 (934)	2,396 (1,215)	2,483 (852)	2,015 (852)
C_{min}, ng/mL	1,167 (787)	1,224 (681)	-	-	1,540 (611)
C_{max}, ng/mL	6,666 (1,287)	6,917 (1,394)	7,737 (1,689)	7,464 (1,517)	6,973 (1,527)
AUC_{24h}, ng.h/mL	74,780 (19,750)	76,490 (20,900)	81,084 (25,151)	79,987 (27,200)	78,410 (20,910)
$C_{ss,av}$, ng/mL	3,116 (823)	3,187 (871)	-	-	3,267 (871)
$t_{1/2, term}$, h	-	-	-	-	-

	DRV/rtv Single Agents 800/100 mg qd		
	Day 7 TMC114-C137	Day 7 TMC114-C181	Day 11 TMC278-C112
DRV formulation	TF036 (F001)	F030	F021
N	7	17	15
t_{max}, h	4.0 (3.0-4.0)	3.0 (1.0-4.0)	2.0 (1.0-5.0)
C_{0h}, ng/mL	1,153 (357)	2,124 (803)	1,887 (1,010)
C_{min}, ng/mL	1,067 (361)	1,988 (701)	1,714 (916)
C_{max}, ng/mL	5,259 (1,576)	6,166 (1,265)	7,586 (1,988)
AUC_{24h}, ng.h/mL	61,106 (22,455)	77,200 (23,520)	82,780 (24,980)
$C_{ss,av}$, ng/mL	2,546 (936)	3,217 (980)	3,449 (1,041)
$t_{1/2, term}$, h	14.4 (5.17)	8.6 (3.8)	-

N=maximum number of subjects with data; qd=once daily.
[a] For study GS-US-216-0115, t_{max} given as median (interquartile range).
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 7; Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-3; TMC114-C137-CRR/Table 8[10]; TMC114-C181-CRR/Table 6[12]; Module 5.3.3.4/TMC278-C112-CRR/Table 9

3.1.3.3. Multiple-Dose PK of DRV in HIV-1 Infected Subjects

The noncompartmental PK of DRV following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects were assessed in a substudy of GS-US-216-0130. Sixty HIV-1 infected subjects (57 ART-naïve and 3 ART-experienced) were enrolled (Section 2.2.5.1).

The mean DRV exposure (C_{max} and AUC_{24h}) following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents was generally higher than for DRV following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve HIV-1 infected subjects (TMC114-C211) (Table 136). The rate of absorption of DRV was similar; the median t_{max} ranged from 3.0 to 3.5 hours.

The mean DRV exposure (C_{max} and AUC_{24h}) following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130

were generally lower than for DRV following multiple-dose administration of DRV/rtv 800/10 mg once daily coadministered as single agents in ART-experienced HIV-1 infected subjects in studies TMC114-C202 and TMC114-C213; however, it should be noted that all but 3 subjects in the PK substudy of study GS-US-216-0130 were ART naïve.

Table 136: Across-Study Comparison of PK Parameters of DRV in HIV-1 Infected Subjects After Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents or DRV/rtv 800/100 mg Once Daily Coadministered as Single Agents (Fed Conditions) (Studies GS-US-216-0130, TMC114-C211, TMC114-C202, TMC114-C213)

	Mean (SD); t_{max}: Median (Range)			
	DRV/COBI Single Agents 800/150 mg qd (ART Naïve and Experienced [a])	DRV/rtv Single Agents 800/100 mg qd (ART Naïve)		
Parameter	Weeks 2-8 GS-US-216-0130	Week 4 TMC114-C211	Week 24 TMC114-C211	Week 48 TMC114-C211
DRV formulation	F030	F021	F021	F021
N	59	9	13	10
t_{max}, h	3.5 (1.0-6.0)	3.0 (1.0-4.1)	3.0 (0.9-4.0)	3.5 (0.8-6.0)
C_{0h}, ng/mL	1,560 (1,328)	1,826 (1,003)	1,786 (838)	2,133 (1,220)
C_{min}, ng/mL	-	1,189 (410)	1,419 (671)	1,352 (688)
C_{max}, ng/mL	7,663 (1,920)	5,471 (1,320)	5,804 (1,558)	6,756 (1,683)
AUC_{24h}, ng.h/mL	81,646 (26,322)	64,230 (18,210)	66,950 (18,610)	75,620 (26,440)
$C_{ss,av}$, ng/mL	-	2,675 (758)	2,808 (767)	3,156 (1,100)
$t_{1/2, term}$, h	10.8 (10.0)	-	-	-

	DRV/rtv Single Agents 800/100 mg qd (ART Experienced)	
	Week 4 TMC114-C202 + TMC114-C213	Week 24 TMC114-C202 + TMC114-C213
DRV formulation	F001	F001
N	9	14
t_{max}, h	4.0 (1.0-6.0)	4.0 (2.0-6.0)
C_{0h}, ng/mL	2,385 (1,178)	2,667 (3,048)
C_{min}, ng/mL	1,898 (945)	1,956 (2,131)
C_{max}, ng/mL	7,534 (2,209)	7,091 (4,400)
AUC_{24h}, ng.h/mL	93,220 (34,677)	91,485 (81,305)
$C_{ss,av}$, ng/mL	3,884 (1,445)	3,812 (3,388)
$t_{1/2, term}$, h	-	-

N=maximum number of subjects with data; qd=once daily.
[a] Only 3 subjects were ART-experienced.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-1, Table 6.2.1.3, and Table 6.3.1.1; Module 5.3.5.1/TMC114-C211-W48-CSR/Table 79; Module 5.3.4.2/TMC114-C926-CPKPD/Table 9

3.1.3.4. Comparison of DRV PK Between Healthy Subjects and HIV-1 Infected Subjects

The mean DRV exposure (C_{max} and AUC_{24h}) following multiple-dose administration of DRV/COBI 800/150 mg once daily as FDC tablet formulations (G003 and G004) or as single agents in healthy subjects was generally comparable to the exposure following administration of DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects

(Table 137). The rate of absorption of DRV was similar for healthy and HIV-1 infected subjects; the median t_{max} ranged between 3.0 and 5.0 hours.

Table 137: Across-Study Comparison of PK Parameters of DRV After Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily as an FDC Tablet or as Single Agents in Healthy Subjects and DRV/COBI 800/150 mg Once Daily as Single Agents HIV-1 Infected Subjects (Fed Conditions) (Studies TMC114IFD1001, GS-US-215-0115, and GS-US-216-0130)

	Mean (SD); t_{max}: Median (Range)			
	Healthy DRV/COBI FDC 800/150 mg qd		Healthy DRV/COBI Single Agents 800/150 mg qd	HIV-1 Infected ART Naïve and Experienced [b] DRV/COBI Single Agents 800/150 mg qd
Parameter	Day 10 TMC114IFD1001	Day 10 TMC114IFD1001	Day 10 GS-US-216-0115 [a]	Weeks 2-8 GS-US-216-0130
DRV formulation	G003	G004	F030	F030
N	33	33	31	59
t_{max}, h	5.0 (2.5-6.0)	4.0 (1.5-5.0)	3.00 (2.72; 3.50)	3.5 (1.0-6.0)
C_{0h}, ng/mL	1,504 (1,114)	1,478 (934)	2,396 (1,215)	1,560 (1,328)
C_{min}, ng/mL	1,167 (787)	1,224 (681)	-	-
C_{max}, ng/mL	6,666 (1,287)	6,917 (1,394)	7,737 (1,689)	7,663 (1,920)
AUC_{24h}, ng.h/mL	74,780 (19,750)	76,490 (20,900)	81,084 (25,151)	81,646 (26,322)
$C_{ss,av}$, ng/mL	3,116 (823)	3,187 (871)	-	-
$t_{1/2, term}$, h	-	-	-	10.8 (10.0)

N=maximum number of subjects with data; qd=once daily.
[a] For study GS-US-216-0115, t_{max} given as median (Q1; Q3).
[b] Only 3 subjects were ART-experienced.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 7; Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-3; Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-1, Table 6.2.1.3, and Table 6.3.1.1

In contrast, the exposure to DRV coadministered with rtv in HIV-1-infected subjects was generally higher than the exposure to DRV, when DRV was coadministered with rtv in healthy subjects (Table 138), which may be partly explained by the higher AAG concentrations in HIV-1 infected subjects and the high protein binding of DRV in plasma.

Table 138: Across-Study Comparison of PK Parameters of DRV After Administration of DRV/rtv 800/100 mg Once Daily Coadministered as Single Agents in Healthy Subjects and HIV-1 Infected Subjects (Fed Conditions) (Studies GS-US-216-0115, TMC114IFD1001, TMC114-C137, TMC114-C181, TMC114-C202, TMC114-C213, and TMC278-C112)

	Mean (SD); t_{max}: Median (Range)					
	Healthy					HIV-1 Infected ART Experienced
Parameter	Day 10 GS-US-216-0115 [a]	Day 10 TMC114 IFD1001	Day 7 TMC114-C137	Day 7 TMC114-C181	Day 11 TMC278-C112	Week 4 TMC114-C202 + TMC114-C213
DRV formulation	F030	F030	TF036 (F001)	F030	F021	F001
N	31	32	7	17	15	9
t_{max}, h	3.00 (3.00; 4.00)	4.0 (1.5-5.0)	4.0 (3.0-4.0)	3.0 (1.0-4.0)	2.0 (1.0-5.0)	4.0 (1.0-6.0)
C_{0h}, ng/mL	2,483 (852)	2,015 (852)	1,153 (357)	2,124 (803)	1,887 (1,010)	2,385 (1,178)
C_{min}, ng/mL	-	1,540 (611)	1,067 (361)	1,988 (701)	1,714 (916)	1,898 (945)
C_{max}, ng/mL	7,464 (1,517)	6,973 (152)	5,259 (1,576)	6,166 (1,265)	7,586 (1,988)	7,534 (2,209)
AUC_{24h}, ng.h/mL	79,987 (27,200)	78,410 (20,910)	61,106 (22,455)	77,200 (23,520)	82,780 (24,980)	93,220 (34,677)
$C_{ss,av}$, ng/mL	-	3,267 (871)	2,546 (936)	3,217 (980)	3,449 (1,041)	3,884 (1,445)

N=maximum number of subjects with data.
[a] For study GS-US-216-0115, t_{max} value given as median (Q1; Q3).
Source: Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-3; Module 5.3.1.1/TMC114IFD1001-CSR/Table 7; TMC114-C137/Table 8[10]; TMC114-C181/Table 6[12]; Module 5.3.4.2/TMC114-C926-CPKPD/Table 9; Module 5.3.3.4/TMC278-C112-CRR/Table 9

3.1.4. Noncompartmental PK of COBI

3.1.4.1. Single-Dose PK of COBI in Healthy Subjects

The noncompartmental PK of COBI in healthy subjects following single-dose administration of DRV/COBI 800/150 mg as the intended commercial FDC tablet (G006) or DRV/COBI 800/150 mg coadministered as single agents was assessed in study TMC114IFD1003 (Module 2.7.1/Section 2.2.1). Exposure to COBI with the DRV/COBI 800/150-mg FDC G006 tablet was bioequivalent to DRV/COBI 800/150 mg coadministered as single agents in this study.

3.1.4.2. Multiple-Dose PK of COBI in Healthy Subjects

The noncompartmental PK of COBI following multiple-dose administration of 2 candidate DRV/COBI 800/150-mg FDC tablet formulations (G003 and G004) and DRV/rtv 800/100 mg coadministered as single agents was assessed in 1 study in healthy subjects (TMC114IFD1001; Module 2.7.1/Section 2.2.1). Exposure (C_{max} and AUC_{24h}) to COBI following administration of DRV/COBI 800/150 mg once daily as the 2 candidate FDC tablet formulations was generally comparable to the exposure to COBI following coadministration of DRV/COBI 800/150 mg once daily as single agents (assessed in study GS-US-216-0115; Module 2.7.1/Section 2.1.1) (Table 139).

Table 139: Across-Study Comparison of PK Parameters of COBI in Healthy Subjects After Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily as an FDC tablet or DRV/COBI 800/150 mg Once Daily as Single Agents (Fed Conditions) (Studies TMC114IFD1001, GS-US-216-0115)

	Mean (SD); t_{max}: Median (Range)		
	DRV/COBI FDC 800/150 mg qd		DRV/COBI Single Agents 800/150 mg qd
Parameter	Day 10 TMC114IFD1001	Day 10 TMC114IFD1001	Day 10 GS-US-216-0115 [a]
COBI formulation	G003	G004	Commercial tablet
N	33	33	32
t_{max}, h	4.0 (2.0-5.0)	4.0 (1.0-5.0)	3.50 (3.00; 4.00)
C_{0h}, ng/mL	39.3 (44.7)	36.3 (47.2)	-
C_{min}, ng/mL	34.0 (37.8)	31.9 (40.1)	-
C_{max}, ng/mL	1,136 (233)	1,158 (250)	1,376 (268)
AUC_{24h}, ng.h/mL	9,386 (2,666)	9,314 (2,652)	10,370 (2,147)
$C_{ss,av}$, ng/mL	391 (111)	388 (111)	-
$t_{1/2, term}$, h	-	-	3.4 (0.6)

N=maximum number of subjects with data; qd=once daily.
[a] For study GS-US-216-0115, t_{max} given as median (Q1; Q3).
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 11; Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-1

3.1.4.3. Multiple Dose PK of COBI in HIV-1 Infected Subjects

The noncompartmental PK of COBI following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects were assessed in a substudy of GS-US-216-0130 (Section 2.2.5.1). The multiple-dose PK of COBI 150 mg when coadministered with DRV 800 mg as single agents was comparable to historical data for COBI 150 mg when administered as part of the EVG/COBI/FTC/TDF 150/150/200/300 mg STR.[47]

3.1.4.4. Comparison of COBI PK Between Healthy Subjects and HIV-1 Infected Subjects

Cobicistat C_{max} and AUC_{24h} following multiple-dose administration of DRV/COBI 800/150 mg once daily as 2 candidate FDC tablet formulations (G003 and G004) or DRV/COBI 800/150 mg once daily as single agents in healthy subjects were approximately 14% and 20% higher, respectively, than the exposure following coadministration of DRV/COBI 800/150 mg once daily as single agents in HIV-1 infected subjects (Table 140).

Table 140: PK Parameters of COBI After Multiple-Dose Administration of DRV/COBI 800/150 mg (G003 and G004) Once Daily as an FDC Tablet or as Single Agents in Healthy Subjects and DRV/COBI 800/150 mg Coadministered as Single Agents in HIV-1 Infected Subjects (Fed Conditions) (Studies TMC114IFD1001, GS-US-216-0115, and GS-US-216-0130)

	Mean (SD); t_{max}: Median (Range)			
	Healthy			HIV-1 Infected
Parameter	Day 10 TMC114IFD1001 DRV/COBI FDC 800/150 mg qd	Day 10 TMC114IFD1001 DRV/COBI FDC 800/150 mg qd	Day 10 GS-US-216-0115[a] DRV/COBI Single Agents 800/150 mg qd	Weeks 2-8 Study GS-US-216-0130 800/150 mg qd DRV/COBI Single Agents
COBI formulation	G003	G004	Commercial tablet	Commercial tablet
N	33	33	32	60
t_{max}, h	4.0 (2.0-5.0)	4.0 (1.0-5.0)	3.50 (3.00; 4.00)	3.5 (0.9-6.0)
C_{max}, ng/mL	1,136 (233)	1,158 (250)	1,376 (268)	991 (331)
AUC_{24h}, ng.h/mL	9,386 (2,666)	9,314 (2,652)	10,370 (2,147)	7,596 (3,657)

N=maximum number of subjects with data; qd=once daily.
[a] For study GS-US-216-0115, t_{max} given as median (Q1; Q3).
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 11; Module 5.3.1.2/GS-US-216-0115-CSR/Table 10-1; Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 6.3.2.1

3.1.5. Population PK of DRV

3.1.5.1. Population PK in HIV-1 Infected Subjects

In population PK analyses, the mean DRV C_{0h} and AUC_{24h} values following multiple-dose administration of DRV/COBI 800/150 mg once daily coadministered as single agents in mostly ART-naïve HIV-1 infected subjects were generally comparable to values for DRV exposure following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve and ART-experienced HIV-1 infected subjects (Table 141).

Table 141: Across-Study Comparison of Population PK Parameter Estimates for DRV in HIV-1 Infected Subjects Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily or DRV/rtv 800/100 mg Once Daily Coadministered as Single Agents (Studies GS-US-216-0130, TMC114-C211, TMC114-C229, TMC114-C202, and TMC114-C213)

	Mean (SD); Median (Range)			
	DRV/COBI Single Agents 800/150 mg qd (ART Naïve and Experienced [a])	DRV/rtv Single Agents 800/100 mg qd (ART-Naïve)	DRV/rtv Single Agents 800/100 mg qd (ART Experienced)	
Parameter	Week 24 GS-US-216-0130	Week 48 TMC114-C211	Week 48 TMC114-C229	Week 24 TMC114-C202 + TMC114-C213
DRV formulation	F030	F021	F030	F001
N	298	335	280	118
C_{0h}, ng/mL	2,043 (1,257)	2,281 (1,168)	NA	1,963 (1,003)
	1,875	2,041	1,896	1,840
	(70-6,890)	(368-7,242)	(184-7,881)	(256-5,868)
AUC_{24h}, ng.h/mL	100,152 (32,043)	93,026 (27,050)	NA	92,670 (33,711)
	96,900	87,854	87,788	89,845
	(34,500-224,000)	(45,000-219,240)	(45,456-236,920)	(25,828-214,040)

N=maximum number of subjects with data; NA=not available.
[a] Only 3 subjects were ART-experienced.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-5; Module 5.3.5.1/TMC114-C211-W48-CSR/Table 78 and Display PK/PD.1; Module 5.3.5.1/TMC114-C229-W48-CSR/Table 83 and Display PK/PD.1; Module 5.3.4.2/TMC114-C926-CPKPD/Table 16

3.1.6. Dose Proportionality and Time Dependency

3.1.6.1. Dose Proportionality

The dose proportionality of DRV exposure when coadministered with COBI has not been investigated.

When DRV was coadministered with rtv as single agents in healthy subjects, the systemic exposure to DRV increased dose proportionally across the DRV/rtv doses of 400/100, 800/100, and 1200/100 mg once daily (TMC114-C137/Section 4.2.5[10]). In ART-experienced HIV-1 infected subjects, the systemic exposure to DRV increased less than dose proportionally across the DRV/rtv doses of 400/100 and 800/100 mg once daily (Section 2.2.6.4).

Cobicistat exhibits nonlinear PK with respect to dose and time, consistent with the properties of a mechanism-based inhibitor. When COBI was administered as a single agent in healthy subjects at single and multiple doses of 50, 100, and 200 mg, the systemic exposure to COBI increased more than dose proportionally and dramatic decreases in CL/F were observed with increases in dose (Section 2.1.4.1). Following single-dose administration, the AUC_{∞} of COBI increased 6.8-fold for the dose increase from 50 to100 mg COBI and 5.1-fold for the dose increase from 100 to 200 mg. Similar results were observed for single-dose administration of COBI 300 and 400 mg, where a 1.9-fold increase in AUC_{∞} was observed following single-dose administration of 400 mg COBI relative to 300 mg COBI (Section 2.1.4.2). Cobicistat exposure following multiple-dose administration also increased more than dose proportionally, with a 4.2-fold

increase in AUC_{24h} for the dose increase from 50 to 100 mg and a 4.7-fold increase for the dose increase from 100 to 200 mg.

3.1.6.2. Time Dependency

The time dependency of DRV or COBI exposure when coadministered as the FDC has not been investigated within a single study. In healthy subjects, a comparison of DRV exposure (C_{max} and AUC) after single-dose administration of DRV/COBI 800/150 mg FDC tablets in study TMC114IFD1003 and multiple-dose (once daily) administration of DRV/COBI 800/150-mg FDC tablets in study TMC114IFD1001 suggested that DRV does not accumulate over time (Table 142). Cobicistat exhibited 1.5- to 1.7-fold increase in exposure following multiple-dose administration of DRV/COBI 800/150 mg in study TMC114IFD1001 relative to single-dose administration in study TMC114IFD1003.

Table 142: Across-Study Comparison of PK Parameters of DRV and COBI Following Single- or Multiple-Dose Administration of Different DRV/COBI 800/150-mg FDC Tablet Formulations in Healthy Subjects (Study TMC114IFD1001 and TMC114IFD1003)

	Mean (SD); t_{max}: Median (Range)			
	Single Dose (Study TMC114IFD1003)		Multiple Dose, Day 10 (Study TMC114IFD1001)	
Parameter	DRV/COBI 800/150 mg (Tablet G006)		DRV/COBI 800/150 mg qd (Tablet G003)	DRV/COBI 800/150 mg qd (Tablet G004)
DRV				
N	40	18	32	33
t_{max}, h	4.0 (1.5-9.1)	4.5 (1.5-6.0)	5.0 (2.5-6.0)	4.0 (1.5-5.0)
C_{max}, ng/mL	6,773 (1,343)	7,053 (1,057)	6,666 (1,287)	6,917 (1,394)
AUC_{24h}, ng.h/mL	-	-	74,780 (19,750)	76,490 (20,900)
AUC_{last}, ng.h/mL	78,942 (26,709)	75,258 (21,632)	-	-
AUC_{∞}, ng.h/mL	78,811 (27,304)	76,165 (22,090)	-	-
COBI				
N	40	18	32	33
t_{max}, h	4.00 (1.00-5.02)	4.98 (1.00-6.00)	4.0 (2.0-5.0)	4.0 (1.0-5.0)
C_{max}, ng/mL	819 (221)	769 (174)	1,136 (233)	1,158 (250)
AUC_{24h}, ng.h/mL	-	-	9,386 (2,666)	9,314 (2,652)
AUC_{last}, ng.h/mL	6,285 (2,735)	5,491 (1,425)	-	-
AUC_{∞}, ng.h/mL	6,388 (2,779)	5,526 (1,478)	-	-

N=maximum number of subjects with data; qd=once daily.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 16, Table 18, Table 20, and Table 22; Module 5.3.1.1/TMC114IFD1001-CSR/Table 7 and Table 11

3.1.7. Intersubject Variability in PK Parameters

Darunavir when coadministered with COBI as an FDC exhibits low to moderate ISV in PK. Coefficients of variation ranged from 14.99% to 19.83% for C_{max} and 28.74% to 34.64% for AUC when given as a single dose under fed conditions (study TMC114IFD1003, Module 5.3.1.2/TMC114IFD1003-CSR/Table 16 and Table 20) and from 19.31% to 20.15% for C_{max} and 26.41% to 27.32% for AUC when given as multiple doses under fed conditions (study TMC114IFD1001, Module 5.3.1.1/TMC114IFD1001-CSR/Table 7) in healthy subjects. The variability for DRV C_{max} and AUC_{24h} when DRV was administered together with COBI as single agents in HIV-1-infected subjects was higher than the variability observed in healthy subjects,

with CV percentages of 25.06% and 32.24% for C_{max} and AUC_{24h}, respectively (PK substudy GS-US-216-0130, Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-1, Table 6.2.1.3, and Table 6.3.1.1).

Cobicistat, when coadministered with DRV as an FDC, exhibits moderate ISV in PK. Coefficients of variation ranged from 22.63% to 26.98% for C_{max} and 42.76% to 43.52% for AUC when given as a single dose under fed conditions (study TMC114IFD1003, Module 5.3.1.2/TMC114IFD1003-CSR/Table 18 and Table 22) and from 20.51% to 21.59% for C_{max} and 28.40% to 28.47% for AUC when given as multiple doses under fed conditions (study TMC114IFD1001, Module 5.3.1.1/TMC114IFD1001-CSR/Table 11) in healthy subjects. The variability for COBI C_{max} and AUC_{24h} when COBI was administered together with DRV as single agents in HIV-1-infected subjects was slightly higher than the variability observed in healthy subjects, with CV percentages of 33.40% and 48.14% for C_{max} and AUC_{24h}, respectively (PK substudy GS-US-216-0130, Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-2, Table 6.2.2.3, and Table 6.3.2.1).

3.2. Effect of Intrinsic Factors on DRV and COBI

3.2.1. Age

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, age was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis between individual parameters and age suggested that age might explain some of the variability in DRV CL/F and V_p/F, but age was not a significant covariate during the model-building process (Section 2.2.6.1). Thus age is not considered to have a relevant effect on the exposure to DRV when administered as DRV/COBI 800/150 mg once daily (as single agents).

This result for DRV/COBI was consistent with the situation when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in study TMC114-C211 in ART-naïve HIV-1 infected subjects and in study TMC114-C229 in ART-experienced HIV-1 infected subjects, where population PK analysis indicated that age also had no relevant effect on the exposure (AUC) to DRV (Section 2.2.6.2 and Section 2.2.6.3, respectively). Population PK analysis in HIV-infected patients using DRV/rtv twice daily also showed that DRV PK are not considerably different in the age range (18 to 75 years; n=12 > 65 years) (Module 5.3.4.2/TMC114-C926-CPKPD/Section 4).

The PK of COBI have not been fully evaluated in older patients (> 65 years); no PK studies have been conducted with COBI in children and adolescents under the age of 18 years.

Caution is recommended when administering DRV/COBI in older patients due to the greater frequency of decreased hepatic function, concomitant disease(s), and/or polypharmacy.

3.2.2. Sex

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, sex was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis between individual parameters and sex suggested that sex might explain some of the variability in DRV CL/F and V_p/F, but sex was not a significant covariate during the model building process (Section 2.2.6.1). Thus, sex is not considered to have a relevant effect on the exposure to DRV when administered as DRV/COBI 800/150 mg once daily (as single agents).

This result for DRV/COBI was consistent with the situation when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in study TMC114-C211 in ART-naïve HIV-1 infected subjects (Section 2.2.6.2). In this study, population PK analysis indicated that although there was a trend towards a higher (1.10-fold) mean exposure to DRV in females compared with males, this difference was not considered to be clinically relevant. In study TMC114-C229, in which DRV was administered as DRV/rtv 800/100 mg once daily (single agents) in ART-experienced HIV-1 infected subjects, population PK analysis indicated that there was also a trend towards higher DRV exposure (1.13-fold) in females compared with males, but again, this difference was not considered to be clinically relevant (Section 2.2.6.3).

3.2.3. Body Weight and Related Measures of Body Size

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, body weight, height, body surface area, and body mass index were assessed as potential covariates that could explain variability in the PK of DRV. A graphical analysis between individual parameters and these covariates indicated that none explained any of the variability in DRV CL/F and V_p/F (Section 2.2.6.1).

This result for DRV/COBI was consistent with the situation when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in study TMC114-C211 in ART-naïve HIV-1 infected subjects and in study TMC114-C229 in ART-experienced HIV-1 infected subjects, where population PK analysis indicated that body weight also had no relevant effect on the exposure (AUC) to DRV (Section 2.2.6.2 and Section 2.2.6.3, respectively).

3.2.4. Hepatic Impairment

The effect of hepatic impairment on the PK of DRV when coadministered with COBI has not been investigated.

In non-HIV-1 infected subjects treated with DRV/rtv 600/100 mg twice daily administered as single agents, the mean C_{max} and AUC_{12h} of DRV were decreased by 12% and 6%, respectively, in subjects with mild hepatic impairment relative to healthy matched control subjects; these parameters were increased approximately 1.20-fold in subjects with moderate hepatic impairment relative to healthy matched control subjects (Section 2.1.6.1). Based on these results, no adjustment of the DRV/rtv dose is required in subjects with mild or moderate hepatic

impairment. Based upon the comparable PK of DRV when coadministered with rtv or COBI (Module 2.7.1/Section 2.2.1), this recommendation is also applicable to the administration of DRV/COBI.

A study of COBI PK was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Section 2.1.6.2). The AUC_{24h} and C_{max} of COBI were generally comparable in subjects with moderate hepatic impairment relative to normal matched control subjects while C_{24h} was increased 2.08-fold, although this was not considered to be clinically relevant. Exploratory analyses indicated no clinically relevant correlations between COBI exposures and Child-Pugh-Turcotte scores or individual liver function laboratory parameters. Overall, no clinically relevant differences in COBI PK were observed between non-HIV-1 infected subjects with moderate hepatic impairment and non-HIV-1 infected subjects with normal hepatic function.

The effect of severe hepatic impairment on the PK of DRV or COBI has not been evaluated.

3.2.5. Renal Impairment

A mass-balance study with ^{14}C-DRV/rtv showed that approximately 7.7% of the administered dose of DRV is excreted in the urine as unchanged drug (Section 3.1.1.3.2). As DRV and rtv are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, creatinine clearance was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis between individual parameters and creatinine clearance indicated that this did not explain any of the variability in DRV CL/F and V_p/F (Section 2.2.6.1).

This result for DRV/COBI was consistent with the situation when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in study TMC114-C211 in ART-naïve HIV-1 infected subjects and in study TMC114-C229 in ART-experienced HIV-1 infected subjects, where population PK analysis indicated that creatinine clearance also had no relevant effect on the exposure (AUC) to DRV (Section 2.2.6.2 and Section 2.2.6.3, respectively).

No PK data for DRV are available in HIV-1-infected patients with severe renal impairment or end stage renal disease. However, because the renal clearance of DRV is limited, a decrease in total body clearance is not expected in patients with renal impairment.

A study of COBI PK performed in non-HIV infected subjects with severe renal impairment ($eGFR_{CG}$ <30. mL/min) found no meaningful differences in COBI PK between subjects with severe renal impairment and healthy subjects ($eGFR_{CG}$ ≥90 mL/min), consistent with the low renal clearance of COBI (Section 2.1.5.2). A study comparing COBI PK in non-HIV infected subjects with mild to moderate renal impairment (eGFR 50 to 79 mL/min) with PK in healthy subjects (eGFR ≥80 mL/min) found higher COBI exposures in subjects with mild to moderate

renal impairment relative to subjects with normal renal function (Section 2.1.5.1), which suggests a change in COBI clearance with or without a change in bioavailability.

3.2.6. Race/Ethnicity

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, race was assessed as a potential covariate that could explain variability in the PK of DRV. A graphical analysis between individual parameters and race indicated that this did not explain any of the variability in DRV CL/F and V_p/F (Section 2.2.6.1).

This result for DRV/COBI was consistent with the situation when DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in study TMC114-C211 in ART-naïve HIV-1 infected subjects (Section 2.2.6.2). Population PK analysis indicated that, although there was an approximately 13% lower exposure in Asian subjects compared with Caucasian subjects in this study, this difference was not considered to be clinically relevant. In study TMC114-C229, in which DRV was administered as DRV/rtv 800/100 mg once daily (as single agents) in ART-experienced HIV-1 infected subjects, population PK analysis indicated there was also a trend toward lower DRV exposure in Asian subjects (approximately 15%) compared with Caucasian subjects, but this difference was also not considered to be clinically relevant (Section 2.2.6.3).

3.2.7. Plasma AAG Concentration

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents, the AAG covariate was retained from the original model and was fixed in the further development of the model, hence the effect of AAG on DRV exposure could not be estimated (Section 2.2.6.1).

When DRV was administered as DRV/rtv 800/100 mg once daily (single agents) in study TMC114-C211 in ART-naïve HIV-1 infected subjects, higher baseline AAG levels resulted in higher exposures to DRV (Section 2.2.6.2). A similar trend was seen in study TMC114-C229, in which DRV was administered as DRV/rtv 800/100 mg once daily (single agents) in ART-experienced HIV-1 infected subjects, with DRV exposure being approximately 38% higher in subjects with a baseline AAG level of >1.11 g/L than in subjects with a baseline AAG level of ≤0.80 g/L (Section 2.2.6.3).

3.3. Effect of Extrinsic Factors on DRV and COBI

3.3.1. Food

The effect of food on drug absorption is described in Module 2.7.1/Section 3.1.2 and Section 3.2.2.

In study TMC114IFD1003, exposure to DRV following single-dose administration of DRV/COBI 800/150 mg as the FDC tablet G006 was increased following a high-fat breakfast relative to fasted conditions. Mean C_{max}, AUC_{last}, and AUC_{∞} values for DRV were increased by

2.27-, 1.63-, and 1.70-fold, respectively. Therefore, it is recommended that DRV/COBI be taken with food.

This effect of concomitant food intake on DRV exposure when administered as the DRV/COBI FDC tablet is consistent with the effect of food on DRV exposure when coadministered with rtv as single agents. The effect of different meal types on the oral bioavailability of DRV when coadministered with rtv was investigated in study TMC114-C143 (Module 2.7.1/Section 2.3.1). Exposure (C_{max} and AUC_{last}) of DRV was decreased by approximately 30% when administered under fasted conditions compared with a standard breakfast. For all 4 meal types (standard breakfast, high-fat breakfast, nutritional protein-rich drink, and croissant and coffee) the exposure of DRV was comparable. Therefore, DRV/rtv should always be taken with food, and the type of meal does not affect exposure to DRV. Based on these results, DRV/rtv is recommended to be taken with food.

The effect of food on the oral bioavailability of COBI when administered as the DRV/COBI G006 FDC tablet was investigated in study TMC114IFD1003 (Module 2.7.1/Section 2.2.1) and when administered as the EVG/COBI/FTC/TDF STR in study GS-US-236-0105 (Module 2.7.1/Section 2.3.2). No clinically relevant effect of food was observed for COBI in either study. However, while COBI can be administered without regard to meals (Module 2.7.1/Section 3.2.2), because a food effect is observed for DRV, it is recommended that the DRV/COBI FDC tablet be taken with food.

3.3.2. Drug-Drug Interactions

No drug-drug interaction studies have been conducted with DRV/COBI (FDC or coadministered as single agents). The drug-drug interaction potential of the DRV/COBI is based on the interactions observed with the single agents.

The in vitro drug interaction potential of COBI has been well studied, including the differences with rtv, as summarized below.

In human hepatic microsomal fractions and tests for enzyme-specific activities, COBI showed good specificity as an inhibitor of CYP3A, with no significant inhibition of CYP1A2, CYP2C9, and CYP2C19 and mild inhibition of CYP2B6 (similar to rtv) (Section 1.2.2.4.1). Cobicistat was a milder inhibitor of CYP2C8 and UGT1A1 activities than rtv. Like rtv, COBI was found to be primarily an inhibitor of CYP3A and CYP2D6, albeit a mild inhibitor of the latter and to a lesser extent than rtv.

Cobicistat was found to be a mild inhibitor of P-gp and the MRP transporters MRP1 and MRP2 (Section 1.2.2.4.2). Cobicistat inhibited P-gp and MRP1 less potently than rtv, while both are mild inhibitors of MRP2. None of these transporter interactions are likely to be clinically relevant at the anticipated COBI plasma concentrations, but transient inhibition of intestinal P-gp during absorption is anticipated. Cobicistat is also an inhibitor of BCRP, MATE1, OATP1B1, and OATP1B3.

At concentrations of up to 10 μM, COBI did not activate the human AhR (similar to rtv) and only mildly activated human PXR in cell-based systems (rtv, in contrast, shows significant activation) (Section 1.2.2.4.3). Cobicistat is thus not expected to be a clinically relevant inducer through activation of AhR or PXR.

Activity and mRNA expression for CYP1A2 (controlled by AhR) and CYP2B6 (controlled by the constitutive androstane receptor) in human hepatocytes were largely unaffected by treatment with COBI at concentrations of up to 30 μM. Expression of CYP3A4 mRNA and CYP3A immunodetectable protein (controlled by PXR) were mildly induced, but CYP3A activity remained low, likely due to persistent inhibition.

A comprehensive drug-drug interaction program has been conducted with DRV/rtv, including a cocktail study to assess the effects of DRV/rtv coadministered as single agents on the metabolism of probe substrates (TMC114-C173-CRR[11]). Interactions are most likely a result of the rtv component because of its inhibitory effects on CYP2D6, CYP3A, and certain transporters, and/or its induction effects on CYP2C9, CYP2C19, and UGT. A summary of the interactions and recommendations for use of DRV/rtv in combination with various drugs is available in the local product labeling for DRV.

As COBI also inhibits CYP3A and CYP2D6 (the latter albeit mildly and to a lesser extent than rtv), most data generated with DRV/rtv coadministered as single agents related to these enzymes can be extrapolated to DRV/COBI. For drugs that are (pure) CYP2D6 or CYP3A substrates, the interaction between DRV/COBI and DRV/rtv is expected to be similar in magnitude.

Coadministration of DRV/rtv (single agents) is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index). These drugs include: alfuzosin, antiarrhythmics (amiodarone, bepridil, quinidine, systemic lidocaine), antihistamines (astemizole, terfenadine), cisapride, ergot derivatives (eg, dihydroergotamine, ergometrine, ergotamine, methylergonovine), HMG CoA reductase inhibitors (lovastatin, simvastatin), neuroleptics (pimozide, sertindole), sildenafil (for treatment of pulmonary arterial hypertension), and sedative/hypnotics (oral midazolam, triazolam). Because DRV is metabolized by CYP3A, potent CYP3A inducers such as lopinavir/ritonavir, rifampicin and St John's wort (*Hypericum perforatum*) are also contraindicated. These contraindications also apply to DRV/COBI. In addition, avanafil, colchicine (in patients with hepatic or renal impairment), dronedarone, quetiapine, ranolazine (CYP3A substrates), and the anticonvulsants carbamazepine, phenobarbital, and phenytoin (CYP3A inducers) are also contraindicated with DRV/COBI.

Coadministration of DRV/COBI with medicinal products that are mild to moderate inducers of CYP3A may result in decreased plasma concentrations of COBI and, consequently, a decrease in DRV boosting, leading to loss of therapeutic effect and possible development of resistance. Some examples include, but are not limited to, etravirine, efavirenz, NVP, boceprevir, telaprevir, and bosentan.

Potential differences between DRV/rtv and DRV/COBI with regard to drug-drug interactions could arise from interaction with transporters including P-gp (rtv appears to inhibit P-gp to a greater extent than COBI in vitro), as well as drug metabolizing enzymes such as CYP1A2, 2B6, 2C8, 2C9, and 2C19 (rtv induces CYP1A2, 2B6, 2C8, 2C9, and 2C19, whereas COBI may have little to no effect on these enzymes) and UGT1A1 (rtv induces UGT1A1). As COBI has fewer overall effects on drug metabolizing enzymes and transporters than rtv, different drug-drug interactions could be expected with DRV/COBI. Drugs primarily metabolized by CYP1A2, 2B6, 2C8, 2C9, 2C19, and/or UGT1A1 that are coadministered with DRV/rtv may eventually increase in exposure when treatment is switched to DRV/COBI. Table 143 summarizes the theoretical drug-drug interactions for DRV/COBI.

Darunavir/COBI should not be used in combination with other ARV agents that require boosting (eg, EVG and other HIV PIs), with medicinal products containing RTV, or with regimens containing RTV.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	/ darunavir / cobicistat / didanosine	Didanosine should be administered on an empty stomach 1 hour before or 2 hours after DRV/COBI (administered with food).
tenofovir disoproxil fumarate	/ darunavir / cobicistat 0 tenofovir	Coadministration of DRV/COBI with tenofovir disoproxil fumarate may increase concentrations of tenofovir (inhibition of P-gp). The increase in tenofovir is not expected to be clinically relevant and no dose adjustment of tenofovir disoproxil fumarate is needed. Monitoring of renal function may be indicated when DRV/COBI is given in combination with tenofovir disoproxil fumarate, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Other NRTIs: abacavir, emtricitabine, lamivudine, stavudine, zidovudine	/ darunavir	Based on the different elimination pathways of the other NRTIs, which are primarily renally excreted, no drug interactions are expected between these drugs and DRV/COBI. Darunavir/COBI can be used with these NRTIs without dose adjustment.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
HIV-1-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz, etravirine, nevirapine	↓ darunavir ↓ cobicistat ↑ nevirapine	Coadministration of DRV/COBI with these NNRTIs may decrease DRV and/or COBI concentrations (induction of CYP3A) which may result in loss of therapeutic effect to DRV. Nevirapine concentrations may be increased when coadministered with DRV/COBI (inhibition of CYP3A). Coadministration of DRV/COBI with these NNRTIs is not recommended.
rilpivirine	↑ darunavir ↑ cobicistat ↑ rilpivirine	Coadministration of DRV/COBI with rilpivirine may increase concentrations of rilpivirine (inhibition of CYP3A). The increase in rilpivirine is not expected to be clinically relevant, and no dose adjustment of rilpivirine is needed.
HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, tipranavir	-	The appropriate dose of DRV/COBI with other HIV PIs have not been established. Coadministration of DRV/COBI with HIV PIs is not recommended.
HIV-1-Antiviral Agents: CCR5 Co-receptor Antagonist (CCR5RA)		
maraviroc	↑ maraviroc	Coadministration of DRV/COBI with maraviroc may increase concentrations of maraviroc (inhibition of CYP3A). When used in combination with DRV/COBI, the recommended dose of maraviroc is 150 mg twice daily.
HIV-1-Antiviral Agents: Integrase Strand Transfer Inhibitors		
dolutegravir	-	Darunavir/COBI and dolutegravir can be coadministered without dose adjustment.
elvitegravir	-	Coadministration of DRV/COBI and elvitegravir/COBI is not recommended.
raltegravir	↓ darunavir	Some clinical studies suggest raltegravir may cause a modest decrease in DRV concentrations (mechanism unknown). At present the effect of raltegravir on DRV concentrations does not appear to be clinically relevant. Darunavir/COBI and raltegravir can be used without dose adjustments.
Other Agents		
α_1-Adrenoreceptor Antagonists: alfuzosin	↑ alfuzosin	Coadministration of DRV/COBI with alfuzosin may increase alfuzosin concentrations (inhibition of CYP3A). Coadministration of DRV/COBI with alfuzosin is contraindicated.
Antacids: aluminum/magnesium hydroxide, calcium carbonate	↓ darunavir ↓ cobicistat	Based on mechanistic considerations (decreased gastric acidity), no interaction is expected between antacids and DRV/COBI. Darunavir/COBI and antacids can be used without dose adjustment.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antiangina/ Antiarrhythmics: bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone	0 antiarrhythmics	Coadministration of DRV/COBI with these antiarrhythmics may increase concentrations of the antiarrhythmic (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring, if available, is recommended for the antiarrhythmics when coadministered with DRV/COBI.
digoxin	0 digoxin	Coadministration of DRV/COBI with digoxin may increase concentrations of digoxin (inhibition of P-gp). The lowest possible dose of digoxin should initially be prescribed. Digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect, while assessing the overall clinical state of the subject.
amiodarone, dronedarone, quinidine, ranolazine		Coadministration of DRV/COBI with amiodarone, dronedarone, quinidine, or ranolazine is contraindicated.
Antibacterials: clarithromycin	0 darunavir 0 cobicistat 0 clarithromycin	Coadministration of DRV/COBI with clarithromycin may increase concentrations of DRV, COBI and/or the clarithromycin (inhibition of CYP3A). Caution should be exercised when clarithromycin is combined with DRV/COBI.
Anticoagulants: apixaban, dabigatran etexilate, rivaroxaban, warfarin	0 anticoagulants	Coadministration of DRV/COBI with these anticoagulants may increase concentrations of the anticoagulant (inhibition of CYP3A and/or P-gp). Coadministration of DRV/COBI and rivaroxaban is not recommended. When used in combination with DRV/COBI, the recommended dose of apixaban is 2.5 mg twice daily. Clinical monitoring, including a coagulation test, is recommended when DRV/COBI is coadministered with dabigatran etexilate. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure. Coadministration of DRV/COBI with warfarin may affect warfarin concentrations. The international normalized ratio should be monitored when DRV/COBI is coadministered with warfarin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ darunavir ↓ cobicistat	Coadministration of DRV/COBI with carbamazepine, phenobarbital, or phenytoin may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect to DRV. Coadministration of DRV/COBI and these anticonvulsants is contraindicated.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antidepressants: (selective serotonin reuptake inhibitors or tricyclics) desipramine, paroxetine, sertraline, trazodone	0 antidepressant	Coadministration of DRV/COBI and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). If these antidepressants are to be used with DRV/COBI, the combination should be used with caution, and a lower dose of antidepressant should be considered.
Antidiabetic metformin	0 metformin	Coadministration of DRV/COBI with metformin may increase concentrations of metformin (inhibition of MATE1). Clinical monitoring and dose adjustment of metformin may be needed.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole	0 darunavir 0 cobicistat 0 antifungal	Coadministration of DRV/COBI with these antifungals may increase concentrations of DRV, COBI, and/or the antifungal (inhibition of CYP3A and/or P-gp). Clinical monitoring is recommended when coadministering DRV/COBI with these antifungals. When used in combination with DRV/COBI, the dose of itraconazole or ketoconazole should not exceed 200 mg per day.
voriconazole		Voriconazole should not be used unless the possible benefit is considered to outweigh the risks associated with the unpredictable effect on plasma concentrations.
Antigout Agents: colchicine	0 colchicine	Coadministration of DRV/COBI with colchicine may increase concentrations of colchicine (inhibition of CYP3A and/or P-gp inhibition). A reduction in colchicine dose is recommended in patients with normal renal or hepatic function if treatment with DRV/COBI is required. The combination of colchicine and DRV/COBI is contraindicated in patients with renal or hepatic impairment.
Antimalarials: artemether/lumefantrine	0 artemether 0 lumefantrine	Coadministration of DRV/COBI with artemether/lumefantrine may increase concentrations of artemether and lumefantrine (inhibition of CYP3A). Darunavir/COBI and artemether/lumefantrine can be used without dose adjustment; however, due to the expected increase in lumefantrine exposure, the combination should be used with caution.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antimycobacterials: rifabutin, rifapentine	1 darunavir 1 cobicistat 0 rifabutin	Coadministration of DRV/COBI with rifabutin, rifampicin, or rifapentine may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DRV. Rifabutin concentrations may be increased when coadministered with DRV/COBI. Coadministration of DRV/COBI and rifabutin or rifapentine is not recommended. If the combination of DRV/COBI and rifabutin is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (eg, Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin, thus leading to a risk of rifabutin resistance and treatment failure.
rifampicin		Coadministration of DRV/COBI with rifampicin is contraindicated.
Antineoplastic Agents: dasatinib, nilotinib, vinblastine, vincristine	0 antineoplastic agents	Coadministration of DRV/COBI with these antineoplastic agents may increase their concentrations (inhibition of CYP3A), resulting in the potential for increased adverse events usually associated with these antineoplastic medicinal products. Caution should be exercised when coadministering one of these antineoplastic agents with DRV/COBI.
Antipsychotics: quetiapine	0 quetiapine	Coadministration of DRV/COBI with quetiapine may increase quaetiapine concentrations (inhibition of CYP3A) and therefore quetiapine-related toxicity. Coadministration of DRV/COBI with quetiapine is contraindicated.
Beta-Blockers: carvedilol, metoprolol, timolol	0 beta-blocker	Coadministration of DRV/COBI and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when coadministering DRV/COBI with beta-blockers and a lower dose of the beta-blocker should be considered.
Calcium Channel Blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	0 calcium channel blocker	Coadministration of DRV/COBI with calcium channel blockers may increase concentrations of the calcium channel blocker (inhibition of CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with calcium channel blockers.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Contraceptives: ethinyl estradiol, norethindrone	-	No dosing recommendations can be made on the use of DRV/COBI with contraceptives. Alternative methods of nonhormonal contraception are recommended.
Corticosteroids, Inhaled/Nasal: budesonide, fluticasone	0 corticosteroid	Coadministration of DRV/COBI with inhaled or nasal corticosteroids may increase concentrations of the corticosteroid (inhibition of CYP3A). Coadministration of DRV/COBI and budesonide or fluticasone is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid side effects.
Corticosteroid, Systemic: dexamethasone	1 darunavir 1 cobicistat 0 corticosteroid	Coadministration of DRV/COBI with systemic dexamethasone may decrease DRV and/or COBI concentrations (induction of CYP3A). Systemic dexamethasone should be used with caution when combined with DRV/COBI.
prednisone		Corticosteroid concentrations may be increased when coadministered with DRV/COBI (inhibition of CYP3A). Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when coadministering DRV/COBI with corticosteroids.
Endothelin Receptor Antagonist: bosentan	1 darunavir 1 cobicistat	Coadministration of DRV/COBI with bosentan may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DRV. Bosentan concentrations may be increased when coadministered with DRV/COBI.
	0 bosentan	Coadministration of DRV/COBI with bosentan is not recommended.
Ergot Derivatives: dihydroergotamine, ergometrine, ergotamine, methylergonovine	0 ergot derivative	Coadministration of DRV/COBI with ergot derivatives may increase ergot derivative concentrations (inhibition of CYP3A). Coadministration of DRV/COBI with ergot derivatives is contraindicated.
Gastrointestinal Motility Agent: cisapride	0 cisapride	Coadministration of DRV/COBI with cisapride may increase cisapride concentrations (inhibition of CYP3A). Coadministration of DRV/COBI with cisapride is contraindicated.
H_2-Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine	/ darunavir / cobicistat	Based on mechanistic considerations (decreased gastric acidity), no interaction is expected between H_2-receptor antagonists and DRV/COBI. Darunavir/COBI and H_2-receptor antagonists can be coadministered without dose adjustments.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Hepatitis C Virus (HCV) Direct-Acting Agents, **NS3-4A Protease Inhibitors**: boceprevir, telaprevir	1 darunavir 1 cobicistat 1 HCV PI	Coadministration of DRV/COBI with boceprevir or telaprevir may decrease DRV, boceprevir, and/or telaprevir concentrations (mechanism unknown). Coadministration of DRV/COBI with boceprevir or telaprevir is not recommended.
Herbal Product: St. John's wort (*Hypericum perforatum*)	1 darunavir 1 cobicistat	Coadministration of DRV/COBI with St. John's wort may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DRV. Coadministration of DRV/COBI with St. John's wort is contraindicated.
HMG-CoA Reductase Inhibitors: atorvastatin, pitavastatin, pravastatin, rosuvastatin	0 HMG-CoA reductase inhibitor	Coadministration of DRV/COBI with HMG-CoA reductase inhibitors may increase concentrations of the lipid lowering agent (inhibition of CYP3A and/or transport), which may lead to AEs such as myopathy. When administration of HMG-CoA reductase inhibitors and DRV/COBI is desired, it is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety.
lovastatin, simvastatin		Coadministration of DRV/COBI with lovastatin or simvastatin is contraindicated.
Immunosuppressants: ciclosporin, everolimus, sirolimus, tacrolimus	0 immunosuppressant	Coadministration of DRV/COBI and these immunosuppressants may increase concentrations of the immunosuppressants (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring is recommended for the immunosuppressant when coadministered with DRV/COBI.
Inhaled Beta Agonist: salmeterol	0 salmeterol	Coadministration of DRV/COBI with salmeterol may increase concentrations of salmeterol (inhibition of CYP3A). The combination may result in increased risk of cardiovascular AEs associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. Coadministration of DRV/COBI with salmeterol is not recommended.
Narcotic Analgesics: fentanyl, oxycodone, tramadol	0 analgesic	Coadministration of DRV/COBI with these analgesics may increase concentrations of the analgesic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with these analgesics.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Narcotic Analgesics/Treatment of Opioid Dependence: buprenorphine, buprenorphine/naloxone, naloxone, methadone	0 buprenorphine 0 norbuprenorphine / naloxone 0 methadone	No dose adjustment of buprenorphine, methadone, and/or naloxone may be required when coadministering with DRV/COBI. However, clinical monitoring is recommended as the dose of buprenorphine, methadone, and/or naloxone may need to be adjusted in some patients. For buprenorphine, careful clinical monitoring for signs of opiate toxicity is recommended.
Neuroleptics: perphenazine, risperidone, thioridazine	0 neuroleptic	Coadministration of DRV/COBI and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with perphenazine, risperidone, or thioridazine, and a lower dose of the neuroleptic should be considered.
pimozide, sertindole		Coadministration of DRV/COBI with pimozide or sertindole is contraindicated.
Phosphodiesterase (PDE)-5 Inhibitors: sildenafil, tadalafil, vardenafil avanafil	0 PDE-5 inhibitor	Coadministration of DRV/COBI and PDE-5 inhibitors may increase concentrations of the PDE-5 inhibitor (inhibition of CYP3A), which may lead to AEs such as hypotension, syncope, visual disturbances, and priapism. *Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH)*: Coadministration of DRV/COBI with sildenafil for the treatment of PAH is contraindicated. Coadministration of tadalafil with DRV/COBI for the treatment of PAH is not recommended. *Use of PDE-5 inhibitors for erectile dysfunction*: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased clinical monitoring for PDE-5 inhibitor-associated AEs. Coadministration of DRV/COBI with avanafil is contraindicated.
Proton Pump Inhibitors: dexlansoprazole esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	/ darunavir / cobicistat	Based on mechanistic considerations (decreased gastric acidity and CYP2C19 inhibition), no interaction is expected between proton pump inhibitors and DRV/COBI. Darunavir/COBI and proton pump inhibitors can be coadministered without dose adjustment.

Table 143: Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Sedatives/Hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	0 sedatives/hypnotics	Coadministration of DRV/COBI with these sedatives/hypnotics may increase concentrations of the sedative or hypnotic (inhibition of CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Caution should be used with co administration of DRV/COBI and parental midazolam. Coadministration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of DRV/COBI with oral midazolam or triazolam is contraindicated.

3.3.2.1. Interactions With NRTIs

Nucleoside/nucleotide reverse transcriptase inhibitors for which the interaction with DRV (coadministered with rtv) has been investigated include ddI (Section 3.3.2.1.1) and TDF (Section 3.3.2.1.2). Based on the different elimination pathways of the other NRTIs (eg, abacavir, FTC, lamivudine, stavudine, or zidovudine) that are primarily renally excreted, no drug interactions are expected between these NRTIs and DRV/rtv; DRV/COBI can be used with these NRTIs without dose adjustment.

3.3.2.1.1. Didanosine

When DRV/rtv 600/100 mg twice daily and ddI 400 mg once daily were coadministered in healthy subjects, the mean steady-state exposure (AUC_{12h}) to DRV was not affected, and the mean exposure (AUC_{24h}) to ddI was decreased slightly (9%, which was not considered to be clinically relevant), as compared with their administration alone (Section 2.1.7.1.1). The mean exposure (AUC_{12h}) to rtv (100 mg twice daily) was decreased by 14% when coadministered with DRV in the presence of ddI, but the mean C_{min} and C_{0h} were slightly increased, 1.05- and 1.32-fold, respectively. These changes in rtv exposure were not considered clinically relevant.

There are no metabolic interactions expected between ddI and COBI. Also, COBI solubility is not affected by pH. As no clinically relevant interaction is expected with DRV/COBI, DRV/COBI and ddI can be coadministered without dose adjustments, but their administration should be separated in time due to meal requirements (ddI is recommended for administration on an empty stomach and DRV/COBI must be taken with food). Therefore, ddI should be administered 1 hour before or 2 hours after DRV/COBI.

3.3.2.1.2. Tenofovir Disoproxil Fumarate

Tenofovir is eliminated by a combination of glomerular filtration and active tubular secretion, and is not metabolized. In the presence of rtv, tenofovir (administered as the prodrug TDF) increased DRV exposure 1.21-fold, and DRV/rtv increased tenofovir exposure 1.22-fold (Section 2.1.7.1.2). The exposure to rtv (100 mg twice daily), when coadministered with DRV, was not affected to any relevant degree by the presence of tenofovir. The analysis of integrated data from the primary 24-week analyses of studies TMC114-C202 and TMC114-C213 in HIV-1 infected subjects indicated that concomitant use of TDF had no apparent effect on the exposure to DRV (Section 2.2.6.4). Thus, on account of the modest changes in exposure seen in study TMC114-C124 and the apparent lack of any effect seen in studies TMC114-C202 and TMC114-C213, no dose adjustments of DRV, rtv, or TDF are required when these drugs are coadministered.

Coadministration of DRV/COBI with TDF is expected to increase tenofovir exposure to a similar magnitude as DRV/rtv. In the Phase 3b study GS-US-216-0130, DRV/COBI was mostly (97%) combined with TDF/FTC (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 8.3) and was, in general, safe and well tolerated (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.10). Therefore, DRV/COBI and TDF can be coadministered without dose adjustments. Monitoring of renal function may be indicated when DRV/COBI is coadministered with TDF, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.

3.3.2.2. Interactions with NNRTIs

Non-nucleoside reverse transcriptase inhibitors for which the interaction with DRV (coadministered with rtv) has been investigated include EFV (Section 3.3.2.2.1), NVP (Section 3.3.2.2.3), etravirine (Section 3.3.2.2.2), and rilpivirine (Section 3.3.2.2.4), all of which are CYP3A inducers with the exception of rilpivirine.

3.3.2.2.1. Efavirenz

Efavirenz (600 mg once daily) decreased the exposure (AUC) to DRV (oral solution, coadministered with rtv at a dose of 300/100 mg twice daily) by 13%, and DRV coadministration resulted in a 1.21-fold increase in EFV exposure (Section 2.1.7.1.3). The exposure to rtv (100 mg twice daily), when coadministered with DRV, was decreased by 28% in the presence of EFV. Based on the PK/PD relationships and dose-response relationships observed in studies TMC114-C202 and TMC114-C213 in ART-experienced HIV-1 infected subjects, the 13% decrease in DRV exposure due to EFV coadministration is not considered clinically relevant (Section 2.2.7.4). Efavirenz can be coadministered with DRV/rtv without any dose adjustments.

Coadministration of COBI with efavirenz did not affect the AUC_{last} or AUC_{∞} of efavirenz, and the C_{max} of efavirenz was only slightly reduced (13%) (Section 2.1.8.1). However, because COBI is a CYP3A substrate, EFV may lower COBI exposure and consequently also its boosting activity on DRV. It is therefore not recommended to combine DRV/COBI with EFV.

3.3.2.2.2. Etravirine

Etravirine is a substrate of CYP3A, 2C9, and 2C19. At steady-state, coadministration of DRV/rtv 600/100 mg twice daily with etravirine caused a 37% decrease in exposure to etravirine (AUC_{12h}) when etravirine was administered at 100 mg twice daily and a 1.80-fold increase in exposure to etravirine when etravirine was administered at 200 mg twice daily, in both cases compared with administration of etravirine 100 mg twice daily alone (Section 2.1.7.1.5). For DRV exposure, only the mean AUC_{12h} was increased (1.15-fold) after coadministration of etravirine 200 mg twice daily. The mean AUC_{12h} of rtv was decreased by 14% and 11%, respectively, after coadministration of etravirine 100 mg and 200 mg twice daily. Based on the results of this study, the dosing regimen of etravirine 200 mg twice daily can be coadministered with DRV/rtv without any dose adjustments.

As COBI is a CYP3A substrate, etravirine may lower COBI exposure and consequently also its boosting activity on DRV. It is therefore not recommended to combine DRV/COBI with etravirine.

3.3.2.2.3. Nevirapine

When compared with historical data, NVP (200 mg twice daily) increased the exposure to DRV (tablet formulation, coadministered with rtv at a dose of 400/100 mg twice daily) 1.24-fold, and DRV induced a 1.27-fold increase in NVP exposure (Section 2.1.7.1.4), which may be due to CYP3A inhibition by DRV coadministered with rtv. The exposure to rtv (100 mg twice daily), when coadministered with DRV, was increased 1.10-fold when DRV/rtv was coadministered with NVP. These changes were not considered clinically relevant. No dose adjustments of DRV, rtv, or NVP are required when these drugs are coadministered.

As COBI is a CYP3A substrate, NVP may lower COBI exposure (inhibition of CYP3A) and consequently also its boosting activity on DRV. It is therefore not recommended to combine DRV/COBI with NVP.

3.3.2.2.4. Rilpivirine

Rilpivirine is a CYP3A substrate. In healthy subjects, at steady-state conditions, coadministration of rilpivirine 150 mg once daily with DRV/rtv 800/100 mg once daily caused a 2.30-fold increase in the mean AUC_{24h} of rilpivirine and a 1.79-fold increase in the mean C_{max}, as compared with administration of rilpivirine alone (Section 2.1.7.1.6). The increase in rilpivirine C_{max} was below 85% (1.85-fold) and is not expected to be of clinical relevance or cause safety concerns. There was no clinically relevant effect on the mean exposure to DRV/rtv on coadministration with rilpivirine. Darunavir/rtv and rilpivirine can be coadministered without dose adjustments.

Coadministration of DRV/COBI with rilpivirine is expected to increase rilpivirine exposure to a similar extent as DRV/rtv. This increase is not expected to be clinically relevant. No dose adjustment of rilpivirine is required when DRV/COBI is coadministered with rilpivirine.

3.3.2.3. Interactions with Other HIV PIs

The appropriate dose of DRV/COBI for coadministration with other HIV PIs has not been established. Coadministration of DRV/COBI with other HIV PIs is not recommended.

3.3.2.4. Interactions with CCR5RAs

Maraviroc is a CYP3A substrate. The exposure to maraviroc increased 4.05-fold when maraviroc (150 mg twice daily) was coadministered with DRV/rtv (600/100 mg twice daily), as compared with administration of maraviroc alone (Section 2.1.7.1.8). There was no apparent effect of maraviroc on DRV/rtv exposure, as the DRV/rtv exposure in the presence of maraviroc was similar to the exposure observed in healthy subjects in other studies (Module 5.3.3.4/TMC114-A4001052-CSR/Section 7.1.2). When coadministered with DRV/rtv, the dose of maraviroc should be 150 mg twice daily.

Coadministration of DRV/COBI with maraviroc is expected to increase maraviroc exposure to a similar extent as DRV/rtv. Therefore, when coadministration of DRV/COBI with maraviroc is warranted, it is recommended to administer maraviroc at a dose of 150 mg twice daily.

3.3.2.5. Interactions with Integrase Strand Transfer Inhibitors

3.3.2.5.1. Dolutegravir

Dolutegravir (S/GSK1349572, DTG) is an investigational HIV integrase strand transfer inhibitor pending market authorization (MAA submitted December 2012). Dolutegravir is primarily metabolized by glucuronidation (UGT1A1) with CYP3A having a minor role; it is also substrate of P-gp. Dolutegravir does not appear to inhibit or induce CYP, nor does it inhibit P-gp. An open-label, 2-period, 2-sequence crossover study in 15 healthy volunteers was conducted to assess the effect of DRV/rtv on DTG (1-way interaction).[42] In this study, DTG 30 mg once daily alone was administered for 5 days followed by the addition of DRV/rtv 600/100 mg twice daily for 14 days. Dolutegravir PK were assessed on Day 5 of treatment alone and Day 14 of the coadministered treatments. Coadministration of DRV/rtv to DTG decreased DTG AUC_{24h}, C_{max} and C_{24h} by 22%, 11% and 38%, respectively. The decrease in DTG is not considered to be clinically relevant and no dose adjustment is recommended.

3.3.2.5.2. Elvitegravir

In study GS-US-201-0104, exposure to DRV when coadministered with EVG/COBI was increased relative to single-dose administration of DRV alone (Section 2.1.8.2). As EVG is coformulated with COBI (and FTC with TDF), coadministration of EVG/COBI/FTC/TDF with DRV/COBI FDC is expected to double the COBI exposure. The safety of COBI at these anticipated exposures has not been established. Therefore, coadministration of EVG coformulated with COBI (and FTC with TDF) is not recommended.

3.3.2.5.3. Raltegravir

The literature on HIV-infected patients suggests that DRV exposure in plasma may decrease in the presence of raltegravir. This contrasts with the results of a study conducted in healthy

subjects by Merck (in collaboration with Janssen). In this study, no signal for an interaction between DRV/rtv and raltegravir could be detected, although no PK conclusion could be made due to an insufficient sample size (Section 2.1.7.1.7).

The decrease in DRV C_{0h} when DRV/rtv was coadministered with raltegravir, as reported in the literature, ranged from 18% to 39%, for C_{max}, the decrease was approximately 39%, and for AUC, the decrease ranged from 20% to 42%. Intracellular DRV C_{0h} decreased by 31%, with no apparent change in intracellular AUC_{24h} when DRV/rtv 800/100 mg once daily was coadministered with raltegravir 400 mg twice daily in HIV-infected subjects.[25] The mechanism by which raltegravir decreases DRV exposure is unknown.

Raltegravir does not inhibit the major CYP isozymes involved in drug metabolism (CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 2B6), UGT (UGT1A1 and 2B7), or P-gp, and it does not induce CYP3A.[5] In vitro, raltegravir induced the expression of ABCC1 (gene that encodes MRP1), with 1.7-fold increases in gene expression at concentrations of 1 µmol/L and 2.0-fold increases at 10 µmol/L.[58] The geometric mean steady-state raltegravir C_{max} when administered 400 mg twice daily in healthy subjects under fasted conditions or with food (low-, moderate-, or high-fat) ranged from 1.31 to 5.32 µmol/L,[4] suggesting that induction of ABCC1 by raltegravir may occur in vivo. Darunavir, however, does not appear to be a substrate of MRP1.[27]

Treatment with DRV/rtv when coadministered with raltegravir has been shown to be efficacious in the following clinical studies:

- DRV/rtv 800/100 mg once daily with raltegravir 400 mg twice daily as part of an NRTI-sparing regimen (A5262,[49] ANRS 143/NEAT 001, and RADAR[3]).
- DRV/rtv 600/100 mg twice daily with other ARVs including raltegravir 400 mg twice daily (BENCHMRK[44,45] and TRIO[18,55]).
- Subjects on DRV/rtv 600/100 mg twice daily switched from enfuvirtide to raltegravir (EASIER-ANRS 138[17,19]).

Therefore, the reported decreases in plasma concentrations of DRV do not appear to be clinically relevant.

3.3.2.6. Interactions with Other Drugs

3.3.2.6.1. α_1-Adrenoreceptor Antagonists

Cobicistat is a CYP3A inhibitor, and alfuzosin is a CYP3A substrate that is contraindicated with potent CYP3A inhibitors (eg, rtv).[20] Accordingly, DRV/COBI, like DRV/rtv, may increase alfuzosin exposures and coadministration is contraindicated.

3.3.2.6.2. Acid Suppressing Agents Including Antacids, H_2-Receptor Antagonists, and Proton Pump Inhibitors

The exposure to DRV and rtv was not affected when ranitidine (150 mg twice daily) or omeprazole (20 mg once daily) was coadministered with DRV/rtv at a dose of 400/100 mg twice

daily (Section 2.1.7.2.1). No dose adjustments are necessary when DRV/rtv is coadministered with ranitidine or omeprazole.

The solubility of COBI is unaffected by pH, as demonstrated in studies with proton pump inhibitors and H_2-receptor antagonists Section 2.1.8.3 and Section 2.1.8.4).

Therefore, no dose adjustment of DRV/COBI is required when coadministered with acid suppressing agents such as antacids, H_2-receptor antagonists, or proton pump inhibitors.

3.3.2.6.3. Antiangina/Antiarrhythmics

Antiarrhythmic agents, including but not limited to amiodarone, bepridil, disopyramide, dronedarone, flecainide, lidocaine (systemic), mexiletine, propafenone, quinidine, and ranolazine are primarily metabolized by CYP3A and/or CYP2D6 (among other isozymes).[26] Similar to RTV, COBI is a strong mechanism-based CYP3A inhibitor and an inhibitor, albeit mildly, of CYP2D6. Accordingly, exposures of these antiarrhythmic agents are expected to increase with DRV/COBI. Caution is warranted and therapeutic concentration monitoring, if available, is recommended for the antiarrhythmics disopyramide, flecainide, mexiletine, and propafenone when coadministered with DRV/COBI. Coadministration of amiodarone, bepridil, dronedarone, lidocaine (systemic), quinidine, or ranolazine with DRV/COBI is contraindicated due to the potential for a significant increase in their exposure.

Digoxin is a P-gp substrate and is known as a narrow therapeutic index drug. At steady-state, DRV (tablet formulation, coadministered with rtv at a dose of 600/100 mg twice daily) increased the exposure (AUC_{24h}) to digoxin (single dose of 0.4 mg) 1.35-fold (Section 2.1.7.2.2). Coadministration of COBI 150 mg once daily with a single dose of digoxin 0.5 mg resulted in a 1.41-fold increase in C_{max}, which may have been due to transient inhibition of gut P-gp (Section 2.1.8.1). Coadministration of DRV/COBI with digoxin is expected to increase digoxin to a similar extent as DRV/rtv. Given the expected increase in digoxin exposure, it is recommended that the lowest possible dose of digoxin should initially be prescribed. Digoxin concentrations should be monitored and used for titration of the digoxin dose to obtain the desired clinical effect, while assessing the overall clinical state of the subject.

3.3.2.6.4. Antibacterials

Clarithromycin is a substrate of P-gp and CYP3A. At steady state, DRV (tablet formulation, coadministered with rtv at a dose of 400/100 mg twice daily) increased the exposure (AUC_{12h}) to clarithromycin (500 mg twice daily) 1.57-fold and inhibited formation of the active metabolite 14-hydroxy clarithromycin (Section 2.1.7.2.3). These changes are not considered to be clinically relevant. The exposure to DRV (AUC_{12h}) was decreased by 13% when combined with clarithromycin (in the presence of rtv), which was not considered to be clinically relevant. The exposure to rtv was not affected to any relevant degree by the presence of clarithromycin.

Coadministration of DRV/COBI with clarithromycin is expected to increase clarithromycin exposure to a similar magnitude as DRV/rtv. Darunavir/COBI and clarithromycin can be coadministered without dose adjustment in patients with creatinine clearance ≥60 mL/min. For

patients with creatinine clearance <60 mL/min, due to increases in serum creatinine observed with COBI, appropriate dose recommendations with coadministration cannot be made for clarithromycin based on calculated creatinine clearance. Consider alternative antibacterial medications.

3.3.2.6.5. Anticancer Agents

Dasatinib, nilotinib, vinblastine, and vincristine are primarily metabolized by CYP3A (vinblastine is also metabolized by CYP2D6 to a minor extent); accordingly, their exposures are expected to increase when coadministered with COBI, which may result in increased AEs associated with these medicinal products. The dose of dasatinib or nilotinib should be decreased when coadministered with DRV/COBI. Clinical monitoring is recommended when coadministering DRV/COBI with these anticancer agents.

3.3.2.6.6. Anticoagulants

Apixaban and rivaroxaban are CYP3A and P-gp substrates; dabigatran etexilate is a substrate for P-gp.[40] Coadministration of DRV/COBI with these anticoagulants may result in increased plasma concentrations of the anticoagulant. Therefore, coadministration of DRV/COBI and rivaroxaban is not recommended. When coadministered with DRV/COBI, the recommended dose of apixaban is 2.5 mg twice daily. Clinical monitoring, including a coagulation test, is recommended when DRV/COBI is coadministered with dabigatran etexilate. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

Warfarin is metabolized primarily by CYP2C9 with a minor component of CYP3A. Coadministration of DRV/COBI with warfarin may alter warfarin exposure. The international normalized ratio should be monitored when DRV/COBI is coadministered with warfarin.

3.3.2.6.7. Anticonvulsants

Carbamazepine is a substrate and inducer of CYP3A. The coadministration of carbamazepine 200 mg twice daily with DRV/rtv 600/100 mg twice daily had no effect on the mean exposure (AUC_{12h}) to DRV, but the mean exposure to carbamazepine (AUC_{12h}) was increased 1.45-fold and the mean exposure to the metabolite carbamazepine epoxide was decreased by 54%; the mean exposure to rtv was decreased by 49% (Section 2.1.7.2.4). Although carbamazepine is an inducer of CYP3A, it had no clinically relevant effect on the PK of DRV in this study. The decrease in rtv exposure did not affect exposure to DRV, which is consistent with observations from another drug-drug interaction study (ddI) (Section 2.1.7.1.1). Ritonavir is a potent inhibitor of CYP3A metabolism and is able to increase exposure to CYP3A substrates, as was observed for carbamazepine in this study. The inhibition of the CYP3A metabolism of carbamazepine to carbamazepine epoxide likely resulted in the lower exposure to carbamazepine epoxide in the presence of DRV/rtv.

Coadministration of DRV/COBI with carbamazepine is likely to decrease COBI exposure to a similar extent as rtv in the aforementioned study. The effect of lower COBI exposure on DRV exposure has not been established. Because of the potential for decreased COBI and/or DRV

exposure in the presence of carbamazepine, coadministration of DRV/COBI and carbamazepine is contraindicated.

Like carbamazepine, the anticonvulsants phenobarbital and phenytoin are known inducers of CYP isozymes, including CYP3A. The interaction between these antiepileptics and COBI and/or DRV is not known. Because of the potential for decreased COBI and/or DRV exposure, coadministration of phenytoin or phenobarbital and DRV/COBI is contraindicated.

3.3.2.6.8. Antidepressants

Paroxetine is primarily metabolized by CYP2D6 and sertraline is primarily metabolized by CYP3A. The coadministration of paroxetine (20 mg once daily), did not affect the exposure to DRV (coadministered with rtv at a dose of 400/100 mg twice daily), but DRV/rtv coadministration resulted in a 39% decrease in the exposure to paroxetine (Section 2.1.7.2.5). Sertraline (50 mg once daily) did not affect the exposure to DRV (coadministered with rtv at a dose of 400/100 mg twice daily), but DRV coadministration resulted in a 49% decrease in the exposure to sertraline. The mechanism for the decrease in paroxetine and sertraline exposure is not known. Darunavir, paroxetine, and sertraline are all highly bound (>95%) to plasma AAG, so the decrease in paroxetine and sertraline exposure may be due to a protein-binding interaction, resulting in decreased total plasma concentrations of paroxetine or sertraline in the presence of DRV/rtv. The exposure to rtv was increased 1.34-fold in the presence of paroxetine but unaffected by sertraline. Based on the results of this study, if these SSRIs are coadministered with DRV/rtv, the recommended approach is a careful dose titration of the SSRI based on clinical assessment of antidepressant response. In addition, patients on a stable dose of paroxetine who start treatment with DRV/rtv should be monitored for antidepressant response.

Coadministration of DRV/COBI with paroxetine or sertraline is expected to increase paroxetine and sertraline total plasma concentrations via inhibition of CYP2D6 or CYP3A, respectively. However, a protein binding interaction cannot be excluded. Clinical monitoring is recommended when coadministering DRV/COBI with these antidepressants. The combination should be used with caution, and a lower dose of antidepressant should be considered.

Desipramine and trazodone are substrates of CYP2D6 and CYP3A, respectively. Accordingly, their exposures may increase with DRV/COBI coadministration. When desipramine 50 mg was coadministered with COBI 150 mg once daily alone, C_{max} and AUC_{last} increased 1.24- and 1.58-fold, respectively (Section 2.1.8.1). The combination of DRV/COBI and these antidepressants should be used with caution, and a lower dose of antidepressant should be considered.

3.3.2.6.9. Antidiabetics

Metformin is a substrate of OCT1, OCT2, MATE1, and MATE2.[46] Coadministration of DRV/COBI with metformin may alter the renal clearance of metformin and enhance its response. Clinical monitoring and dose adjustment of metformin may be needed.

3.3.2.6.10. Antifungals

Ketoconazole is a substrate and potent inhibitor of CYP3A. Ketoconazole (200 mg twice daily) increased the exposure (AUC_{12h}) to DRV (tablet formulation, coadministered with rtv at a dose of 400/100 mg twice daily) 1.42-fold (Section 2.1.7.2.6). The exposure (AUC_{12h}) to ketoconazole was also significantly increased (by more than 3-fold) when coadministered with DRV/rtv. The exposure to rtv was not affected to any relevant degree by the presence of ketoconazole. Based on these results, a maximum daily dose of 200 mg ketoconazole is recommended when ketoconazole is coadministered with DRV/rtv.

Coadministration of DRV/COBI with ketoconazole is expected to increase DRV, COBI, and ketoconazole exposure to a similar extent as DRV/rtv.

Itraconazole and voriconazole are also substrates of CYP3A. Accordingly, their exposures, as well as DRV and/or COBI exposure, may increase with DRV/COBI coadministration. Clinical monitoring is recommended when coadministering DRV/COBI with these antifungals. When used in combination with DRV/COBI, the dose of itraconazole should not exceed 200 mg per day. Voriconazole should not be used unless the possible benefit is considered to outweigh the risks associated with the unpredictable effect on plasma concentrations.

Fluconazole and posaconazole are substrates of P-gp. Coadministration of DRV/COBI with these antifungals may increase their exposure. Clinical monitoring is recommended when coadministering DRV/COBI with these antifungals.

3.3.2.6.11. Antigout Agents

Colchicine is a substrate of CYP3A and P-gp.[50] Accordingly, colchicine exposure may increase with DRV/COBI coadministration. The recommended dose of colchicine when coadministered with DRV/COBI is similar to the dosing recommendation for colchicine when coadministered with DRV/rtv. Coadministration of DRV/COBI with colchicine is contraindicated in patients with renal or hepatic impairment.

3.3.2.6.12. Antimalarials

Artemether and lumefantrine are CYP3A substrates; artemether is also metabolized to a lesser extent by CYP2B6, 2C9, and 2C19. After single-dose administration of artemether/lumefantrine 80/480 mg in the presence of DRV/rtv 600/100 mg twice daily, the mean C_{max} and AUC_{8h} of artemether were, respectively, 15% and 9% lower than after single-dose administration of artemether/lumefantrine alone (Section 2.1.7.2.7). After multiple-dose administration, the mean C_{max} and AUC_{last} of artemether were decreased by 18% and 16%, respectively, while the C_{min} of artemether was comparable in the presence and absence of DRV/rtv.

After single-dose administration of artemether/lumefantrine in the presence of DRV/rtv, the mean C_{max} and AUC_{8h} of the artemether metabolite DHA were, respectively, increased 1.06- and 1.12-fold compared with after single-dose administration of artemether/lumefantrine alone. After multiple-dose administration, the mean C_{max} and AUC_{last} of DHA were both decreased by 18%,

while the C_{min} of DHA was comparable for in the presence and absence of DRV/rtv (Section 2.1.7.2.7).

After intake of artemether/lumefantrine in the presence of DRV/rtv, C_{min}, C_{max}, and AUC_{264h} of lumefantrine were, respectively, 2.26-, 1.65-, and 2.75-fold higher than in the absence of DRV/rtv (Section 2.1.7.2.7).

After administration of DRV/rtv alone or in the presence of artemether/lumefantrine, the mean C_{max} and AUC_{12h} of DRV were comparable, while the C_{min} of DRV was decreased by 13% in the presence artemether/lumefantrine (Section 2.1.7.2.7). The C_{min} and AUC_{12h} of rtv were comparable in the presence and absence of artemether/lumefantrine, while the mean C_{max} of rtv was decreased by 15% in the presence of artemether/lumefantrine (Section 2.1.7.2.7).

Coadministration of DRV/COBI with artemether/lumefantrine is expected to increase exposure to both artemether and lumefantrine. Clinical monitoring is recommended when coadministering DRV/COBI with artemether/lumefantrine. Darunavir/COBI and artemether/lumefantrine can be used without dose adjustment.

3.3.2.6.13. Antimycobacterials

Rifabutin is a substrate and inducer of CYP3A. The coadministration of rifabutin 150 mg every other day with DRV/rtv 600/100 mg twice daily increased the mean exposure (AUC_{12h}) to DRV 1.57-fold and to rtv 1.66-fold, compared with DRV/rtv 600/100 mg twice daily alone (Section 2.1.7.2.9). Following coadministration with DRV/rtv, the mean exposure (AUC_t) to rifabutin 150 mg every other day was decreased slightly (by 7%), as compared with rifabutin 300 mg once daily alone (ie, when the dose of rifabutin was decreased in the presence of DRV/rtv), and the mean exposure to 25-*O*-desacetylrifabutin was increased 9.81-fold. The combined exposure to 25-*O*-desacetylrifabutin and rifabutin increased 3.13-fold when rifabutin was coadministered with DRV/rtv. When EVG/COBI 150/150 mg once daily was coadministered with rifabutin 300 mg every other day, exposure to rifabutin was unchanged, but the C_{max} and AUC of 25-*O*-desacetylrifabutin were increased 4.84- and 6.25-fold, respectively, relative to administration of rifabutin 300 mg once daily alone (Section 2.1.8.5).

Based on the safety findings in the study with DRV/rtv and rifabutin, a dose reduction in rifabutin of at least 75% (ie, rifabutin 150 mg every other day) is warranted if rifabutin is coadministered with DRV/rtv; in this case, based on the safety findings for DRV in this study and the overall safety profile of DRV, no dose adjustment of DRV is needed.

Coadministration of DRV/COBI with rifabutin may decrease DRV and/or COBI concentrations, which may result in loss of therapeutic effect of DRV. Coadministration of DRV/COBI with rifabutin is expected to increase rifabutin exposure to a similar extent as DRV/rtv. Coadministration of DRV/COBI and rifabutin or rifapentine is not recommended. If the combination of DRV/COBI and rifabutin is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (eg, Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions, including neutropenia and uveitis, is warranted due to an

expected increase in exposure to desacetyl‑rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin, thus leading to a risk of rifabutin resistance and treatment failure.

Rifapentine and rifampicin are also substrates and inducers of CYP3A. Accordingly, coadministration of DRV/COBI with rifapentine is not recommended, and coadministration of DRV/COBI with rifampicin is contraindicated, as rifampicin is a potent inducer of CYP3A.

3.3.2.6.14. Antipsychotics

Quetiapine is a substrate of CYP3A. Coadministration of DRV/COBI with quetiapine may increase quetiapine plasma concentrations and, consequently, quetiapine-related toxicity. Therefore, coadministration of DRV/COBI with quetiapine is contraindicated.[41]

3.3.2.6.15. Beta-Blockers

Carvedilol, metoprolol, and timolol are substrates of CYP2D6.[37] Exposures of these beta-blockers may increase when coadministered with DRV/COBI. Clinical monitoring is recommended when coadministering DRV/COBI with beta-blockers and a lower dose of the beta-blocker should be considered.

3.3.2.6.16. Calcium Channel Blockers

Amlodipine, diltiazem, felodipine, nicardipine, nifedipine, and verapamil are substrates of CYP2D6 and/or CYP3A.[37] Accordingly, exposures of these calcium channel blockers may increase with coadministration of DRV/COBI. Clinical monitoring is recommended when coadministering DRV/COBI with calcium channel blockers.

3.3.2.6.17. Contraceptives

Ethinyl estradiol is a CYP3A and CYP2C9 substrate and norethindrone is a CYP3A substrate. In healthy women, the mean exposure (AUC_{24h}) to ethinyl estradiol and norethindrone was decreased by 44% and 14%, respectively, when DRV/rtv 600/100 mg twice daily was coadministered with ethinyl estradiol 35 µg and norethindrone 1 mg once daily, as compared with administration of ethinyl estradiol and norethindrone alone (Section 2.1.7.2.10).

Coadministration of ethinyl estradiol and norgestimate with COBI was studied in the context of the EVG/COBI/FTC/TDF 150/150/200/300 mg STR (Section 2.1.8.6). Coadministration of the EVG/COBI/FTC/TDF STR with ethinyl estradiol/norgestimate resulted in decreased exposure to ethinyl estradiol and increased exposure to the active metabolite of norgestimate, norelgestromin. Serum progesterone and follicle-stimulating hormone concentrations were comparable with and without the EVG/COBI/FTC/TDF STR, while a greater decrease in serum luteinizing hormone concentrations was observed when ethinyl estradiol/norgestimate was coadministered with the EVG/COBI/FTC/TDF STR relative to administration of ethinyl estradiol/norgestimate alone. These PD results suggest that negative feedback inhibition for the secretion of follicle-stimulating hormone and luteinizing hormone was maintained despite an observed reduction in ethinyl estradiol plasma concentrations.

Given the complex metabolism of estrogen and progesterone derivatives, no dose recommendations can be made on the use of DRV/COBI with contraceptives. Alternative methods of nonhormonal contraception are recommended.

3.3.2.6.18. Corticosteroids, Inhaled/Nasal

Budesonide and fluticasone are substrates of CYP3A. Accordingly, budesonide and fluticasone exposures may increase with coadministration of DRV/COBI. As adrenal suppression and Cushing's syndrome have been observed with these corticosteroids and RTV, alternatives to these corticosteroids should be considered, particularly for long-term use. Coadministration of DRV/COBI and budesonide or fluticasone is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid side effects.

3.3.2.6.19. Corticosteroids, Systemic

When administered systemically, dexamethasone is a moderate inducer of CYP3A. Coadministration of DRV/COBI with systemic dexamethasone is expected to decrease COBI exposures and potentially also the exposure to DRV. Systemic dexamethasone should be used with caution when combined with DRV/COBI.

Corticosteroid concentrations may be increased when coadministered with DRV/COBI. Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when coadministering DRV/COBI with corticosteroids.

3.3.2.6.20. Endothelin Receptor Antagonists

Bosentan is a substrate and moderate inducer of CYP2C9, CYP2C19, and CYP3A.[51] Coadministration of DRV/COBI with bosentan is expected to decrease COBI exposures and potentially also the exposure to DRV. Bosentan concentrations may be increased when coadministered with DRV/COBI. Clinical monitoring is recommended when coadministering DRV/COBI with bosentan, and a dose adjustment of bosentan may be needed

3.3.2.6.21. Ergot Derivatives

Dihydroergotamine, ergometrine, ergotamine, and methylergonovine are substrates of CYP3A. Accordingly, the exposures of these ergot derivatives may increase with coadministration of DRV/COBI. Coadministration of these ergot derivatives with DRV/COBI is contraindicated.

3.3.2.6.22. Gastrointestinal Motility Agents

Cisapride is a substrate of CYP3A. Accordingly, cisapride exposure may increase with coadministration of DRV/COBI. Coadministration of cisapride with DRV/COBI is contraindicated.

3.3.2.6.23. Hepatitis C Virus Direct-Acting Agents, NS3/4A PIs

Telaprevir is a CYP3A and P-gp substrate and inhibitor. Coadministration of telaprevir 750 mg every 8 hours with DRV/rtv 600/100 mg twice daily in healthy subjects resulted in decreased

plasma exposure to DRV (40% to 42%) and telaprevir (32% to 36%), and increased plasma concentrations of rtv (1.37- to 1.48-fold), as compared with administration of telaprevir and DRV/rtv alone (Section 2.1.7.2.11). The mechanism of this interaction is unknown.

Boceprevir is a substrate of CYP3A and a substrate and inhibitor of P-gp. Coadministration of DRV/rtv with boceprevir resulted in decreases in both DRV and boceprevir exposure.[22]

The coadministration of DRV/COBI with telaprevir or boceprevir is not recommended.

3.3.2.6.24. Herbal Products

St. John's wort (*Hypericum perforatum*) is an inducer of CYP3A, 2C9, 2C19, and P-gp.[39] Coadministration of DRV/COBI with St. John's wort is expected to decrease COBI exposure and potentially also the exposure to DRV. Coadministration of DRV/COBI with St. John's wort is contraindicated.

3.3.2.6.25. HMG-CoA Reductase Inhibitors

Atorvastatin is metabolized by CYP3A and is transported by OATP. The results of an interaction study with atorvastatin showed that atorvastatin (10 mg once daily) in combination with DRV (oral solution, coadministered with rtv at a dose of 300/100 mg twice daily) provided exposure to atorvastatin that was comparable to the exposure following administration of atorvastatin alone (40 mg once daily) (Section 2.1.7.2.12). When coadministration of atorvastatin and DRV/rtv is desired, it is recommended to start with atorvastatin 10 mg once daily, and a gradual dose increase (maximum of 20 mg per day) may then be tailored to the clinical response.

Pravastatin is not metabolized by CYP3A to any clinically relevant extent, as indicated by in vitro and in vivo data. Darunavir (coadministered with rtv at a dose of 600/100 mg twice daily) increased exposure to pravastatin (single 40 mg dose) 1.81-fold, but pravastatin did not impact the PK of DRV (or rtv) (Section 2.1.7.2.13). The increase in pravastatin exposure was, however, not consistently found. A subsequent interaction study suggests polymorphisms in solute carrier OATP1B1 may partly explain the variability in interaction.

Pitavastatin is metabolized primarily by UGT to pitavastatin lactone (inactive) with minor involvement of CYP2C8 and 2C9. Darunavir (coadministered with rtv at a dose of 800/100 mg once daily) decreased pitavastatin (4 mg once daily) exposure 26% and pitavastatin lactone exposure by 32%, most likely as a result of UGT induction; pitavastatin had no effect on the PK of DRV (or rtv).[56]

Cobicistat also has the ability to inhibit P-gp and BCRP at the intestinal level, and OATP1B1 and 1B3 at the hepatic uptake level during first pass. The recommendations for the other agents that are not CYP3A substrates and only substrates for transporters are based on data from a study that showed no clinically relevant changes in rosuvastatin exposures (AUC) and/or expected modest interactions that did not necessitate dose modification (Section 2.1.8.5). Fluvastatin and pitavastatin are also substrates of OATP1B1 and are not CYP3A substrates. Accordingly, modest

increases in their exposures are expected when coadministered with DRV/COBI, similar to those observed with rosuvastatin.

Lovastatin and simvastatin are substrates of CYP3A. A significant increase in lovastatin and simvastatin exposure is expected when coadministered with DRV/COBI. Therefore, coadministration of DRV/COBI with lovastatin or simvastatin is contraindicated.

3.3.2.6.26. Immunosuppressants

Ciclosporin, everolimus, sirolimus, and tacrolimus are substrates of CYP3A. Accordingly, exposures of these immunosuppressants may increase on coadministration with DRV/COBI. Caution is warranted and therapeutic concentration monitoring is recommended for the immunosuppressant when coadministered with DRV/COBI.

3.3.2.6.27. Inhaled Beta Agonists

Salmeterol is a substrate of CYP3A. Accordingly, salmeterol exposures may increase with coadministration of DRV/COBI. Coadministration of DRV/COBI with salmeterol may result in increased risk of cardiovascular AEs associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. Therefore, coadministration of DRV/COBI with salmeterol is not recommended.

3.3.2.6.28. Narcotic Analgesics

Fentanyl, oxycodone, and tramadol are metabolized by CYP2D6 and/or CYP3A.[21] Coadministration of DRV/COBI with these narcotic analgesics may increase concentrations of the analgesic. Clinical monitoring is recommended when coadministering DRV/COBI with these analgesics.

3.3.2.6.29. Narcotic Analgesics/Treatment of Opioid Dependence

Buprenorphine is metabolized by the CYP3A and 2C, and UGT families. Naloxone is metabolized by UGT2B7 and 1A1, and CYP2C18, and 2C19. Buprenorphine/naloxone exposure (AUC_{24h}) was not affected by coadministration with DRV/rtv 600/100 mg twice daily (Section 2.1.7.2.14). The exposure to the active metabolite norbuprenorphine increased 1.46-fold. Modest increases in buprenorphine and naloxone exposures (1.35-fold and 1.42-fold, respectively) were observed upon coadministration with COBI/EVG.[6] However, these modest changes in exposure did not lead to clinical opiate overdose or withdrawal when assessed with standardized scales and, therefore, are not considered to be clinically relevant.

Methadone is primarily metabolized by CYP2B6 and 2C19. When DRV/rtv 600/100 mg twice daily was added to a stable, individualized methadone maintenance therapy, the mean C_{min}, C_{max}, and AUC_{24h} values of biologically active R(-) methadone were decreased by 15%, 24%, and 15%, respectively, as compared with methadone alone (Section 2.1.7.2.15). The mean C_{min}, C_{max}, and AUC_{24h} values of inactive S(+) methadone were decreased by 40%, 44%, and 36%, respectively. There were no increases in symptoms of opiate withdrawal during the study, and no methadone dose adjustments were needed during the coadministration phase. Cobicistat shows no inductive or inhibitory effects on CYP2B6 and/or 2C19.

No dose adjustment of buprenorphine, methadone, and/or naloxone may be required when coadministering with DRV/COBI. However, clinical monitoring is recommended, as the dose of buprenorphine, methadone, and/or naloxone may need to be adjusted in some patients. For buprenorphine, careful clinical monitoring for signs of opiate toxicity is recommended.

3.3.2.6.30. Neuroleptics

Perphenazine, pimozide, risperidone, sertindole, and thioridazine are substrates of CYP2D6 and/or CYP3A. Accordingly, the exposures of these neuroleptics may increase with coadministration of DRV/COBI. Clinical monitoring is recommended when coadministering DRV/COBI with perphenazine, risperidone, or thioridazine, and a lower dose of the neuroleptic should be considered. Coadministration of DRV/COBI with pimozide or sertindole is contraindicated.

3.3.2.6.31. Phosphodiesterase-5 Inhibitors

Phosphodiesterase-5 inhibitors such as avanafil, sildenafil, tadalafil, and vardenafil are primarily metabolized by CYP3A. When sildenafil (single dose of 25 mg) was given with DRV (coadministered with rtv at a dose of 400/100 mg twice daily), the exposure to sildenafil was comparable to administration of sildenafil (single dose of 100 mg) alone (Section 2.1.7.2.16). The metabolite *N*-desmethyl sildenafil, which is 50% less active than the parent compound sildenafil, was hardly formed in the presence of DRV/rtv. This increase in sildenafil exposure is likely due to CYP3A inhibition.

Thus, in the presence of DRV/COBI, dose adjustment for sildenafil is likely to be required. When coadministered with DRV/COBI, no more than 25 mg sildenafil is recommended over a 48-hour period when sildenafil is used for treatment of erectile dysfunction. The findings from this study can be extrapolated to other PDE-5 inhibitors when used for treatment of erectile dysfunction (vardenafil: single dose not exceeding 2.5 mg in 72 hours; tadalafil: single dose not exceeding 10 mg in 72 hours) when coadministered with DRV/COBI. Coadministration of DRV/COBI with avanafil for the treatment of erectile dysfunction is contraindicated.[43] Coadministration of DRV/COBI with sildenafil for pulmonary arterial hypertension is contraindicated because a safe and effective dose of sildenafil in the presence of DRV/rtv for the treatment of pulmonary arterial hypertension has not been established. Coadministration of DRV/COBI with tadalafil for pulmonary arterial hypertension is not recommended.

3.3.2.6.32. Sedatives/Hypnotics

Buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, and zolpidem are all substrates of CYP3A. Accordingly, exposures of these sedative/hypnotic agents may increase with coadministration of DRV/COBI. Clinical monitoring is recommended when coadministering DRV/COBI with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Parenteral midazolam should be coadministered with DRV/COBI in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam

is administered. Coadministration of DRV/COBI with oral midazolam or triazolam is contraindicated.

3.4. PD Characteristics of DRV and COBI

3.4.1. Characteristics of Exposure-Response Relationships

3.4.1.1. Antiviral Activity

3.4.1.1.1. ART-naïve HIV-1 Infected Subjects

In the ART-naïve group of study GS-US-216-0130, in which subjects were treated with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with 2 NRTIs, there was no apparent relationship between the decrease in log_{10} plasma viral load from baseline at Week 24 and DRV exposure (Section 2.2.7.1). Virologic success (plasma viral load of <50 HIV-1 RNA copies/mL) was comparable across the first to third DRV exposure quartiles (93.8% to 97.2% for AUC_{24h} and 93.7% to 97.3% for C_{0h}) and was modestly lower in the fourth (ie, highest) DRV exposure quartile (86.2% for AUC_{24h} and 86.4% for C_{0h}).

A similar result was observed in study TMC114-C211, in which ART-naïve HIV-1 infected subjects were treated with DRV/rtv 800/100 mg once daily coadministered as single agents in combination with a fixed background regimen of TDF and FTC (Section 2.2.7.2). There was no apparent relationship between the PK of DRV and the decrease in log_{10} viral load from baseline at Week 48 or virologic response, defined as a plasma viral load of <50 or <400 HIV-1 RNA copies/mL.

A GAM analysis, exploring the relationship between DRV C_{0h} and virologic response in study TMC114-C211, showed no indication that lower values within the observed DRV C_{0h} range lead to lower estimated virologic response. The mean predicted virologic response was 92.8% in the total population (Module 5.3.4.2/TMC114-C0000009-CPK/Section 3.1).

In study GS-US-216-0130, a GAM analysis was used to generate predictions of a smoothed spline for virologic response (defined as a plasma load of <50 HIV-1 RNA copies/mL) at Week 24 by DRV AUC_{24h} or C_{0h} in ART-naïve subjects. Inverse relationships were observed among ART-naïve subjects for both DRV AUC_{24h} and C_{0h} (Section 2.2.7.1). There was no obvious explanation for this finding, which contrasted with the lack of an exposure-response relationship seen for this virologic response parameter with DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve subjects, as observed in study TMC114-C211 (see above).

Inverse exposure-response relationships for virologic success have been observed previously in ART-experienced subjects treated with DRV/rtv 800/100 mg once daily coadministered as single agents. In study TMC114-C229, the decrease in log_{10} viral load from baseline at Week 48 tended to be smaller in subjects with higher AUC_{24h} values, while no relevant relationship between AUC_{24h} and the decrease in log_{10} viral load was observed in the DRV/rtv 600/100 twice daily

group (Section 2.2.7.3). A similar trend was seen for virologic success, defined as a plasma viral load of <50 HIV-1 RNA copies/mL, at Week 48.

These inverse exposure-response relationships for virologic response are difficult to interpret. Possible reasons include higher DRV exposure being driven by higher plasma AAG levels in subjects with more advanced disease, and "white coat compliance", whereby subjects who are non-adherent (and potentially failing virologically) may take DRV prior to the clinic visit to appear compliant.[38]

3.4.1.1.2. ART-experienced HIV-1 Infected Subjects

In the ART-experienced group of study GS-US-216-0130, the decrease in $\log_{10}$ viral load from baseline at Week 24 appeared greater in subjects within the 2 highest quartiles compared with the second lowest quartile (Section 2.2.7.1). Thus, there was a trend towards higher virologic success with higher exposures. Likewise, a GAM analysis used to generate predictions of a smoothed spline for virologic response (defined as a plasma viral load of <50 HIV-1 RNA copies/mL) at Week 24 by DRV AUC_{24h} or C_{0h} in ART-experienced subjects revealed trends for positive relationships between DRV PK parameters and virologic response. However, in both of these analyses, the clinical relevance of these findings should be interpreted with caution due to the small sample size (N=18).

These findings for ART-experienced subjects were not consistent with the results of study TMC114-C229, in which ART-experienced HIV-1 infected subjects were treated with DRV/rtv 800/100 mg once daily coadministered as single agents. In study TMC114-C229, a graphical analysis indicated that there was no clinically relevant relationship between DRV C_{0h} and the decrease in $\log_{10}$ viral load from baseline at Week 48, although the decrease in $\log_{10}$ viral load from baseline tended to be smaller in subjects with higher AUC_{24h} values, suggesting an inverse relationship (Section 2.2.7.3). Similarly, there was no consistent relationship between DRV C_{0h} and virologic success (defined as a plasma viral load of <50 HIV-1 RNA copies/mL at Week 48), although the virologic success was lower in the highest quartile of C_{0h} values, compared with the other C_{0h} quartiles (Section 2.2.7.3). The plasma viral load of <50 HIV-1 RNA copies/mL at Week 48 tended to be smaller in subjects with higher AUC_{24h} values.

A GAM analysis exploring the relationship between DRV C_{0h} and virologic response in study TMC114-C229 showed an inverse relationship between DRV C_{0h} and virologic response in the ART-experienced HIV-1 infected population of study TMC114-C229; virologic response was somewhat lower in the highest 2 deciles of the observed DRV C_{0h} range, suggesting a counterintuitive relationship (Section 2.2.7.3). However, in the first 8 deciles (DRV C_{0h} values up to 2,961 ng/mL), there was no clear relationship between DRV C_{0h} and virologic response at the observed rate, and variability was higher in the last 2 deciles.

Because DRV $C_{!}$ was notably lower when coadministered with COBI relative to rtv in the Phase 1 studies (ie, GS-US-0216-0115 and TMC114IFD1001), the impact of a potential reduction of DRV C_{0h} was further explored using the GAM. The same model used to predict virologic response was used to simulate a similar population with a 10%, 20%, 30%, 40%, and

50% reduction in DRV C_{0h}. Based on this analysis, a reduction in DRV C_{0h} of up to 50% did not negatively impact the mean predicted response.

3.4.1.2. Safety

In ART-naïve and ART-experienced HIV-1 infected subjects in study GS-US-216-0130, in which subjects were treated with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with 2 NRTIs, no apparent PK/PD relationships were observed between DRV AUC_{24h} or C_{0h} and the occurrence of rash, diarrhea, nausea, or vomiting, or between DRV AUC_{24h} and the worst toxicity grade in ALP, ALT, AST, amylase, lipase, glucose, total cholesterol, LDL, HDL, or triglycerides (Section 2.2.7.1.3.2). Higher DRV AUC_{24h} or C_{0h} were observed in subjects with grade 3 cholesterol and grade 4 lipase changes, but this analysis was limited by small sample sizes (N=4 and 3, respectively).

This lack of an exposure-response relationship for safety after administration of DRV/COBI coadministered as single agents is consistent with the lack of exposure-response relationships observed previously after administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve and ART-experienced HIV-1 infected subjects. In study TMC114-C211 in ART-naïve subjects, no apparent relationship was observed between the PK parameters for DRV and the occurrence of rash-, cardiac-, gastrointestinal-, liver-, lipid-, and glucose-related AEs, or AEs in the nervous system disorders or psychiatric disorders SOCs (Section 2.2.7.2). Similarly, in study TMC114-C229 in ART-experienced subjects, no apparent relationships were observed between the PK parameters for DRV and the occurrence of AEs leading to permanent discontinuation of study drug, or rash-, cardiac-, gastrointestinal-, liver-, lipid-, and glucose-related AEs, or AEs of the nervous system disorders or psychiatric disorders SOCs, or laboratory lipid abnormalities (Section 2.2.7.3). In the integrated analysis of studies TMC114-C202 and TMC114-C213, no apparent relationship was observed between the PK of DRV and the occurrence of AEs of interest (Section 2.2.7.4).

3.4.1.2.1. QT or QTc Interval

No specific studies with DRV/COBI (FDC or coadministered as single agents) have been conducted to investigate potential effects on the QT interval. In ART-naïve and ART-experienced HIV-1 infected subjects in study GS-US-216-0130, in which subjects were treated with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with 2 NRTIs, there were no clinically relevant ECG findings suggesting a potential effect of DRV/COBI on the QT interval (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.9.1).

A thorough QT/QTc study has been conducted in healthy subjects to evaluate the effect of DRV/rtv coadministered as single agents at doses of 1,600/100 mg once daily and 800/100 mg twice daily on ECG parameters (Section 2.2.3). Based on the overall population, the results of this study were interpreted as negative according to the ICH E14 Guidelines. The DRV treatments at the doses evaluated in this study were associated with small prolongations in QTc interval when compared to QTc changes observed in the placebo group. The 2-sided 90% CIs of the time-matched mean changes versus placebo showed that the upper bounds of both DRV/rtv groups for the overall population did not exceed 10 ms following single or multiple doses of

DRV/rtv. A linear mixed model was developed to estimate the relationship between QTcF and plasma DRV concentration. The slope of this relationship was estimated to be 0.000659 ms.mL/ng, with a 90% 2-sided CIs of 0.000184 to 0.001135 ms.mL/ng. This observation suggests that the relationship between concentration and QTcF is "shallow" in that for every 1,000 ng/mL increase in DRV concentration, a small additional shift in QTcF of 0.66 ms is predicted.

In a thorough QT/QTc study with COBI administered as a single agent, single doses of COBI 250 and 400 mg did not prolong the QTc interval. (Section 2.2.4) The upper bounds of the 2-sided 90% CIs for baseline-adjusted mean differences in QTcF did not exceed 10 ms at all timepoints after dosing. Therefore, this study met the ICH E14 definition of a negative "thorough QT/QTc study."

3.4.2. Genetic Differences in PD Response

Darunavir and COBI are primarily metabolized by CYP3A. The effect of genetic polymorphisms in CYP3A5 on the PK of DRV and/or COBI have not been established.

The ARV activity of DRV can be affected by mutations in HIV protease. Eleven HIV-1 protease mutations associated with DRV resistance (RAMs: V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V, or L89V) were identified from a pooled analysis of the DRV/rtv 600/100 mg twice daily groups in studies with ART-experienced subjects. These data suggest that the ARV activity of DRV/rtv is compromised in the presence of ≥3 DRV RAMs. For further details, refer to Summary of Virology Module 2.7.2.

3.5. Justification of Dose and Dosing Regimen

The DRV/COBI 800/150-mg FDC tablet is intended to be used in the same population for which DRV/rtv 800/100 mg once daily (administered as single agents) is registered, ie for the treatment of HIV-1 infection in HIV-1 infected ART-naïve adult subjects and ART-experienced adult subjects with no DRV RAMs and with a viral load <100,000 HIV-1 RNA copies/mL and CD4+ cell count ≥100 x 10^6 cells/L.

The development of the DRV/COBI FDC tablet is based primarily on the development programs of both single agents, complemented by a PK bridging clinical program to support the registration of the DRV/COBI 800/150-mg FDC tablet.

The dosing recommendation of DRV/rtv 800/100 mg once daily in ART-naïve HIV-1 infected subjects was registered based on the demonstration of noninferiority in virologic response of DRV/rtv 800/100 mg once daily coadministered as single agents when compared with LPV/rtv 800/200 mg once daily FDC, both in combination with a fixed background regimen of TDF/FTC (Module 5.3.5.1/TMC114-C211-W48-CSR). In the ART-experienced HIV-1 infected subjects with no DRV RAMs, noninferiority in virologic response of DRV/rtv 800/100 mg once daily coadministered as single agents was shown in comparison to DRV/rtv 600/100 mg twice daily coadministered as single agents, both in combination with ≥2 NRTIs (Module 5.3.5.1/TMC114-C229-W48-CSR).

Cobicistat is registered for use as a PK enhancer to increase systemic exposure to drugs metabolized by CYP3A enzymes, including DRV, ATV, and EVG.

For the current submission for the DRV/COBI 800/150-mg FDC tablet, 3 biopharmaceutic studies were conducted in healthy subjects to support the development of the DRV/COBI FDC tablet formulation intended for marketing. The first study, GS-US-216-0115 (Module 2.7.1/Section 2.1.1), showed that a 150-mg dose of COBI led to similar DRV exposures as a 100-mg dose of rtv, in each case when coadministered with DRV 800 mg (Module 5.3.1.2/GS-US-216-0115-CSR). The second study, TMC114IFD1001, compared the PK of DRV from 2 different DRV/COBI 800/150-mg FDC tablet formulations (G003 and G004) with that of DRV 800 mg coadministered with rtv 100 mg (administered as single agents) (refer to Module 2.7.1/Section 2.1.2). Based on the results of this study, which showed that the exposure (C_{max} and AUC_{24h}) to DRV with these 2 DRV/COBI FDC tablets (G003 and G004) was comparable to DRV administered as a single agent with rtv, the G004 FDC tablet formulation was selected for further development in a modified form as the G006 FDC tablet formulation (identical to the G004 tablet except for the nonfunctional coating color). The third study, TMC114IFD1003, demonstrated that the exposure (C_{max} and AUC_{24h}) to DRV with the DRV/COBI 800/150-mg FDC G006 tablet was bioequivalent to DRV 800 mg administered as a single agent with COBI 150 mg under both fasted and fed conditions (refer to Module 2.7.1/Section 2.2.1).

The results of these biopharmaceutic studies therefore indicate that the findings obtained in earlier clinical studies with DRV/rtv 800/100 mg once daily coadministered as single agents can be extrapolated to the intended commercial DRV/COBI 800/150-mg FDC G006 tablet. They also indicate that findings obtained with DRV/COBI 800/150 mg once daily coadministered as single agents, as in study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects (Section 2.2.5.1), can be extrapolated to the intended commercial DRV/COBI 800/150-mg FDC G006 tablet.

In study TMC114IFD1003, exposure to DRV following single-dose administration of DRV/COBI 800/150 mg as the FDC G006 tablet was increased with a high-fat breakfast relative to fasted conditions. This effect of concomitant food intake on DRV exposure when administered as the DRV/COBI FDC tablet is consistent with the effect of food on DRV exposure when coadministered with rtv as single agents (refer to Module 2.7.1/Section 3.1.2). The effect of a high-fat breakfast relative to fasted conditions was also evaluated for COBI; there was no apparent food effect (refer to the Module 2.7.1/Section 3.2.2). Based on the results of study TMC114IFD1003 and studies with DRV/rtv, it is therefore recommended that the DRV/COBI FDC tablet is taken with food.

Taken together, these considerations support the use of the DRV/COBI 800/150-mg G006 FDC tablet, in combination with other ARVs, for the treatment of HIV-1 infection in HIV-1 infected ART-naïve adult subjects and ART-experienced adult subjects with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100 x 10^6 cells/L.

DRV/COBI 800/150 mg once daily should be administered with food.

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APPENDIX

Appendix 1: Clinical Pharmacology Studies

DRV/COBI or DRV/rtv Clinical Pharmacology Studies									
Study ID	Objectives	Subjects	Dose	Route	DRV and/or COBI Formulation	Included in Pop PK	Pivotal [a]	Section in Module 2.7.2	Location of Report
Phase 1 - DRV/rtv:									
TMC114-C109	Mass-balance	Healthy	DRV 400 mg single dose rtv 100 mg bid	oral	FK4811	-	-	2.1.1	Module 5.3.3.1
TMC114-C134	Hepatic impairment	Healthy and subjects with mild or moderate hepatic impairment	DRV/rtv 600/100 mg bid	oral	F016	-	-	2.1.6.1	Module 5.3.3.3
TMC114-C123	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.1.1	Module 5.3.3.4
TMC114-C124	Drug-drug interaction	Healthy	DRV/rtv 300/100 mg bid	oral	TF019			2.1.7.1.2	Module 5.3.3.4
TMC114-C111	Drug-drug interaction	Healthy	DRV/rtv 300/100 mg bid	oral	TF019			2.1.7.1.3	Module 5.3.3.4
TMC114-C119	Drug-drug interaction	HIV-1	DRV/rtv 300/100 mg bid; 400/100 mg bid	oral	TF019, F001			2.1.7.1.4	Module 5.3.3.4
TMC125-C176	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F001, F002			2.1.7.1.5	Module 5.3.3.4
TMC278-C112	Drug-drug interaction	Healthy	DRV/rtv 800/100 mg qd	oral	F021			2.1.7.1.6	Module 5.3.3.4
TMC114-MK0518	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.1.7	Module 5.3.3.4
TMC114-A4001052	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.1.8	Module 5.3.3.4
TMC114-C122	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	F001			2.1.7.2.1	Module 5.3.3.4
TMC114-C150	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.2	Module 5.3.3.4

DRV/COBI or DRV/rtv Clinical Pharmacology Studies									
Study ID	Objectives	Subjects	Dose	Route	DRV and/or COBI Formulation	Included in Pop PK	Pivotal [a]	Section in Module 2.7.2	Location of Report
TMC114-C142	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	F001			2.1.7.2.3	Module 5.3.3.4
TMC114-C172	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.4	Module 5.3.3.4
TMC114-C121	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	F001			2.1.7.2.5	Module 5.3.3.4
TMC114-C129	Drug-drug interaction	Healthy	Panel 1: DRV 400 mg bid Panel 2: DRV/rtv 400/100 mg bid	oral	F002			2.1.7.2.6	Module 5.3.3.4
TMC125VIR1001	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F032			2.1.7.2.7	Module 5.3.3.4
TMC114-C107	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	F001			2.1.7.2.8	Module 5.3.3.4
TMC114-C163	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.9	Module 5.3.3.4
TMC114-C131	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.10	Module 5.3.3.4
VX950-C124	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.11	Module 5.3.3.4
TMC114-C133	Drug-drug interaction	Healthy	DRV/rtv 300/100 mg bid	oral	TF019			2.1.7.2.12	Module 5.3.3.4
TMC114-C120	Drug-drug interaction	Healthy	DRV/rtv 600/100 mg bid	oral	TF019			2.1.7.2.13	Module 5.3.3.4
TMC114-C171	Drug-drug interaction	Non-HIV subjects on stable buprenorphine/ naloxone maintenance therapy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.14	Module 5.3.3.4

DRV/COBI or DRV/rtv Clinical Pharmacology Studies									
Study ID	Objectives	Subjects	Dose	Route	DRV and/or COBI Formulation	Included in Pop PK	Pivotal [a]	Section in Module 2.7.2	Location of Report
TMC114-C127	Drug-drug interaction	Non-HIV subjects on stable methadone therapy	DRV/rtv 600/100 mg bid	oral	F016			2.1.7.2.15	Module 5.3.3.4
TMC114-C128	Drug-drug interaction	Healthy	DRV/rtv 400/100 mg bid	oral	F001			2.1.7.2.16	Module 5.3.3.4
TMC114-C153	Thorough QT/QTc	Healthy	DRV/rtv 1600/100 mg qd; 800/100 mg bid	oral	F001			2.2.3	Module 5.3.4.1
Phase 1 - COBI without DRV:									
GS-US-216-0111	Mass-balance	Healthy	150 mg qd	oral	Phase 1			2.1.2	Module 5.3.3.1
GS-US-216-0101	Dose escalation	Healthy	50, 100, 200 mg qd	oral	Phase 1			2.1.4.1	Module 5.3.4.1
GS-US-216-0113	Dose escalation	Healthy	300 mg qd, 400 mg	oral	Phase 1			2.1.4.2	Module 5.3.3.1
GS-US-216-0121	Renal impairment	Healthy and subjects with mild to moderate renal impairment	150 mg qd	oral	BE batch Phase 3/ Commercial			2.1.5.1	Module 5.3.3.3
GS-US-216-0124	Renal impairment	Healthy and subjects with severe renal impairment	150 mg qd	oral	Phase 3/ Commercial			2.1.5.2	Module 5.3.3.3
GS-US-183-0133	Hepatic impairment	Healthy and subjects with moderate hepatic impairment	150 mg qd	oral	Phase 3/ Commercial			2.1.6.2	Module 5.3.3.3
GS-US-216-0112	Drug-drug interaction	Healthy	150 mg qd	oral	BE batch			2.1.8.1	Module 5.3.3.4
GS-US-201-0104	Drug-drug interaction	Healthy	150 mg qd	oral	BE batch			2.1.8.2	Module 5.3.3.4

DRV/COBI or DRV/rtv Clinical Pharmacology Studies									
Study ID	Objectives	Subjects	Dose	Route	DRV and/or COBI Formulation	Included in Pop PK	Pivotal [a]	Section in Module 2.7.2	Location of Report
GS-US-216-0120	Drug-drug interaction	Healthy	150 mg qd	oral	BE batch			2.1.8.3	Module 5.3.3.4
GS-US-216-0122	Drug-drug interaction	Healthy	150 mg qd	oral	Phase 3/ Commercial			2.1.8.4	Module 5.3.3.4
GS-US-216-0123	Drug-drug interaction	Healthy	150 mg qd	oral	Phase 3/ Commercial			2.1.8.5	Module 5.3.3.4
GS-US-236-0106	Drug-drug interaction	Healthy female	150 mg qd	oral	Stribild Phase 1			2.1.8.6	Module 5.3.3.4
GS-US-216-0107	Thorough QT/QTc	Healthy	250, 400 mg single dose	oral	Phase 1			2.2.4	Module 5.3.4.1
Phase 2 - DRV/rtv:									
TMC114-C202 [b]	Dose-finding, efficacy	ART-experienced HIV-1	DRV/rtv 400/100 mg qd; 400/100 mg bid; 800/100 mg qd; 600/100 mg bid	oral	F001, F002			2.2.5.4	Module 5.3.4.2/ TMC114-C926-CPKPD
TMC114-C213 [b]	Dose-finding, efficacy	ART-experienced HIV-1	DRV/rtv 400/100 mg qd; 400/100 mg bid; 800/100 mg qd; 600/100 mg bid	oral	F001, F002			2.2.5.4	Module 5.3.4.2/ TMC114-C926-CPKPD
Phase 3 - DRV/rtv									
TMC114-C211	Efficacy	ART-naïve HIV-1	DRV/rtv 800/100 mg qd	oral	F021			2.2.5.2	Module 5.3.5.1
TMC114-C229	Efficacy	ART-experienced HIV-1	DRV/rtv 800/100 mg qd, 600/100 mg bid	oral	F030 F032			2.2.5.3	Module 5.3.5.1
Phase 3 - DRV/COBI:									
GS-US-216-0130 [c] (Week-24 analysis)	Safety, tolerability, antiviral activity	ART-naïve and -experienced HIV-1	DRV/COBI 800/150 mg qd	oral	DRV: F030 COBI: Phase 3/ Commercial	x	x	2.2.5.1	Module 5.3.5.2

bid=twice daily; qd=once daily.

[a] PK and/or PK/PD results described in proposed product labeling.

[b] Data from studies TMC114-C202 and TMC114-C213 were summarized together in the PK/PD integrated analysis TMC114-C926-CPKPD.

[c] This is an ongoing study. Week-48 data will be submitted at a later date.

Appendix 2: Bioavailability PK Parameters for DRV Across Clinical Studies with DRV/COBI

Bioavailability PK Parameters of DRV After Single- and Multiple-Dose Administration of DRV/COBI 800/150 mg (FDC or Single Agents) (All Clinical Pharmacology and Biopharmaceutic Studies)

Dose (mg)	Formu-lation	N	t_{max} (h) Min	-	Max	Median	C_{max} (ng/mL) Mean	SD	Median	AUC [a] (ng•h/mL) Mean	SD	Median	$t_{1/2}$ (h) Mean	SD	Median	Study ID
Single Dose																
800	G006	40	1.5	-	9.1	4.0	6,773	1,343	6,495	78,811	27,304	73,964	6.7	3.4	6.7	TMC114IFD1003-Panel 2
800	G006	18	1.5	-	6.0	4.5	7,053	1,057	6,910	76,165	22,090	73,795	6.6	3.2	6.6	TMC114IFD1003-Panel 3
Multiple Dose																
800	G003	32	2.5	-	6.0	5.0	6,666	1,287	6,815	74,780	19,750	72,440	-	-	-	TMC114IFD1001
800	G004	33	1.5	-	5.0	4.0	6,917	1,394	6,510	76,490	20,900	72,810	-	-	-	TMC114IFD1001
800	F030	59	1.0	-	6.0	3.5	7,663	1,920	7,435	81,646	26,322	80,091	10.8	10.0	7.2	GS-US-216-0130

[a] AUC_2 for single dose; AUC_{24h} for multiple dose.

Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 16, Table 20, Display 30, and Display 48; Module 5.3.1.1/TMC114IFD1001-CSR/Table 7 and Display 07; Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-1, Table 6.2.1.3, and Table 6.3.1.1

Appendix 3: Bioavailability PK Parameters for COBI Across Clinical Studies with DRV/COBI

Bioavailability PK Parameters of COBI After Single- and Multiple-Dose Administration of DRV/COBI 800/150 mg (FDC or Single Agents) (All Clinical Pharmacology and Biopharmaceutic Studies)

Dose (mg)	Formu-lation	N	t_{max} (h) Min - Max	t_{max} (h) Median	C_{max} (ng/mL) Mean	C_{max} (ng/mL) SD	C_{max} (ng/mL) Median	AUC (ng•h/mL) Mean	AUC (ng•h/mL) SD	AUC (ng•h/mL) Median	$t_{1/2}$ (h) Mean	$t_{1/2}$ (h) SD	$t_{1/2}$ (h) Median	Study ID
Single Dose														
150	G006	40	1.0 - 5.0	4.0	819	221	789	6,388	2,779	5,931	3.8	0.8	3.8	TMC114IFD1003-Panel 2
150	G006	18	1.0 - 6.0	5,0	769	174	742	5,526	1,478	5,405	3.9	0.7	3.9	TMC114IFD1003-Panel 3
Multiple Dose														
150	G003	33	2.0 - 5.0	4.0	1,136	233	1,110	9,386	2,666	8,803	-	-	-	TMC114IFD1001
150	G004	33	1.0 - 5.0	4.0	1,158	250	1,140	9,314	2,652	8,731	-	-	-	TMC114IFD1001
150	-	60	0.9 - 6.0	3.5	991	331	899	7,596	3,657	6,803	3.8	3.5	3.3	GS-US-216-0130

AUC: AUC_2 for single dose; AUC_{24h} for multiple dose.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 18, Table 22, Display 39, and Display 57; Module 5.3.1.1/TMC114IFD1001-CSR/Table 11 and Display 23; Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 10-2, Table 6.2.2.3, and Table 6.3.2.1

Janssen Research & Development

Summary of Virology

Darunavir/Cobicistat 800/150 mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

Status:	Approved
Date:	11 September 2013
Prepared by:	Janssen Infectious Diseases - Diagnostics BVBA
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ABBREVIATIONS

3TC	lamivudine
ABC	abacavir
APV	amprenavir
Ag	antigen
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AUC	area under the curve
AZT	zidovudine
bid	twice daily
CC_{50}	50% cytotoxic concentration
COBI	cobicistat
CYP	cytochrome P450
ddI	didanosine
DRV	darunavir
EC_{50}	50% effective concentration in cell-based assays
EC_{90}	90% effective concentration in cell-based assays
EFV	efavirenz
EVG	elvitegravir
FC	fold change in EC_{50} values
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
HIV-1	human immunodeficiency virus type 1
HIV-2	human immunodeficiency virus type 2
IAS	International Antiviral Society
IC_{50}	concentration that results in 50% inhibition in enzymatic assays
IDV	indinavir
INSTIs	integrase strand-transfer inhibitors
LPV	lopinavir
K_d	dissociation constant
K_D	derived affinity constant
K_i	inhibitory constant
M21	cobicistat metabolite (carbamate cleavage); also named E1, GS-9454, and GS-342006
M26	cobicistat metabolite (dealkylation at methylurea); also named E5 and GS-341842
M31	cobicistat metabolite (isopropyl methine hydroxylated); also named E3, GS-9612, and GS-364751
M/Ms	human monocytes/macrophages
MOI	Multiplicity of Infection
MTT	3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
PBMC	peripheral blood mononuclear cell
PI	protease inhibitor
PR	protease
qd	once daily
RAL	raltegravir

RAM	resistance-associated mutation
RNA	ribonucleic acid
RT	reverse transcriptase
RTV	ritonavir
rtv	low-dose ritonavir
SDM	site-directed mutant/mutagenesis
SI	selectivity index
SIV	simian immunodeficiency virus
SQV	saquinavir
SVR	suboptimal virologic response
T-20	enfuvirtide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TMC	Tibotec Medicinal Compound
TMC114-C211	study TMC114-C211, referred to as ARTEMIS
TMC114-C229	study TMC114-TiDP31-C229, referred to as ODIN
TOA	time of addition
TPV	tipranavir
TLOVR	time-to-loss-of-virologic-response
VF	virologic failure
VR	virologic rebound
WT	wild-type

1. OVERALL SUMMARY OF VIROLOGY

The darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI). Cobicistat has recently been registered to be coadministered as a pharmacokinetic enhancer of DRV and atazanavir (ATV). Comprehensive drug development programs have been conducted for the individual compounds DRV (in combination with low-dose ritonavir [rtv] as pharmacokinetic enhancer) and COBI.

The intended indication of the DRV/COBI 800/150 mg FDC is the same as the approved indication of the DRV/rtv 800/100 mg once daily regimen, ie, for the treatment of HIV-1 infection in antiretroviral therapy (ART)-naïve and ART-experienced adult subjects with no DRV resistance-associated mutations (RAMs), and with plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L. This is a so called 'substitution indication' of an already approved regimen, ie, the single agents have already been licensed for combined use at the same dose levels as in the FDC. This Summary of Virology supports the use of the DRV/COBI FDC tablet in combination with other antiretroviral (ARV) treatments.

An extensive program of nonclinical studies was conducted in support of the marketing authorization of DRV and COBI. Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (PR) (dissociation constant [K_d] of 4.5 x 10^{-12}M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells (PBMCs) and human monocytes/macrophages (M/Ms) with median 50% effective concentration (EC_{50}) values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). Darunavir demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from <0.1 to 4.3 nM. These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 μM to >100 μM. In addition, DRV is not an inhibitor of human cellular PRs. The EC_{50} value of DRV increased by a median factor of 5.4 in the presence of 50% human serum. Thermodynamic studies showed that DRV binds tightly to HIV-1 PR to form a highly stable complex with both wild-type (WT) and mutant PRs. These results along with the results of in vitro selection studies provided evidence of a high genetic barrier to the development of resistance to DRV. In vitro selection of DRV-resistant virus from WT HIV-1 was lengthy (>3 years). The selected viruses were unable to grow in the presence of DRV concentrations above 400 nM. There was no evidence of antagonism between DRV and any of the current HIV-1 ARVs.

Cobicistat, a structural analogue of RTV, was found to be a potent mechanism-based inhibitor of human hepatic microsomal cytochrome P450 (CYP)3A activity. Cobicistat is devoid of anti-HIV activity (HIV protease concentration that results in 50% inhibition [IC_{50}] >30 μM) and exhibited no antiviral activity against 17 HIV-1 and 2 HIV-2 primary isolates, consistent with results in T-cell lines and PBMCs. Cobicistat does not antagonize the antiviral effect of DRV.

The resistance profile of DRV/COBI FDC is driven by DRV. Due to its lack of antiviral activity, COBI does not select any HIV resistance mutations. Eleven PR mutations associated with DRV resistance (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V) were previously identified based on an analysis of a pooled dataset of studies with ART-experienced subjects who received treatment including DRV/rtv 600/100 mg twice daily. In these previous analyses, a lower and upper clinical cut-off of 10 and 40 were determined.

The clinical development program for DRV/COBI FDC is primarily based on the clinical development programs of the 2 individual compounds and on the pharmacokinetic bridging clinical program. A Phase 3b, open-label, single-arm study (GS-US-216-0130) was conducted to generate additional supportive safety, pharmacokinetic, and efficacy data on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents, in combination with other ARVs, in HIV-1 infected ART-naïve and ART-experienced adults with no DRV RAMs. In addition, the Week-24 resistance analysis of study GS-US-216-0130 further supports the use of the FDC tablet in the proposed indication.

In the Week-24 analysis of study GS-US-216-0130 resistance development to DRV or other PIs and nucleoside reverse transcriptase inhibitors (NRTIs) was rare. Of the 313 subjects who received at least 1 dose of the study medication (DRV/COBI 800/150 mg once daily), 10 met the criteria for postbaseline resistance analysis (5 ART-naïve subjects: 1 subject with suboptimal virologic response [SVR], 2 subjects with virologic rebound [VR], and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit; and 5 ART-experienced subjects: 1 SVR, 2 VR, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One ART-experienced subject had developed a DRV RAM at position I84 as a mixture with WT (I84I/V). The subject had poor pill bottle returns indicative of poor adherence. No phenotypic resistance to DRV or other PIs was observed. None developed any other primary or secondary PI RAMs. No subjects developed NRTI resistance mutations (or phenotypic resistance) to their concomitant NRTI regimen.

An extrapolation of the clinical data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-1 infected subjects can be made based on the comparable exposures to DRV (AUC_{24h}) achieved by both pharmacokinetic enhancers. The clinical resistance profile of DRV/rtv 800/100 mg once daily has been established based on the Phase 3 studies TMC114-C211 (192-week study in 343 ART-naïve HIV-1 infected subjects) and TMC114-C229 (48-week study in 294 ART-experienced HIV-1 infected adult subjects without DRV RAMs). Low levels of resistance development were observed in the DRV/rtv 800/100 mg once daily treatment arms of the TMC114-C211 and the TMC114-C229 study. The comparable low levels of resistance development observed in the GS-US-216-0130 study confirms the clinical resistance profile of DRV/rtv 800/100 mg once daily in ART-naïve and ART-experienced subjects and the high genetic barrier of DRV, whether boosted with COBI or rtv.

2. Tabulation of the Virology Studies

2.1. Tabulation of the in Vitro Virology Studies

Table 1: Tabular Summary of In Vitro Virology Studies of Darunavir and Cobicistat

Study Type	Methodology	Results	Synopsis	Section /Reference
DARUNAVIR				
Mechanism of Action				
HIV-1 PR Inhibition	Steady state kinetics	- Binding of DRV to the HIV-1 PR: K_i WT<0.09 nM. - Increases in *K*i's for the inhibition by DRV of the mutant PRs V82A and I84V were lower than for SQV, RTV or NFV.	The K_i of DRV was lower than those of other PIs indicating a greater potency.	4.1.1.1/[11]/[15]/Module 4.2.1.1/TMC114-20050009-VRR
Inhibition of the HIV-1 PR Dimerization	Intermolecular fluorescence resonance energy transfer-based HIV-1 expression assay	- DRV inhibits the HIV-1 PR dimerization at concentrations of as low as 0.01 µM.	DRV has a dual mechanism of action: inhibition of both the catalytic activity and dimerization of HIV-1 PR.	4.1.1.2/[12]
Thermodynamics of Darunavir–HIV-1 PR Interaction	Isothermal titration calorimetry	- Binding of PI to the WT PR: K_d DRV=4.5x10^{-12} M.	DRV binds tightly to HIV-1 protease to form a highly stable complex with both WT and mutant proteases.	4.1.1.3/[10]
Kinetics of Darunavir–HIV-1 PR Binding	Surface plasmon resonance	- Binding of DRV to the WT PR: K_D=4.11 10^{-13} M.	DRV binds tightly to HIV-1 protease to form highly stable complex with both WT and mutant proteases.	4.1.1.3/[5]/Module 4.2.1.1/TMC114-20050007-VRR
Three-Dimensional Crystal Structure of Darunavir–HIV-1 PR Complex	X-ray crystallography	- At least 6 hydrogen bonds formed between DRV and the HIV-1 PR that did not form between APV and the HIV-1 PR. - Hydrogen-bonding interactions between DRV and the HIV-1 PR involved main-chain atoms. - DRV bound within the PR binding substrate consensus volume. - In the DRV-multi drug resistant PR (L63P, V82T, and I84V) complex, flexibility of both the protein and the ligand appeared to compensate for any potential reduction in interactions resulting from the mutations.	Increased hydrogen bonding in the DRV-PR complex made it more stable than the APV-PR complex. DRV interacted with main-chain atoms of the PR and fitted for the most part within the substrate consensus volume making the interactions of DRV with mutated PR stronger than those of other PIs.	4.1.1.4/[10]/[13]/[15]

Study Type	Methodology	Results	Synopsis	Section /Reference
Inhibition of the Activity of Human Proteases	Spectrofluorometric quantitation of substrate cleavage	- The inhibitory activity of DRV (10 μM) was determined against 13 human cellular PRs: angiotensin converting enzyme, caspase 3, caspase 7, cathepsin C, cathepsin D, cathepsin E, factor VIIa, factor Xa, matrix metalloproteinase-2, matrix metalloproteinase-9, metalloproteinase neutral endopeptidase, thrombin and renin. There were no significant inhibitory activities of DRV (ie inhibition ≥50%) with any of these enzymes. - In the DRV-MDR PR (L63P, V82T, and I84V) complex, flexibility of both the protein and the ligand appeared to compensate for any potential reduction in interactions resulting from the mutations.	These data showed the lack of activity of DRV on these human cellular PRs and its specificity for the HIV-1 PR.	4.1.1.5/Module 4.2.1.1/TMC114-20050003-VRR/TMC114-20050004-VRR

In Vitro Antiviral Activity Against WT HIV-1, HIV-2 and SIV in T-Cell Lines	Phenotypic assays in MT2 and MT4 cells. Direct measurement of viral replication in MT4-LTR-EGFP cells. Determination of cell viability by MTT.	- MT4 cells:
		  - EC_{50}=2.29 to 6.26 nM for HIV-1/IIIB or HIV-1/NL4-3
		  - EC_{50}=4.70 to 8.49 nM for HIV-2/ROD
		  - EC_{50}=9.28 nM for SIV/MAC251
		- MT2 cells:
		  - EC_{50} =3 nM for HIV-1/LAI
		  - EC_{50}=3 nM for HIV-2/ROD and 6 nM for HIV-2/EHO
			DRV is a potent inhibitor of WT HIV-1, HIV-2 and SIV.	4.1.1.6/[2]/[13]/Module 4.2.1.1/TMC114-20050012-VRR/ TMC114-20050014-VRR

In vitro Antiviral Activity Against WT HIV-1 in Human Primary Cells	Phenotypic assay in PBMCs and M/Ms infected with HIV-1. Quantification of supernatant p24 Ag. Quantification of supernatant RT activity.	- EC_{50}=1.2 (0.7 ng/mL) to 5.0 nM (2.7 ng/mL). - EC_{90}=2.8 nM (1.5 ng/mL) to 8.0 nM (4.4 ng/mL).	EC_{50} values observed in primary cells (PBMCs and M/Ms) were comparable to those observed in MT2 and MT4 cells.	4.1.1.6/[2]/Module 4.2.1.1/TMC114-20050011-VRR/ TMC114-20050014-VRR

In vitro Antiviral Activity Against HIV-1 Group M and Group O Clinical Isolates	HIV-1 primary isolates in PBMC based assays. Quantification of supernatant RT activity.	- HIV-1 Group M:
		  - EC_{50}=<0.10 to 4.28 nM
		- HIV-1 Group O:
		  - EC_{50}=1.59 to 2.54 nM.
			These results indicated that DRV was active against Group M and Group O primary isolates of HIV-1.	4.1.1.6/[2]/Module 4.2.1.1/TMC114-20050011-VRR

Study Type	Methodology	Results	Synopsis	Section /Reference
In Vitro Cytotoxicity	In vitro effect on cell proliferation assessed using MTT.	- A549, HeLa, HepG2, and MT4 cells: - CC_{50} >100 μM - MRC-5 cells - CC_{50}=87 μM - Selectivity Index - SI >26,000	The SI for DRV was >26,000, indicating that DRV was a selective inhibitor of HIV in vitro.	4.1.1.7/Module 4.2.1.1/TMC114-200500016-VRR
Multiplicity of Infection	Phenotypic assay in MT4 cells. Determination of cell viability by MTT.	- For all PIs, increasing the MOI from 0.01 to 1 resulted in an increase in EC_{50}.	The effect of the MOI on the antiviral activity of DRV was consistent with the mode of action of a PI.	4.1.1.8/TMC114-20050008-VRR[17]
Time of Addition	Phenotypic assay in MT4 cells. Quantification of supernatant p24 Ag.	- Effective inhibition of virus replication by DRV was achieved with addition of the drug up to 19 hours after initial infection.	The DRV TOA virus inhibition pattern was consistent with the mode of action of a PI.	4.1.1.9/[2]/Module 4.2.1.1/TMC114-20050009-VRR
Effect of Human Serum Proteins	Phenotypic assay in MT4 cells. Direct measurement of viral replication in MT4-LTR-EGFP cells Determination of cell viability by MTT or resazurin.	- Determination of median EC_{50} ratio[a] in HIV-1/IIIB: - EC_{50} ratio = 5.4 for 50% Human Serum.	The EC_{50} value of DRV increased by a median factor of 5.4 in the presence of 50% human serum.	4.1.1.10/Module 4.2.1.1/TMC114-20050010-VRR
In Vitro Drug Resistance				
In Vitro Selection From WT HIV-1	Sequential passage of WT HIV-1 in the presence of increasing drug concentrations. Phenotypic and genotypic analysis by Virco.	- The DRV concentration could not be raised above 400 nM after >3 years of selection. - Emerging mutations were found at positions 37, 41, 55, 69, 70, 74, 77, and 85 in PR. - Selected viruses showing decreased susceptibility to DRV (range: 23-50-fold) harboured 2 to 4 amino acid substitutions in the PR gene.	In vitro selection of DRV-resistant virus from WT HIV-1 was lengthy. There was no clear correlation between genotypes and DRV susceptibility of the selected viruses.	4.1.2.1/Module 4.2.1.1/TMC114-20050012-VRR

[a] EC_{50} ratio = EC_{50} value in the presence of human serum proteins divided by the EC_{50} value determined in absence of human serum proteins

Study Type	Methodology	Results	Synopsis	Section /Reference
In Vitro Selection From PI Resistant HIV-1	Sequential passage of PI-resistant viruses in the presence of increasing DRV concentrations. Phenotypic and genotypic analysis by Virco.	- 9 PI-resistant viruses were cultured for between 162 and 251 days (final selection concentration of DRV ranging from 1.2 to 12 μM). - 22 DRV in vitro selection mutations were selected (L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V and I84V were present in more than 50%). - Final DRV fold change in EC_{50} values ranged from 52.9 to 641.0. - 6 of the 7 DRV-resistant viruses with phenotypic data for TPV remained susceptible to TPV.	Starting from PI-resistant HIV, an overall total of 22 DRV in vitro selection mutations emerged from 9 viruses under the selective pressure of DRV.	4.1.2.2/Module 4.2.1.1/TMC114-20050012-VRR/ TMC114-20050013-VVR
Antiviral Activity Against 20 Selected HIV-1 Recombinant Clinical Isolates	Phenotypic assay in MT4 cells. Direct measurement of viral replication in MT4-LTR-EGFP cells. Determination of cell viability by MTT.	- 90% of isolates had a $EC_{50} \leq 10$nM - 90% of isolates had a FC≤4 - 2 isolates had FC>4:	DRV had a FC≤ 4 against 90% of the isolates from this panel of PI-resistant HIV-1.	4.1.2.3/[2]/Module 4.2.1.1/TMC114-20050017-VRR

Antiviral Activity Against 3,309 Circulating HIV-1 Quasispecies	Phenotypic and genotypic analysis by Virco.	- Phenotypic data for 3309 PI-resistant recombinant clinical isolates:
		  - $EC_{50} \leq 10$ nM in 78% of the isolates
		  - $EC_{50} > 100$ nM in 3% of the isolates
		  - FC ≤ 4 in 80% of the isolates
		  - FC > 10 in 10% of the isolates.
		- Genotypic data for 1113 PI-resistant recombinant clinical isolates:
		  - DRV median FC ≤ 4 for subgroups of viruses harboring up to 3 primary-PI mutations and/or up to 8 PI resistance-associated mutations.
			DRV has a <10-fold decreased susceptibility against 90% of 3,309 clinical isolates resistant to APV, ATV, IDV, LPV, NFV, RTV, SQV, and/or TPV showing that viruses resistant to most PIs remain susceptible to DRV.	4.1.2.4/[2]/Module 4.2.1.1/TMC114-20050005-VRR

Antiviral Activity Against 57 PI Resistant HIV-1 SDM	Mutations introduced into HIV-1/HXB2. Phenotypic analysis by Virco.	- 56 of the 57 HIV-1 SDM did not lose susceptibility to DRV.
		  - FC=5.1 for the M46I + I47V + I50V SDM.
		  - 16 of the 57 viruses had a FC>4 for APV.
			All but 1 of these 57 PI-resistant SDM had a FC ≤ 4 for DRV.	4.1.2.5/TMC114-20050019-VRR[18]

Study Type	Methodology	Results	Synopsis	Section /Reference
Antiviral Activity Against 14 PI Resistant HIV-1 Primary Isolates	HIV-1 primary isolates in PBMC based assays. Quantification of supernatant p24 Ag or RT activity.	- Among the PI-resistant primary isolates analyzed a FC > 4 was found for: - 14% (2 of 14) for DRV - 57% (8 of 14) for SQV - 65% (9 of 14) for APV - 93% (13 of 14) for NFV - 100% (14 of 14) for RTV - 100% (7 of 7) for LPV.	Eighty-six percent of the isolates remained susceptible to DRV, which was greater than the percentages of isolates susceptible to the other PIs tested (0% to 43%).	4.1.2.6/[13]/TMC114-20050002-VRR[16]
Combination Studies				
Antiviral Activity in Combination With Current ARVs	Cell-based assay using HIV-1 infected MT4 cells. Determination of synergy by the isobologram method.	- No antagonism. - Additivity: NRTIs, NtRTI, NNRTIs, PIs (IDV, SQV, LPV, ATV, TPV), fusion inhibitor (T-20). - Synergy: PIs (RTV, NFV, APV).	Additivity to synergy was observed with all anti-HIV-1 registered drugs. No antagonism was observed.	4.1.2.7/[1]/[2]/Module 4.2.1.1/TMC114-20050006-VRR and TMC125-20060004-VRR
COBICISTAT				
In Vitro Antiviral Activity				
Activity Against HIV-1	In vitro enzymatic assay	- COBI did not have any effect on the HIV-1 PR enzymatic activity at concentrations up to 30 μM - IC_{50} for RTV was 0.6 nM	COBI is not an inhibitor of the HIV-1 PR	4.2.1/Module 4.2.1.2/PC-216-2001
Activity Against Host Proteases	In vitro enzymatic assay	- COBI did not exhibit any activity towards cathepsin D.	Unlike RTV, COBI did not exhibit any activity towards cathepsin D.	4.2.2/Module 4.2.1.2/PC-216-2001
Anti-HIV-1 Activity in MT-2 Cells	5-day in vitro HIV-1 cytopathic assay in human T-cell line (MT-2).	- No inhibition of HIV-1 replication in the presence of 30 μM COBI	No inhibition of HIV-1 replication in the presence of COBI.	4.2.3/Module 4.2.1.2/PC-216-2002
Anti-HIV-1 Activity of COBI Metabolites	5-day in vitro HIV-1 cytopathic assay in human T-cell line (MT-2).	- None of the tested metabolites of COBI, M21 (GS-9454), M31 (GS-9612), and M26 (GS-341842), were found to have HIV-1 antiviral activity, up to a concentration of 30 μM.	None of the tested metabolites were found to have HIV-1 antiviral activity.	4.2.3/Module 4.2.1.2/PC-216-2002

Study Type	Methodology	Results	Synopsis	Section /Reference
Evaluation of Antiviral Activity Against HIV Primary Isolates	ARV activity of COBI in PBMCs against a panel of 17 HIV-1 and 2 HIV-2 primary isolates (groups of HIV-1 M, N, O, as well as the most prevalent group M subtypes A, B, C, D, E, F, and G). EC_{50} values were determined by HIV-1 p24 ELISA, except for HIV-1 group O and HIV-2 (activity determined by virion-associated RT assay).	- No inhibition of HIV-1 and HIV-2 replication in the presence of COBI.	No inhibition of HIV-1and HIV-2 replication in the presence of COBI.	4.2.3/Module 4.2.1.2/PC-216-2011
Cytotoxicity profile	The in vitro cytotoxicity of COBI and RTV was evaluated in MT-2 lymphoblastoid T-cells and in HepG2 hepatoma cells.	- COBI was less cytotoxic than RTV in MT2 cells (CC_{50} of 89 µM and 38 µM, respectively). - COBI showed similar cytotoxicity as RTV in HepG2 cells (CC_{50} of 44 µM and 64 µM, respectively).	COBI was less cytotoxic than RTV in MT-2 cells and showed a level of cytotoxicity similar to RTV in HepG2 cells.	4.2.4/Module 4.2.1.1/PC-216-2003
Combination Studies				
Antiviral Activity of HIV Inhibitors in Combination with COBI	Fold change in EC_{50} of NRTI/ NtRTIs (TFV, FTC, ABC, 3TC, AZT); NNRTIs (EFV, NVP); INSTIs (RAL, EVG); and PIs (ATV, DRV) in MT-2 cells infected with HIV-1, in the presence or absence of 5 µM COBI.	- No significant changes were observed in the activity of any of the tested ARVs in the presence of 5 µM COBI.	COBI does not antagonize the antiviral activity of DRV.	4.2.5/Module 4.2.1.1/PC-216-2005

Abbreviations used in this table are defined in the List of Abbreviations

2.2. Tabulation of the Clinical Virology Studies

Table 2: Tabular Summary of Clinical Virology Studies With Darunavir/ritonavir 800/100 mg Once Daily and Darunavir/Cobicistat Fixed Dose Combination

Study Type	Methodology	Results	Synopsis	Section/Reference
DARUNAVIR/COBICISTAT FIXED DOSE COMBINATION				
GS-US-216-0130: Phase 3b Open-Label, Single-Arm Study in HIV-1 Infected, ART-Naïve Subjects or ART-Experienced Subjects with no DRV RAMs; 24-Week Data	Amplicor HIV-1 monitor% test (Roche). PR/RT genotyping and phenotyping (PhenoSense™ GT assay) by Monogram Biosciences. Postbaseline genotype and phenotype analysis in subjects who had ≥400 copies/mL of HIV-1 RNA due to SVR[a] or VR[b] , ≥400 copies/mL by Week 48 or study discontinuation, or any subject who did not meet SVR or VR criteria but had a sustained viral load ≥400 copies/mL while on study drug at these time points (or within 72 hours of discontinuation of study treatment)	- 10 subjects met the criteria for postbaseline resistance analysis: 5 ART-naïve subjects (1 confirmed suboptimal virologic response , 2 virologic rebounds , and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit) and 5 ART-experienced subjects (1 confirmed suboptimal virologic response, 2 virologic rebounds, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit). - No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. - 1 ART-experienced subject developed a DRV RAM I84I/V. None developed any other primary or secondary PI RAMs. - No phenotypic resistance to DRV or other PIs was observed. - 1 ART-experienced patient developed an NRTI RAM, which was not associated with a decreased susceptibility to the NRTIs included in the treatment regimen. - No subjects developed phenotypic resistance to their concomitant NRTI regimen.	In the Week-24 analysis of study GS-US-216-0130 resistance development to DRV, or other PIs, and NRTIs was rare.	5.1/Module 5.3.5.2/GS-US-216-0130-W24-CSR

[a] Confirmed suboptimal virologic response: HIV-1 RNA <1 $\log_{10}$ reduction from baseline and ≥50 copies/mL at the Week 8 visit, confirmed at a scheduled or unscheduled visit following Week 8.

[b] Virologic rebound: At any visit, after achieving HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥400 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; or at any visit, >1 $\log_{10}$ increase in HIV-1 RNA from the nadir which is subsequently confirmed at the following scheduled or unscheduled visit.

Study Type	Methodology	Results	Synopsis	Section/Reference
DARUNAVIR/RITONAVIR 800/100 MG ONCE DAILY				

TMC114-C211: Randomized, Controlled, Open-label Phase 3 Study in Treatment-Naïve Patients; DRV/rtv 800/100 mg qd Versus LPV/rtv 800/200 mg daily; 192-Week Data	Amplicor HIV-1 monitor% test (Roche). Genotype and Phenotype (Antivirogram%) by Virco. Changes in genotypes and phenotypes between baseline and endpoint were studied in subjects experiencing virologic failure. VFs, rebounders and subjects who were never suppressed, defined as loss of or never achieving a viral load < 50 HIV-1 RNA copies/mL, respectively, were identified using the TLOVR non-VF censored algorithm (Phenotypic and genotypic testing was performed on samples from VFs with HIV-1 RNA ≥50 copies/mL).	- Of the 343 DRV/rtv subjects, 55 (16.0%) experienced virologic failure versus 71 out of 346 (20.5%) LPV/rtv subjects.
		  - DRV/rtv group: 39 (11.4%) subjects were rebounders and 16 (4.7%) subjects were never suppressed.
		  - LPV/rtv group: 49 (14.2%) subjects were rebounders and 22 (6.4%) subjects were never suppressed.
		- 43 and 57 VFs with paired baseline/endpoint genotypic profiles in the DRV/rtv and LPV/rtv groups, respectively.
		- 4 (9.3%) DRV/rtv subjects and 9 (15.8%) LPV/rtv subjects with developing PI RAMs at endpoint were identified. None of the developing PI RAMs were primary (major) PI mutations.
		- All DRV/rtv and LPV/rtv VFs, for which paired baseline/endpoint phenotypes were available (39 and 52 subjects in the DRV/rtv and LPV/rtv group, respectively), remained susceptible to DRV, LPV, APV, ATV, IDV, SQV, and TPV.
		- 4 (9.3%) DRV/rtv subjects and 7 (12.3%) LPV/rtv subjects with developing NRTI RAMs at endpoint were identified.
		- The development of the NRTI RAM at position 184 was associated with a decreased susceptibility to FTC included in the treatment regimen (n=4 for DRV/rtv subjects and n=5 for LPV/rtv subjects).
			The virologic failure rate was 16.0% in the DRV/rtv group and 20.5% in the LPV/rtv group.
			There were no developing primary PI mutations identified in the VFs of both treatment groups.
			All VFs remained susceptible to DRV, LPV, APV, ATV, IDV, SQV, and TPV.
				5.2.1/Module 5.3.5.1/TMC114-C211-W192-CRR

Study Type	Methodology	Results	Synopsis	Section/Reference

TMC114-C229: Randomized, Controlled, Open-label Phase 3 Study in Early Treatment-Experienced HIV-1 Infected Subjects with 0 DRV RAMs; DRV/rtv (800/100 mg) qd versus DRV/rtv (600/100 mg) bid; 48-Week Data	Amplicor HIV-1 monitor% test (Roche). Genotype and Phenotype (Antivirogram%) by Virco. Changes in genotypes and phenotypes between baseline and endpoint were studied in subjects experiencing virologic failure. VFs, rebounders and subjects who were never suppressed, defined as loss of or never achieving a viral load < 50 HIV-1 RNA copies/mL, respectively, were identified using the TLOVR non-VF censored algorithm (Phenotypic and genotypic testing was performed on samples from VFs with HIV-1 RNA ≥50 copies/mL).	- Of 294 DRV/rtv qd subjects, 65 (22.1%) experienced virologic failure (viral load ≥ 50 copies/mL) versus 54 of 296 (18.2%) DRV/rtv bid subjects.
		  - DRV/rtv qd group: 11 (3.7%) subjects were rebounders and 54 (18.4%) subjects were never suppressed.
		  - DRV/rtv bid group: 11 (3.7%) subjects were rebounders and 43 (14.5%) subjects were never suppressed.
		- 60 and 42 VFs with paired baseline/endpoint genotypic profiles in the DRV/rtv qd and bid groups, respectively.
		- 1 subject (DRV/rtv qd group) developed primary PI mutations (including 3 DRV RAMs), and lost susceptibility to DRV. All the VFs from DRV/rtv 600/100 mg bid group retained susceptibility to DRV.
		- All VFs, except 2 in the DRV/rtv qd group, remained susceptible to all currently available PIs.
		- 4 (6.7%) and 3 (7.1%) VFs developed 1 or 2 NRTI RAMs in the DRV/rtv qd and the DRV/rtv bid groups, respectively.
		- In 3 and 2 of these VFs in the DRV/rtv qd and the DRV/rtv bid groups, respectively, the development of these NRTI RAMs was associated with a decreased susceptibility to a NRTI included in the treatment regimen.
			The virologic failure rate was comparable between the DRV/rtv qd group and DRV/rtv bid group. Resistance development was infrequent among VFs in both treatment groups.	5.2.2/Module 5.3.5.1/TMC114-C229-W48-CRR

Abbreviations used in this table are defined in the List of Abbreviations

3. BACKGROUND OF THE SUMMARY OF VIROLOGY

3.1. Introduction

The DRV/COBI FDC tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved HIV-1 PI. Cobicistat has recently been registered to be coadministered as a pharmacokinetic enhancer of DRV and ATV. Comprehensive drug development study programs have been conducted for the individual compounds DRV (in combination with rtv as pharmacokinetic enhancer) and COBI. The development program of the FDC tablet is primarily based on these development programs. This Summary of Virology supports the use of the DRV/COBI FDC tablet once daily, in combination with other ARVs, for the treatment of HIV-1 infection in ART-naïve and ART-experienced adults without DRV RAMs and with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥$100x10^6$ cells/L.

Darunavir

DRV was selected for its potency against WT HIV-1 and HIV strains resistant to currently approved PIs.

Treatment with DRV/rtv 800/100 mg once daily in combination with other ARV treatments has been shown to provide substantial and durable efficacy in HIV-1 treatment, with a high genetic barrier to the development of resistance, helping preserve future therapeutic options (more information can be found in Module 5.3.5.1/TMC114-C211-W48-CRR/ TMC114-C211-W192-CRR/TMC114-C229-W48-CRR). Eleven PR mutations associated with DRV resistance (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V)[9] were previously identified based on an analysis of a pooled dataset of studies with ART-experienced subjects who received treatment including DRV/rtv 600/100 mg twice daily.[3,4] The clinical study data showed that virologic response to DRV/rtv was decreased when 3 or more DRV RAMs were present at baseline. In these previous analyses, a lower and upper clinical cut-off of 10 and 40 were determined.

The efficacy of the DRV/rtv 800/100 mg once daily regimen is demonstrated by the 192-week study TMC114-C211 in 343 ART-naïve HIV-1 infected adult subjects, and by the 48-week study TMC114-C229 in 294 ART-experienced HIV-1 infected adult subjects without DRV RAMs at screening. In ART-naïve subjects, DRV/rtv 800/100 mg once daily was compared to a daily dose of lopinavir (LPV)/rtv 800/200 mg, both treatments coadministered with a fixed background regimen of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) over a treatment period of 192 weeks. In the ART-experienced subjects, DRV/rtv 800/100 mg once daily was compared to DRV/rtv 600/100 mg twice daily, both in combination with an optimized background regimen of ≥2 NRTIs over a treatment period of 48 weeks. In both studies, noninferiority in virologic response was shown versus the comparator group (more information can be found in Module 5.3.5.1/TMC114-C211-W48-CRR/TMC114-C211-W192-CRR/ TMC114-C229-W48-CRR).

Cobicistat

Cobicistat is a new chemical entity developed by Gilead Sciences Inc. (Gilead) and recently licenced for use as a pharmacokinetic enhancer to increase systemic exposure of coadministered ARVs metabolized by CYP3A enzymes, including the PIs DRV, ATV, and the integrase strand transfer inhibitor elvitegravir (EVG). COBI has no detectable antiviral activity in cell culture against HIV-1 and does not antagonize the antiviral activity of DRV. COBI has been shown to provide DRV exposures comparable to those obtained with rtv (refer to Module 5.3.1.2/GS-US-216-0115-CSR).

On 24 May 2013, the European Commission granted marketing authorization for the single tablet regimen EVG/COBI/FTC/TDF (STRIBILD®), film-coated tablets intended for treatment of HIV-1 infection in adults aged 18 years and over who are ART-naïve, or who are infected with HIV-1 without known mutations associated with resistance to any of the 3 ARV agents in STRIBILD.[14]

DRV/COBI FDC

The intended indication of the DRV/COBI FDC 800/150 mg is the same as the approved indication at the same dose level of the single agents, ie, for the treatment of HIV-1 infection in HIV-1 infected ART-naïve adult subjects and ART-experienced adult subjects with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L (substitution indication). The development of a FDC tablet of DRV with its pharmacokinetic enhancer in a once-daily regimen offers the option to simplify DRV-containing ARV regimens by reducing pill burden.

The clinical program for DRV/COBI FDC is based on the comprehensive development programs of the 2 individual compounds and on the pharmacokinetic bridging clinical program. No comparative efficacy study was conducted. The comparable exposures to DRV (AUC_{24h}) with DRV/rtv 800/100 mg and DRV/COBI 800/150 mg coadministered as single agents (study GS-US-216-0115) or as FDC (study TMC114IFD1001) in healthy subjects allows the extrapolation of efficacy data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects (refer to Summary of Clinical Pharmacology Studies in Module 2.7.2). The bioequivalence between DRV/COBI 800/150 mg coadministered as single agents and the FDC is further demonstrated in study TMC114IFD1003. The Phase 3b, open-label, single-arm study GS-US-216-0130 was conducted to generate additional supportive safety data (primary objective) and efficacy and pharmacokinetic data (secondary objectives) on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects.

The current Summary of Virology presents a summary of in vitro virology data of the single agents DRV and COBI. In addition, the clinical virology data of the Week-24 primary analysis of the Phase 3b study GS-US-216-0130 are presented in support of the FDC tablet of DRV/COBI 800/150 mg once daily for the treatment of HIV-1 infected, ART-naïve and ART-experienced adult subjects with no DRV RAMs. A summary of the resistance analysis of the

DRV/rtv 800/100 mg once daily group of study TMC114-C211, in ART-naïve HIV-1 infected adult subjects, and study TMC114-C229, in ART-experienced HIV-1 infected adult subjects with no DRV RAMs, is presented to describe the clinical resistance profile of DRV/rtv 800/100 mg once daily treatment in ART-naïve and ART-experienced HIV-1 infected adult subjects with no DRV RAMs.

3.2. Overall Structure of the Summary of Virology

A summary of in vitro virology data obtained from a virology research program that was designed to provide information on the mechanism of action of DRV, its in vitro antiviral activity against a range of WT and PI resistant viruses in different cell types, its cytotoxicity, the possible mechanisms of resistance to DRV in vitro, and its activity in combination with other ARVs is presented in section 4.1. In section 4.2, a summary of studies showing lack of in vitro antiviral activity of COBI in different cell types and antiviral activity of current HIV-1 inhibitors in combination with COBI is presented.

Section 5 contains clinical virology data on the Phase 3b study GS-US-216-0130, and the Phase 3 studies TMC114-C211 and TMC114-C229.

4. IN VITRO VIROLOGY DATA

4.1. Darunavir

4.1.1. Mechanism of Action

4.1.1.1. Inhibition of HIV-1 Protease

Using steady state kinetics, inhibitory constants (K_i) were calculated for the inhibition of the cleavage activity of WT HIV-1 PR in the presence of DRV and other PIs. The K_i for DRV was <0.09 nM, in comparison to <0.10 nM for LPV, and higher for other PIs (ranging from 0.09 to 0.24 nM) (more information can be found in Module 4.2.1.1/TMC114-20050009-VRR).

Mutants harbouring the V82A or the I84V mutation were also tested.[11] For the V82A, the increase in K_i for DRV (1.3-fold) was lower than the published increases for all the other PIs (from 1.7 to 11.2-fold). For the I84V PR, the increase in K_i for DRV (3.2-fold) was lower than the published data for ritonavir (RTV), nelfinavir (NFV), and saquinavir (SQV) (11.2-fold, 3.5-fold, and 10.7-fold, respectively).

4.1.1.2. Inhibition of the HIV-1 Protease Dimerization

Using an intermolecular fluorescence resonance energy transfer-based HIV-1 expression assay, Koh *et al*. have shown that DRV also inhibits the HIV-1 PR dimerization at concentrations of as low as 0.01 µM.[12] Dimerization of HIV-1 PR subunits is essential for its proteolytic activity. This dual inhibition mechanism of DRV, which was not observed for other clinically used PIs (amprenavir [APV], ATV, indinavir [IDV], LPV, NFV, RTV, and SQV), except for tipranavir (TPV), leads to a highly potent inhibition of HIV-1.

4.1.1.3. Binding Kinetics of the DRV-HIV-1 Protease Interaction

Isothermal titration calorimetry showed that DRV binds tightly to HIV-1 PR to form a highly stable complex with WT (K_d of 4.5 $x10^{-12}$ M) PRs.[10] A derived affinity constant (K_D) of $4.11x10^{—13}$ M for WT HIV-1 PR has also been demonstrated using surface plasmon resonance and was lower than that of the other tested PIs (more information can be found in Module 4.2.1.1/TMC114-20050007-VRR). Darunavir also binds tightly to mutant HIV-1 PRs to form a highly stable complex.[5]

4.1.1.4. Cocrystallization of Darunavir With HIV-1 Proteases

Examination of crystal structures identified several features that increased the ability of DRV to maintain its inhibitory activity against mutant PRs.[10,13,15] Increased hydrogen bonding in the DRV-PR complex made it more stable than the APV-PR complex (at least 6 hydrogen bonds formed between DRV and the HIV-1 PR that did not form between APV and the HIV-1 PR). DRV interacted with main-chain atoms of the PR and fitted for the most part within the substrate consensus volume making the interactions of DRV with mutated PR stronger than those of other PIs. In the DRV-multi drug resistant PR (L63P, V82T, and I84V) complex, flexibility of both the

protein and the ligand appeared to compensate for any potential reduction in interactions resulting from the mutations.

4.1.1.5. Inhibition of the Activity of Human Proteases

The inhibitory activity of DRV at 10 μM against the human cellular PRs: angiotensin converting enzyme, caspase 3, caspase 7, cathepsin C, cathepsin D, cathepsin E, factor VIIa, factor Xa, matrix metalloproteinase-2, matrix metalloproteinase-9, metalloproteinase neutral endopeptidase, thrombin, and renin was determined by spectrofluorometric quantitation of the cleavage of a substrate specific for each protease, in the presence and the absence of DRV (more information can be found in Module 4.2.1.1/TMC114-20050003-VRR and TMC114-20050004-VRR). The absence of significant responses (ie inhibition ≥50%) for all these proteases showed the lack of activity of DRV on these human cellular PRs and its specificity for the HIV PR.

4.1.1.6. In Vitro Antiviral Activity

DRV exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines (MT4 and MT2) (see Table 3) (more information can be found in Module 4.2.1.1/TMC114-20050012-VRR and TMC114-20050014-VRR), human peripheral blood mononuclear cells (PBMCs) and human monocytes/macrophages (M/Ms) (see Table 4) (more information can be found in Module 4.2.1.1/TMC114-20050011-VRR and TMC114-20050014-VRR) with median EC_{50} values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). The DRV EC_{50} values observed in primary cells were comparable to these observed in cell lines (see Table 3 and Table 4). DRV demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from <0.10–4.28 nM and 1.59–2.54 nM, respectively (see Table 5) (more information can be found in Module 4.2.1.1/TMC114-20050011-VRR).

Table 3: In Vitro Antiviral Activity of DRV in T-cell lines

	HIV-1/IIIB or NL4-3[a]	HIV-2/ROD[a]	SIV/MAC251[a]	HIV-1/LAI[b]	HIV-2/ROD and EHO[b]
Median EC_{50} values (nM)	2.29-6.26	4.70-8.49	9.28	3[c]	3 and 6[c]

SIV: Simian immunodeficiency virus
[a] MT4-cells
[b] MT2 cells
[c] Mean
Source: Module 4.2.1.1/TMC114-20050012-VRR and TMC114-20050014-VRR

Table 4: In Vitro Antiviral Activity of DRV in HIV-1 Infected Primary Cells (PBMCs and M/Ms)

Median EC_{50} value (nM)	1.2 (0.7 ng/mL) to 5.0 (2.7 ng/mL)
Median EC_{90} value (nM)	2.8 (1.5 ng/mL) to 8.0 (4.4 ng/mL)

PBMCs: human peripheral blood mononuclear cells; M/Ms: human monocytes/macrophages
Source: Module 4.2.1.1/TMC114-20050011-VRR and TMC114-20050014-VRR

Table 5: In Vitro Antiviral Activity of DRV Against Primary Isolates in Human PBMCs

	HIV-1 Group M	HIV-1 Group O
EC_{50} range (nM)	<0.10–4.28	1.59–2.54

PBMCs: human peripheral blood mononuclear cells
Source: Module 4.2.1.1/TMC114-20050011-VRR

4.1.1.7. In Vitro Cytotoxicity

The in vitro effects of DRV on the cell proliferation and the viability of MT4, HeLa (epithelial cervix, adenocarcinoma), HepG2 (epithelial liver, hepatoblastoma) MRC-5 (normal fetal lung fibroblast) and A549 (epithelial lung carcinoma) cells were investigated. The 50% cytotoxic concentration (CC_{50}) was found to be greater than 100 µM (except for the MRC-5, for which the CC_{50} was 87 µM), with a median EC_{50} of 3.8 nM using the MTT assay in MT4 cells; a selectivity index ($SI=CC_{50}/EC_{50}$) >26,000 was determined (more information can be found in Module 4.2.1.1/TMC114-20050016-VRR).

The 50% cytotoxic concentration of TMC114 was determined to be greater than 100 µM for all cell types studied, except for the MRC-5, for which the 50% cytotoxic concentration was 87 µM.

4.1.1.8. Multiplicity of Infection

The effect of Multiplicity of Infection (MOI) on the antiviral activity of DRV and other PIs was assessed in MT4 cells using an MTT-based colorimetric assay. For all the tested PIs, increasing the MOI from 0.01 to 1.0 resulted in an increase in EC_{50} (more information can be found in TMC114-20050008-VRR[17]). The data were consistent with the mode of action of PIs, which inhibit a late step of the HIV-1 replication cycle.

4.1.1.9. Time of Addition

A time of addition (TOA) experiment was carried out in order to confirm the stage in the HIV-1 life cycle at which DRV acts (more information can be found in Module 4.2.1.1/TMC114-20050009-VRR). The inhibition profiles obtained for all the control compounds were consistent with their mode of action. With DRV, effective inhibition of virus replication could be achieved by addition of the drug up to 19 hours after initial infection. This was consistent with the mode of action of DRV as a PI.

4.1.1.10. Effect of Human Serum Proteins

The influence of human serum on the antiviral activity of DRV and other PIs was assessed (more information can be found in Module 4.2.1.1/TMC114-20050010-VRR). The EC_{50} value of DRV increased by a median factor of 5.4 in the presence of 50% human serum.

4.1.2. In Vitro Drug Resistance

4.1.2.1. In Vitro Selection Experiments Starting From WT HIV-1

In vitro selection experiments were performed by culturing WT HIV-1/IIIB, HIV-1/NL4-3 and recombinant clinical isolates from ART-naïve subjects in the presence of increasing concentrations of DRV. In vitro selection of DRV resistant virus from WT HIV-1 was lengthy

(372 passages and >3 years). The selected viruses were unable to grow in the presence of DRV concentrations above 400 nM.

Genotypic analyses of the strains developing under selective pressure of DRV starting from WT HIV-1 laboratory strains showed the presence of 2 to 4 PR mutations, S37D/N, R41E/S/T, H69Q, K70E, V77I, and I85V, while in strains developing in selection experiments starting from recombinant HIV-1 clinical isolates obtained from ARV ART-naïve patients, PR mutations R41I, K55Q, and T74S were observed (see Table 6). The highest mutation frequency was observed at PR position 41.

Phenotypic analyses of the selected strains (see Table 6) showed no clear correlations between the concentrations of DRV in the culture media at the time of the selection and the EC_{50} values observed for the respective viruses. Seven in vitro selection experiments starting from WT HIV-1 strains resulted in the selection of 3 viruses with a DRV FC>10 (low CCO) (range: 23- to 50-fold) at the end of the experimental procedure. Analyses of the phenotypic profile of these viruses showed some loss of susceptibility to the other currently approved PIs in this phenotypic assay (see Table 7).

The introduction of the PR mutations S37D, S37N, R41T, R41E, K70E, and the combinations R41T + K70E, S37N + K70E and R41T +K70E + V77I, found in the HIV-1 viruses selected under selective pressure of DRV, into a WT (HXB2) background by site-directed mutagenesis (SDM), did not result in increased EC_{50} values for DRV or any of the currently approved PIs tested (more information can be found in Module 4.2.1.1/TMC114-20050012-VRR).

4.1.2.2. In Vitro Selection Experiments Starting From Protease Inhibitor-Resistant HIV-1

Nine in vitro selection experiments were performed by growing viruses previously selected by the PIs APV, ATV, LPV, and NFV, from a recombinant clinical isolate from ART-experienced studies, or from an HIV-1 PI cross-resistant recombinant clinical isolate; in the presence of increasing concentrations of DRV. The duration of the passaging cultures ranged from 162 to 251 days with DRV concentrations at the end of selection ranging from 1.20 to 12.00 μM (300- to 3,000-fold the DRV EC_{50} value against HIV-1/IIIB). Baseline viruses had EC_{50} values ranging from <0.15 to 110.31 nM. By the end of the selection process the resulting HIV-1 strains had DRV FC ranging from 52.9 to 641.0. In the 9 HIV-1 strains harboring multiple PI RAMs overall 22 mutations emerged in the PR, of which L10F, V32I, L33F, S37N, M46I, I47V, I50V, L63P, A71V and I84V were present in more than 50% of these 9 DRV-resistant isolates. A minimum of 8 of these DRV in vitro selected mutations, from which at least 2 were already present in the PR prior to selection, were required in the HIV-1 PR to render a virus resistant (FC >10) to DRV. Seven of these 9 DRV-resistant viruses had phenotypic data for TPV. Six of those showed a FC<3 for TPV, indicative of limited cross-resistance between these 2 PIs. (more information can be found in Module 4.2.1.1/TMC114-20050013-VRR).

Table 6: Overview of the in Vitro Selection Studies Performed With WT HIV-1 in the Presence of DRV

Initial HIV-1 Strain	Exp #	Original Protease Genotype[d]	PI[a] Initial Conc. (nM)	PI[a] Initial EC_{50}[b] (nM)	PI[a] Day (Passage)	PI[a] Final Conc. (nM)	PI[a] Final EC_{50}[b] (nM)	Final HIV-1 Strain[c]	Mutations Emerging in the Protease at the end of the Selection Experiment[d]
DRV									
IIIB	367	V03I	5	2.35	1218 (345)	300	80.94	T24020	S37D, K70E, I85V
IIIB	369	V03I	1	2.35	920 (263)	200	49.39	T24099	R41E, K70E
IIIB	697	V03I	10	2.35	328 (94)	200	1.34	T14505	S37N, R41S, K70E
IIIB	717	V03I	10	2.35	1308 (372)	400	206.27	T23365	R41T, H69Q, K70E, V77I
NL4.3	738	V03I, S37N	10	3.10	205 (59)	40	6.26	T14493	R41S
r14054	361	V03I, E35D/E, S37D/N, I64V	10	0.68	376 (107)	50	14.56	T15585	K55Q, T74S
r14055	960	V03I, L63S, K70R	10	1.60	408 (117)	50	2.71	T15620	R41I

[a] MT4-LTR-EGFP cells were acutely infected with WT HIV-1 at a MOI of 0.001 to 0.01. Cells were suspended in 10 mL of complete media at a density of 1.5 x 10^5/mL. When extensive cytopathic effect was observed, cultures were centrifuged to remove cells debris, and the cell-free supernatants containing HIV-1 were used for the next round of infection. An aliquot of the supernatants was stored for further analysis. Compound concentrations were increased as needed when viral growth became comparable to control.

[b] In vitro susceptibility testing was done at Virco®. Virus stocks from the selected passages were grown in the absence of the PI and titrations were performed. These new virus stocks were used for susceptibility testing.

[c] Final strain for which the geno and pheno data were available, is shown.

[d] Genotypic analysis were performed directly from the original supernatant by automated population-based sequencing at Virco. Sequence data were aligned to the WT HIV-1/$HXB2_{CG}$ reference and reported as amino acid changes along the PR.

Conc.: concentration; Exp: experiment.

Source: Module 4.2.1.1/TMC114-20050012-VRR/Table 2

Table 7: Phenotypic Profile of Viruses With DRV FC>10 Obtained From HIV-1/IIIB Under Selective Pressure of DRV

HIV-1 Strain	Phenotype[a](FC) DRV	APV	ATV	IDV	LPV	NFV	SQV	TPV[b]
T24020	37.6	15.5	20.7	30.3	32.1	10.7	N.D.[c.]	28.3
T24099	22.9	4.2	9.3	17.3	8.0	3.0	17.3	1.9
T23365	50.0	12.4	39.5	31.5	24.6	13.0	41.4	23.2

[a] Experiments performed at Virco®

[b] Data from TPV or TPV racemate are included

[c] Not done (N.D.)

Source: Module 4.2.1.1/TMC114-20050012-VRR/Table 4

4.1.2.3. Antiviral Activity Against a Screening Panel of 20 Protease Inhibitor-Resistant Recombinant Clinical Isolates

The antiviral activities of DRV was determined on a screening panel of 20 PI resistant recombinant viruses[2] (more information can be found in Module 4.2.1.1/ TMC114-20050017-VRR). Eighteen of the 20 (90.0%) viruses were susceptible to DRV showing no significant increases in EC_{50} value compared with HIV-1/IIIB (EC_{50} ≤10nM, FC≤4).

4.1.2.4. Antiviral Activity of Darunavir Against Circulating HIV-1 Quasispecies

The antiviral activity of DRV was determined against 3,309 recombinant HIV-1 isolates with a decreased susceptibility (FC>4) to at least 1 of the following PIs: APV, ATV, IDV, LPV, NFV, RTV, SQV, or TPV. Darunavir EC_{50} values were ≤10 nM for 78% of the isolates, while an EC_{50} >100 nM was observed for only 3% of the isolates. Eighty percent of the isolates exhibited a DRV FC≤4 and 10% a DRV FC>10. Genotypic data were available for 1,113 of the PI resistant viruses. Subgroups of the viruses with up to 3 primary PI mutations and/or up to 8 PI resistance-associated mutations had a median fold change ≤4 for DRV (which was lower than all other PIs except TPV to which it was equivalent) (more information can be found in Module 4.2.1.1/TMC114-20050005-VRR).

4.1.2.5. Antiviral Activity Against Site Directed Mutants of HIV-1 Carrying Mutations in the Protease

Site directed mutants (SDMs) were constructed on the basis of data obtained from selection experiments in the presence of DRV and on the basis of mutations reported to be associated with resistance to APV (more information can be found in TMC114-20050019-VRR[18]). Loss of DRV susceptibility (FC=5.1) was observed for 1 of the 57 HIV-1 SDMs studied. This virus harbored the PI resistance-associated mutations: M46I, I47V, and I50V. In contrast, a loss of susceptibility (FC>4) was observed for 16 of the 57 SDMs tested with APV.

4.1.2.6. Antiviral Activity of Darunavir Against HIV-1 Primary Clinical Isolates Resistant to Protease Inhibitors

The antiviral activity of DRV has been determined against 14 HIV-1 PI-resistant primary isolates in PBMCs[13] (more information can be found in TMC114-20050002-VRR[16]). Only 14% (2 of 14) of the isolates had a FC>4 for DRV compared with 57% (8 of 14) for SQV and 65% (9 of 14) for APV, 93% (13 of 14) for NFV, 100% (14 of 14) for RTV, and 100% (7 of 7) for LPV.

Cross-resistance between DRV and the NRTIs, the NNRTIs, the entry inhibitors or the integrase inhibitors, is unlikely because the viral targets for those inhibitors are different.

4.1.2.7. Antiviral Activity in Combination With Current HIV-1 Inhibitors

Combination of DRV with HIV-1 inhibitors were studied in an anti-HIV-1/IIIB MT4 cell-based assay. A combination index was calculated using the isobologram model for combinations. DRV did not show antagonism when studied in combination with the PIs APV, ATV, IDV, LPV, NFV, RTV, SQV, or TPV, NRTIs abacavir (ABC), didanosine (ddI), FTC, lamivudine (3TC), stavudine, TFV, zalcitabine, or zidovudine (AZT), the non-nucleoside reverse transcriptase

inhibitors (NNRTIs) delavirdine, efavirenz (EFV), etravirine, nevirapine (NVP), or rilpivirine[1] and the fusion inhibitor enfuvirtide (T-20). The data indicate additivity with all NRTIs and NNRTIs. A modest synergistic effect with APV, NFV and RTV was observed whereas additive effect was described for the combination with ATV, IDV, LPV SQV, and TPV and with T-20 (more information can be found in Module 4.2.1.1/TMC114-20050006-VRR and TMC125-20060004-VRR).

4.2. Cobicistat

4.2.1. Inhibition of HIV-1 Proteases

COBI (GS-9350) and RTV were evaluated in an in vitro enzymatic assay for their inhibitory effect on HIV-1 PR enzymatic activity (more information can be found in Module 4.2.1.2/PC-216-2001). COBI did not have any effect on the HIV-1 PR enzymatic activity at concentrations up to 30 μM. In comparison, the IC_{50} for RTV was 0.6 nM when tested in parallel under the same assay conditions. These enzyme inhibition data indicate that COBI is not an inhibitor of the HIV-1 PR.

4.2.2. Inhibition of the Activity of Human Proteases

The potential inhibitory activity of COBI was evaluated against cathepsin D (more information can be found in Module 4.2.1.2/PC-216-2001). Unlike RTV, COBI did not exhibit any activity towards this enzyme.

4.2.3. In Vitro Antiviral Activity

The in vitro antiviral activity of COBI was evaluated in a 5-day, HIV-1 cytopathic assay in MT-2 cells (more information can be found in Module 4.2.1.2/PC-216-2002). There was no inhibition (100% activity remaining) of HIV replication in the presence of 30 μM COBI relative to the untreated control. The EC_{50} values of COBI in the presence of 40% human serum were >90 μM. None of the tested metabolites of COBI, M21, M26, and M31, were found to have HIV-1 antiviral activity, up to a concentration of 30 μM.

The antiviral activity of COBI was tested in PBMCs against a panel of 17 HIV-1 and 2 HIV-2 primary isolates (more information can be found in Module 4.2.1.2/PC-216-2011). Different groups of HIV-1 (M, N, and O), as well as the most prevalent group M subtypes (A, B, C, D, E, F, and G), were represented among the tested isolates. There was no inhibition of HIV-1 replication in the presence of COBI. Ritonavir was used as a control and exhibited the expected level of antiviral activity across all tested isolates. Two HIV-2 isolates were also evaluated; no selective antiviral activity of COBI was observed against the tested isolates.

Consistent with in vitro studies on the HIV-1 PR enzymatic activity, and in T-cell lines, these findings further support the conclusion that COBI is devoid of HIV antiviral activity.

4.2.4. In Vitro Cytotoxicity

The in vitro cytotoxicity of COBI and RTV was evaluated in MT-2 lymphoblastoid T-cells and in HepG2 hepatoma cells (more information can be found in Module 4.2.1.2/PC-216-2003).

COBI was less cytotoxic (CC_{50} = 89 µM) than RTV (CC_{50} = 38 µM) in MT-2 cells and showed a level of cytotoxicity similar to RTV in HepG2 cells (CC_{50} of 44 µM and 64 µM, respectively).

4.2.5. Antiviral Activity of Current HIV-1 Inhibitors in Combination With COBI

The potential for drug-drug interactions with COBI and clinically approved or investigational ARV drugs was evaluated. The selected drugs included several representative of each class, namely NRTIs, including TFV, FTC, ABC, 3TC, and AZT; NNRTIs, including EFV and NVP; integrase strand-transfer inhibitors (INSTIs), including raltegravir (RAL) and elvitegravir (EVG); and PIs, including ATV and DRV. Overall, no significant changes were observed in the activity of any of the tested ARV drugs in the presence of 5 µM COBI (more information can be found in Module 4.2.1.2/PC-216-2005).

4.3. Darunavir/Cobicistat Fixed Dose Combination

No in vitro virology studies have been performed with the DRV/COBI FDC. The resistance profile of DRV/COBI FDC is driven by DRV. Due to its lack of antiviral activity, COBI does not select any HIV resistance mutations.

5. CLINICAL VIROLOGY DATA

5.1. Studies With DRV/COBI Once Daily: Summary of Results of the Phase 3 Study GS-US-216-0130

5.1.1. Study Synopsis

Study GS-US-216-0130 is a Phase 3b open-label, single-arm, multicenter study in HIV-1 infected, ART-naïve or ART-experienced adult subjects with no DRV RAMs. The primary objective of this 48-week study is to evaluate the safety and tolerability of DRV/COBI single agents plus 2 NRTIs after 24 weeks of treatment.

A total of 314 subjects were enrolled, and 313 subjects received at least 1 dose of study medication (DRV/COBI 800/150 mg once daily coadministered as single agents). Of these 313 subjects, 295 (94.2%) were ART-naïve and 18 (5.8%) were ART-experienced. For details on inclusion and exclusion criteria, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/ Section 7.3.

Subjects were scheduled to receive DRV/COBI 800/150 mg once daily coadministered as single agents plus 2 fully active investigator-selected NRTIs, selected after resistance testing (GenoSure™ MG assay; Monogram Biosciences Inc, South San Francisco, CA) at screening. All treatments were to be administered orally under fed conditions for a treatment period of 48 weeks. In subjects with the M184I or V reverse transcriptase mutation present at screening, FTC or 3TC could be included as a third (not-fully active) NRTI for the purpose of maintaining the M184V mutation.

The primary Week-24 analysis (safety, efficacy and resistance analysis) was performed when all subjects had been treated for 24 weeks or discontinued earlier (cut-off date [redacted]). The primary efficacy endpoint was the proportion of subjects who achieved HIV-1 RNA <50 copies/mL at Week 24 using the snapshot analysis. Of note, HIV-1 viral loads in Study GS-US-216-0130 were measured using the COBAS Amplicor HIV-1 Monitor Test Version 1.5 (Roche Molecular Diagnostics, Inc.; Pleasanton, CA).

Subjects who were on study medication and experienced either SVR or VR were considered to have virologic failure and were included in the resistance analysis. For the definitions of SVR and VR, see below.

Suboptimal Virologic Response (SVR):

- HIV-1 RNA <1 $\log_{10}$ reduction from baseline and ≥50 copies/mL at the Week 8 visit, confirmed at the following scheduled or unscheduled visit following Week 8.

Resistance testing on samples from subjects who met the criteria for SVR was managed according to the protocol schema provided in Figure 1.

Virologic Rebound (VR):

- At any visit, after achieving HIV-1 RNA <50 copies/mL, a rebound in HIV-1 RNA to ≥400 copies/mL, which is subsequently confirmed at the following scheduled or unscheduled visit; or

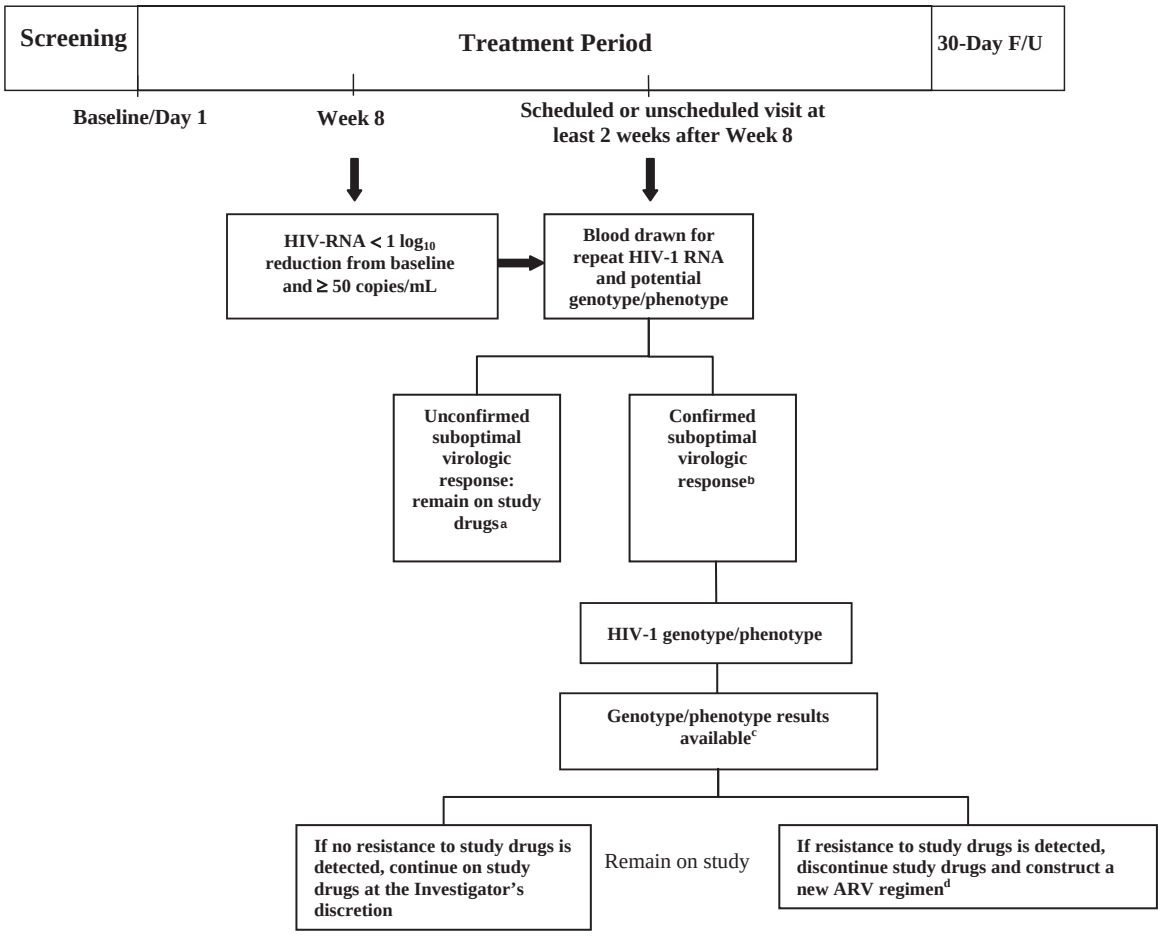
- At any visit, a >1 $\log_{10}$ increase in HIV-1 RNA from the nadir which is subsequently confirmed at the following scheduled or unscheduled visit.

Resistance testing on samples from subjects meeting the criteria for VR was managed according to the schema provided in Figure 2 (refer to Module 5.3.5.2/GS-US-216-0130-CTP and Module 5.3.5.2/GS-US-216-0130-SAP-W24-Virology).

Any subject who had ≥400 copies/mL of HIV-1 RNA due to confirmed SVR or VR, ≥400 copies/mL by Week 48 or study discontinuation, or any subject who did not meet SVR or VR criteria but had a sustained viral load ≥400 copies/mL while on study drug at these time points (or within 72 hours of discontinuation of study treatment) met the criteria for postbaseline PR/ reverse transcriptase (RT) genotype and phenotype analysis to investigate the emergence of PR/RT genotypic and phenotypic resistance.

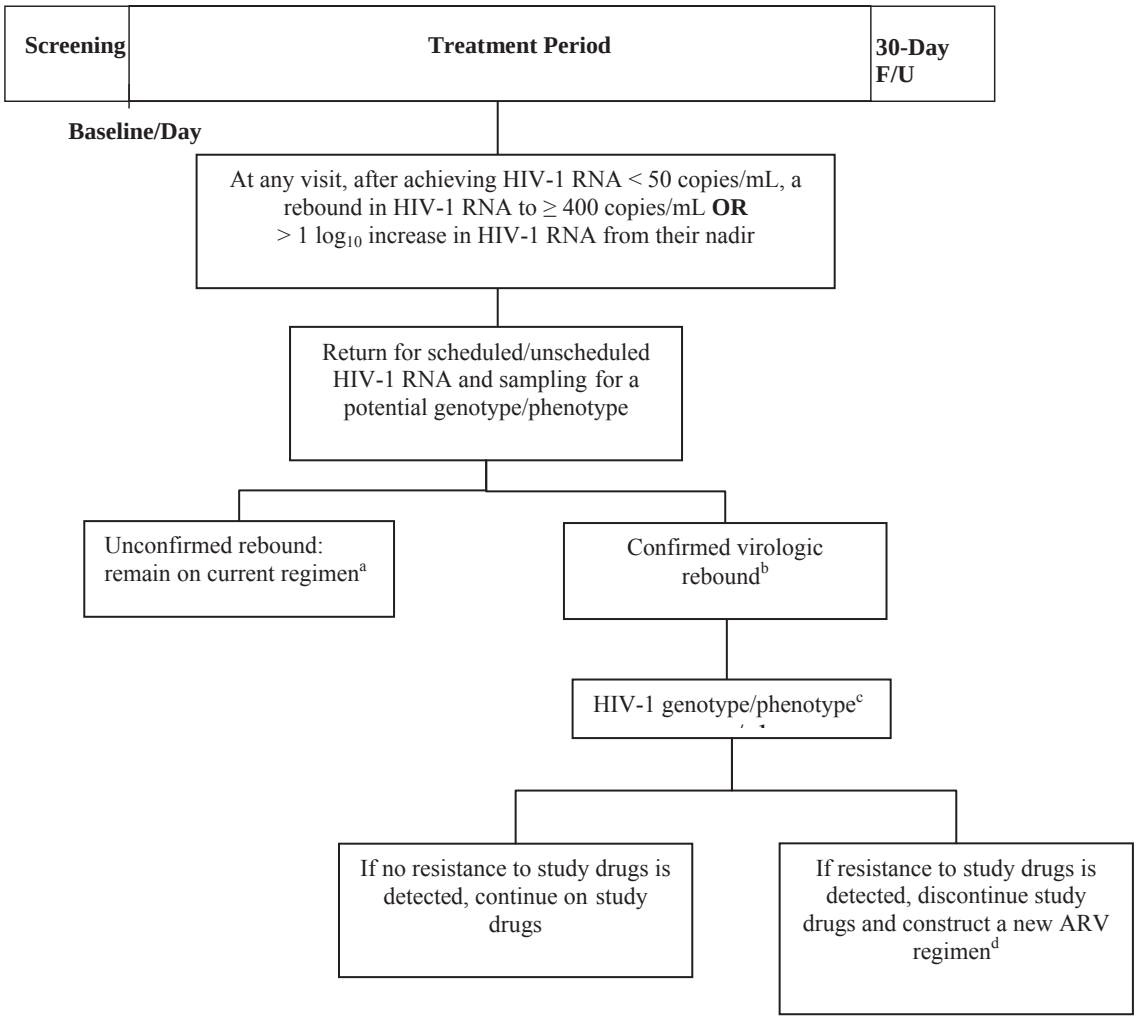
For subjects with confirmed VF, the plasma sample corresponding to the confirmed VF time point was analyzed. The PhenoSense™ GT assay (Monogram Biosciences Inc, South San Francisco, CA) was used to determine the subjects' PR/RT genotypes and phenotypes at the time of confirmed VF. Baseline PR/RT phenotyping was performed retrospectively on subjects with confirmed VF only if they showed evidence of reduced susceptibility to any of the study drugs or NRTIs from background regimen (Figure 1 and Figure 2). Subjects with phenotypically WT viruses at VF (FC for study drugs below their respective cut-off) were not analyzed for PR/RT phenotype at baseline, and the screening genotype was used as a "baseline" comparator in order to determine the genotypic changes while on treatment.

Figure 1: Suboptimal Virologic Response Schema



[a] If suboptimal virologic response is not confirmed, the subject will remain on its assigned study drug.
[b] If suboptimal virologic response is confirmed, the HIV-1 genotype and phenotype (reverse transcriptase and protease) will be analyzed.
[c] Based on the results of the genotype/phenotype assays, the subject will remain on study drugs or study drugs will be discontinued at the next scheduled or unscheduled visit, whichever occurs first.
[d] A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study.

Figure 2: Virologic Rebound Schema



[a] If virologic rebound is not confirmed, the subject will remain on its current regimen.
[b] If virologic rebound is confirmed, the HIV-1 genotype and phenotype (reverse transcriptase and protease) will be analyzed.
[c] Based on the results of the genotype/phenotype assays, the subject will remain on study drugs or study drugs will be discontinued.
[d] A new ARV regimen will be configured, at the Investigator's discretion, and the subject will remain in the study.

5.1.2. Demographics and Baseline Characteristics

Of the 313 treated subjects, 295 were ART-naïve and 18 were ART-experienced at the time of enrollment. The majority of subjects in the ART-naïve group were male (266 of 295 subjects, 90.2%). The mean age was 36 years (range 18 to 72 years), most were white (176 of 295 subjects, 59.7%) or black (101 of 295 subjects, 34.2%), and non-Hispanic/Latino (231 of 295 subjects, 78.3%). In the ART-experienced group, 13 of 18 subjects (72.2%) were male. The mean age was 45 years (range 22 to 69 years); most were white (11 of 18 subjects, 61.1%) or black (7 of 18 subjects, 38.9%), and not-Hispanic/Latino (14 of 18 subjects, 77.8%).

In the ART-naïve group, the mean baseline HIV-1 RNA value was 4.8 $\log_{10}$ copies/mL, mean baseline CD4+ cell count was $378x10^6$ cells/L, and mean baseline CD4+ cell percentage was 22.6%. In the ART-experienced group, the mean baseline HIV-1 RNA value was 4.8 $\log_{10}$ copies/mL, the mean baseline CD4+ cell count was $198x10^6$ cells/L, and mean CD4+ cell percentage was 11.9%. The median number of years since HIV diagnosis was 8.5 years (range 2 to 24 years) in the ART-experienced group.

The majority of subjects received TDF-based ARV medications during the study (294 of 295 subjects [99.7%] in the ART-naïve group, and 17 of 18 [94.4%] subjects in the ART-experienced group), with FTC/TDF being the most commonly administered TDF-based ARV medication (292 of 295 subjects [99.0%] in the ART-naïve group and 11 of 18 subjects [61.1%] in the ART-experienced group). One ART-experienced subject had a switch in background therapy during the study (discontinuation of AZT from a background regimen of AZT+FTC/TDF), refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 8.3.

According to the GenoSure MG assay, most study subjects (96.2%) had subtype B HIV-1 virus regardless of their level of ARV treatment experience. The PR/RT resistance mutations list, used for the resistance analyses, is defined according to the definitions of the International AIDS Society (IAS USA November 2011[8]) as well as any additional PR/RT resistance mutations reported by the GenoSure MG assay algorithm (refer to Module 5.3.5.2/ GS-US-216-0130-SAP-W24-Virology). The number of baseline resistance mutations is shown in Table 8.

As expected in the ART-naïve group, only 9 subjects (3.1%) had 1 primary PI RAM, with the most prevalent mutations M46I or L and Q58E found in 3 and 4 subjects, respectively. Mutations V82L and L90M were observed in 1 subject each. One or more secondary PI RAMs were found in 95.9% of subjects, reflecting the strong polymorphic nature of these mutations. One or more NNRTI RAMs were found in 25.1% of subjects, and 12.2% of subjects had NRTI RAMs. The most prevalent resistance mutation found at baseline was the K103N and/or S NNRTI RAM (11.2%), indicating transmitted resistance (K103N is a major NNRTI RAM with a potential to reduce NVP and EFV susceptibility). All other NNRTI RAMs were present at a frequency <5% (E138A, G, or R were observed in 4.1% of the ART-naïve baseline samples). Two subjects in the ART-naïve cohort also had the M184V mutation, also suggesting some transmitted resistance (M184V is a major NRTI RAM with a potential to reduce 3TC and FTC susceptibility). NRTI RAM M41L was observed in 2% of the ART-naïve baseline samples.

In the ART-experienced subjects, 1 subject (5.6%) had 2 primary PI RAMs (M46I and I54V) and the other 17 subjects had none. One or more secondary PI RAMs mutations were found in 17 of the 18 subjects (94.4%). Nearly three-quarters (72.2%) of the subjects had 1 or more NNRTI RAMs, K103N being the most prevalent (44.4%). The M184I and/or V mutation was the most prevalent NRTI RAM (33.3%, 6 of 18 subjects); one or more NRTI RAMs were found in 38.9% of subjects. The presence of these mutations is often correlated with prior use of ARV agents.

Of note, 1 or more DRV RAMs were found in only 5 subjects (1.4%) who were screened for this study (data not shown). As a result of the screening criteria, no enrolled subjects had HIV-1 harboring any of the DRV RAMs, and all were fully active to DRV as well as to 2 NRTIs in their background regimen based on genotypic assessment.

Table 8: Summary of Baseline Resistance Mutations – GS-US-216-0130 Week-24 Analysis

Mutations[a] at Baseline	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Number of Subjects With ≥1 RAM, n (%)			
DRV RAMs	0	0	0
Primary PI RAMs	9 (3.1)	1 (5.6)	10 (3.2)
Secondary PI RAMs	283 (95.9)	17 (94.4)	300 (95.8)
NNRTI RAMs	74 (25.1)	13 (72.2)	87 (27.8)
NRTI RAMs	36 (12.2)	7 (38.9)	43 (13.7)
Number of RAMS, Mean[b]			
Primary PI RAMs	1.0	2.0	1.1
Secondary PI RAMs	3.2	3.6	3.2
NNRTI RAMs	1.1	1.7	1.2
NRTI RAMs	1.1	1.3	1.2

N=total number of subjects; n=number of observations
[a] IAS-USA 2011 list[8] and additional PR/RT resistance mutations reported by the GenoSure MG assay algorithm.
[b] Mean calculated based on the number of subjects with at least 1 RAM at baseline.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-3

5.1.3. Efficacy Data

The main efficacy parameter was virologic response defined as the percentage of subjects with plasma viral load <50 copies/mL at Week 24 in the Food and Drug Administration (FDA)-defined snapshot analysis (Table 9).

In the ART-naïve group, virologic success was achieved at Week 24 by 247 subjects (83.7%). There were 29 subjects (9.8%) with VF at Week 24, and 19 subjects (6.4%) had no virologic data in the Week-24 window. Seventeen subjects with VF due to HIV-1 RNA #50 copies/mL were observed. Fourteen of the 17 subjects with VF were still in the study at Week 36. Ten of these 14 had HIV-1 RNA levels available at the cut-off date for this analysis; 6 of these 10 had HIV-1 RNA levels <50 copies/mL (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Listing 4.1).

Of the 18 ART-experienced subjects, virologic success was achieved at Week 24 by 11 subjects (61.1%). There were 7 subjects (38.9%) with VF at Week 24, including 5 (27.8%) subjects with HIV-1 RNA ≥50 copies/mL at Week 24 and 2 subjects (11.1%) that had discontinued with their

last available HIV-1 RNA ≥50 copies/mL (Table 9). (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 4.2.1.2).

Table 9: Proportion of Subjects With HIV-1 RNA Levels <50 Copies/mL at Week 24 (Snapshot Analysis) – GS-US-216-0130 Week-24 Analysis

HIV-1 RNA Category, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Virologic Success at Week 24			
HIV-1 RNA <50 Copies/mL	247 (83.7)	11 (61.1)	258 (82.4)
95% Confidence Intervals (CIs)[a]	79.0 - 87.8	35.7 - 82.7	77.8 - 86.5
Virologic Failure at Week 24	**29 (9.8)**	**7 (38.9)**	**36 (11.5)**
HIV-1 RNA ≥50 Copies/mL	17 (5.8)	5 (27.8)	22 (7.0)
Discontinued due to Lack of Efficacy	0	0	0
Discontinued due to Other Reasons and Last Available HIV-1 RNA ≥50 Copies/mL	12 (4.1)	2 (11.1)	14 (4.5)
No Virologic Data in Week 24 Window[b]	**19 (6.4)**	**0**	**19 (6.1)**

N=total number of subjects; n=number of observations
[a] 95% CI is the 2-sided exact 95% CI for binomial proportions.
[b] Window 20-30 weeks.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-1

For more details on the efficacy data of the Phase 3b study GS-US-216-0130 refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR.

5.1.4. Resistance Data

5.1.4.1. Influence of Baseline Genotype on Response

The effect of 5 baseline genotype characteristics on treatment response was explored: HIV-1 subtype, presence of NNRTI resistance mutations, presence of the K103N and/or S mutation, presence of NRTI resistance mutations, and presence of the M184I and/or V mutation. In both the ART-naïve and ART-experienced subjects, none of these 5 characteristics had an impact on treatment response (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 9.2.2).

5.1.4.2. Development of Resistance

Of the 313 subjects who received at least 1 dose of the study medication (DRV/COBI 800/150 mg once daily), 10 met the criteria for postbaseline PR/RT genotype and phenotype analysis (Section 5.1.1) (5 ART-naïve subjects: 1 SVR, 2 VR, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit, and 5 ART-experienced subjects: 1 SVR, 2 VR, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit). Nine of these 10 subjects were virologic failures (VFs) at Week 24 according to the snapshot analysis (7 subjects with HIV-1 RNA #50 copies/mL and 2 discontinued study medication due to other reasons and their last available HIV-1 RNA #50 copies/mL). One subject had confirmed virologic rebound at Week 12 followed by confirmed virologic suppression <50 copies/mL.

Of the 10 subjects who met the criteria for postbaseline PR/RT genotype and phenotype analysis, 1 ART-experienced subject developed a primary PI RAM as a mixture with WT: DRV RAM I84I/V. The subject had poor pill bottle returns indicative of poor adherence. None developed

any other primary or secondary PI RAMs. No phenotypic resistance to DRV or other PIs was observed. None developed any other primary or secondary PI RAMs.

One other instance of resistance mutation development was observed in a ART-experienced subject who developed 2 RT mutations: NRTI RAM L74I/L and NNRTI RAM P225H/P, which are known to be associated with resistance to ddI and ABC, and EFV, respectively. The subject's background regimen however consisted of FTC+TDF+AZT, and these mutations were not associated with the development of phenotypic resistance to the NRTIs in the background regimen. The phenotypic resistance to FTC that was observed in this subject was associated with the presence of the M184I/V at baseline and postbaseline.

For further details on the resistance analyses for this study, refer to the CSR in Module 5.3.5.2/GS-US-216-0130-W24-CSR.

5.2. Studies With DRV/rtv Once Daily

The efficacy analyses of the 192-week study TMC114-C211 in ART-naïve HIV-1 infected adult subjects, and the 48-week study TMC114-C229 in ART-experienced HIV-1 infected adult subjects with no DRV RAMs, are presented in the Summary of Clinical Efficacy (refer to Module 2.7.4).

The resistance profile of DRV/COBI FDC is driven by DRV. An extrapolation of the clinical efficacy data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-1 infected subjects can be made based on the comparable exposures to DRV (AUC_{24h}) achieved by both pharmacokinetic enhancers. The clinical resistance profile of DRV/rtv 800/100 mg once daily has been established based on the Phase 3 studies TMC114-C211 (192-week study in 343 ART-naïve HIV-1 infected adult subjects) and TMC114-C229 (48-week study in 294 ART-experienced HIV-1 infected adult subjects without DRV RAMs).

5.2.1. Phase 3 Study TMC114-C211 (ARTEMIS) Week-192 Analysis

TMC114-C211 was a 192-week randomized, controlled, open-label Phase 3 study in ART-naïve HIV-1 infected subjects comparing efficacy, safety and tolerability of DRV/rtv 800/100 mg once daily with LPV/rtv 800/200 mg per day (given as a twice daily or as a once daily regimen). Both arms used a fixed background regimen consisting of TDF and FTC. Analysis of the development of resistance was performed in subjects with VF (based on viral load ≥50 copies/mL; ITT – time to loss of virologic-response [TLOVR] non-VF censored). Phenotypic and genotypic testing was performed on samples from VFs with HIV-1 RNA ≥50 copies/mL.

In the 192-week analysis of the TMC114-C211 study, of the 343 DRV/rtv subjects, 55 (16.0%) experienced virologic failure versus 71 of 346 (20.5%) LPV/rtv subjects. In the DRV/rtv group, 39 (11.4%) subjects were rebounders and 16 (4.7%) subjects were never suppressed. In the LPV/rtv group, 49 (14.2%) subjects were rebounders and 22 (6.4%) subjects were never suppressed. There were 43 and 57 VFs with paired baseline/endpoint genotypes in the DRV/rtv and LPV/rtv group, respectively. Four (9.3%) DRV/rtv subjects and 9 (15.8%) LPV/rtv subjects with developing PI RAMs at endpoint were identified. One of these 4 DRV/rtv subjects

developed a DRV RAM (V11I). None of the developing (IAS-USA[6]) PI RAMs were primary (major) PI mutations. All VFs (DRV/rtv and LPV/rtv), for which paired baseline/endpoint phenotypes were available (39 and 52 subjects in the DRV/rtv and LPV/rtv group, respectively), remained susceptible to DRV, LPV, APV, ATV, IDV, SQV, and TPV. In 4 VFs of the DRV/rtv group and 7 VFs of the LPV/rtv group, a maximum of 2 developing (IAS-USA[6]) NRTI RAMs were identified. The development of the NRTI RAM at position 184 was associated with a decreased susceptibility to FTC included in the background regimen (n=4 for DRV/rtv subjects and n=5 for LPV/rtv subjects) (more information can be found in Module 5.3.5.1/TMC114-C211-W192-CRR).

5.2.2. Phase 3 Study TMC114-C229 (ODIN) Week-48 Analysis

TMC114-C229 was a 48-week randomized, controlled, open-label Phase 3 study to compare the efficacy, safety and tolerability of DRV/rtv (800/100 mg) once daily versus DRV/rtv (600/100 mg) twice daily in ART-experienced HIV-1 infected subjects with 0 DRV RAMs. Eleven PR mutations associated with DRV resistance (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V[8]) were identified from a pooled analysis of DRV/rtv 600/100 mg twice daily groups of ART experienced studies.[2,4] The presence of these DRV RAMs at baseline was an exclusion criterion for subjects participating in the TMC114-C229 study. Analysis of the development of resistance was performed in subjects who experienced VF (based on viral load ≥50 copies/mL; ITT – TLOVR non-VF censored). Phenotypic and genotypic testing was performed on samples from VFs with HIV-1 RNA ≥50 copies/mL.

In the 48-week analysis of the TMC114-C229 study the proportion of VFs was comparable in the DRV/rtv 800/100 mg once daily group and the DRV/rtv 600/100 mg twice daily group. Of the 294 DRV/rtv 800/100 mg once daily subjects, 65 (22.1%) experienced virologic failure versus 54 (18.2%) of 296 DRV/rtv 600/100 mg twice daily subjects. In the DRV/rtv 800/100 mg once daily group, 11 (3.7%) subjects were rebounders and 54 (18.4%) subjects were never suppressed. In the DRV/rtv 600/100 mg twice daily group, 11 (3.7%) subjects were rebounders and 43 (14.5%) subjects were never suppressed. In the VFs with available genotypes/phenotypes (60 and 42 subjects in the DRV/rtv once daily and DRV/rtv twice daily groups, respectively) in the DRV/rtv 800/100 mg once daily group 7 of 60 subjects (11.6%) with developing (IAS-USA[7]) PI RAMs were identified, compared to 4 of 42 subjects (9.5%) in the DRV/rtv 600/100 mg twice daily group. One of these subjects in the DRV/rtv 800/100 mg once daily group developed primary (ie major) PI mutations (V32I, M46I, L76V, and I84V), which included 3 DRV RAMs (V32I, L76V, and I84V), resulting in a decreased susceptibility to DRV. Of the viruses isolated from subjects receiving DRV/rtv 800/100 mg once daily and experiencing VF, 0% to 4% that were susceptible at baseline to DRV, APV, ATV, IDV, LPV, SQV or TPV lost susceptible to these PIs after treatment (1/58, 1/58, 2/56, 2/57, 1/58, 0/56, and 0/58, respectively). In the VFs receiving DRV/rtv 600/100 mg twice daily and who were susceptible at baseline to DRV, APV, ATV, IDV, LPV, SQV or TPV 0/41, 0/40, 0/40, 0/40, 0/40, 0/40, and 0/41 lost susceptible to these PIs, respectively. Four (6.7%) and 3 (7.1%) VFs developed 1 or 2 (IAS-USA[7]) NRTI RAMs in the DRV/rtv 800/100 mg once daily and the DRV/rtv 600/100 mg twice daily groups, respectively. In 3 and 2 of these VFs in the DRV/rtv 800/100 mg once daily and the DRV/rtv 600/100 mg twice daily groups, respectively, the development of these NRTI RAMs was

associated with a decreased susceptibility to a NRTI included in the treatment regimen (more information can be found in Module 5.3.5.1/TMC114-C229-W48-CRR).

5.3. Comparison of Results Across Studies

An overview of the development of resistance mutations in the Phase 3b study GS-US-216-0130 and in the Phase 3b DRV/rtv studies (DRV/rtv 800/100 mg once daily arms of TMC114-C211 and TMC114-C229) in subjects who met the criteria for postbaseline PR/RT genotype analysis is provided in Table 10. Of note, criteria for postbaseline resistance analysis, time point of postbaseline resistance analysis, and mutations lists used in the resistance analysis varied between studies.

As seen in the GS-US-216-0130 study, low rates of development of PI and NRTI resistance mutations were observed in the DRV/rtv 800/100 mg once daily treatment arms of the TMC114-C211 ART-naïve study and the TMC114-C229 ART-experienced study (with 0 DRV RAMs) (Table 10).

Table 10: Development of Mutations Across Studies

Number of subjects[a] developing ≥1 mutation[b], n/N	Week-24 GS-US-216-0130 DRV/COBI 800/150 mg qd Treatment-naïve N=295	Week-24 GS-US-216-0130 DRV/COBI 800/150 mg qd Treatment-experienced N=18	Week-192 TMC114-C211 DRV/rtv 800/100 mg qd Treatment-naïve N=343	Week-48 TMC114-C229 DRV/rtv 800/100 mg qd Treatment-experienced N=294	Week-48 TMC114-C229 DRV/rtv 600/100 mg bid Treatment-experienced N=296
DRV RAMs	0/5	1/5	1/43	1/60	0/42
Primary PI RAMs	0/5	1/5	0/43	1/60	0/42
PI RAMs[c]	0/5	1/5	4/43	7/60	4/42
NRTI RAMs	0/5	1/5	4/43	4/60	3/42

N=total number of subjects; n=number of observations

[a] Subjects (virologic failures) who met the criteria for postbaseline genotype analysis and with paired baseline/postbaseline genotypes.

[b] For GS-US-216-0130: IAS-USA 2011 list[8] and additional PR/RT resistance mutations reported by the Genosure MG assay algorithm; for TMC114-C211: IAS-USA 2009 list[6]; for TMC114-C229: IAS-USA 2008 list.[7]

[c] Includes all primary and secondary mutations.

Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR
Module 5.3.5.1/TMC114-C211-W192-CRR
Module 5.3.5.1/TMC114-C229-W48-CRR

Phenotypic resistance to DRV and other PIs and NRTIs included in the background regimen was not or rarely observed in these 3 studies. No phenotypic resistance to DRV or other PIs was observed in GS-US-216-0130 in ART-experienced (N=5) and ART-naïve (N=5) patients with postbaseline phenotype data. All DRV/rtv VFs in TMC114-C211, for which paired baseline/endpoint phenotypes were available (N=39), remained susceptible to DRV, LPV, APV, ATV, IDV, SQV, and TPV. Of the viruses isolated from subjects receiving DRV/rtv 800/100 mg once daily in TMC114-C229 and experiencing VF, 0% to 4% that were susceptible at baseline to DRV, APV, ATV, IDV, LPV, SQV or TPV lost susceptible to these PIs after treatment (1/58,

1/58, 2/56, 2/57, 1/58, 0/56, and 0/58, respectively). In the VFs receiving DRV/rtv 600/100 mg twice daily in TMC114-C229 and who were susceptible at baseline to DRV, APV, ATV, IDV, LPV, SQV or TPV 0/41, 0/40, 0/40, 0/40, 0/40, 0/40, and 0/41 lost susceptible to these PIs, respectively.

6. Conclusion

A comprehensive program of nonclinical studies was conducted in support of the marketing authorization of DRV, and an extensive nonclinical program has been conducted for COBI. Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 PR. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Darunavir has potent in vitro activity against WT and multi-drug resistant HIV-1 strains. In vitro selection studies and the high binding affinity of DRV with HIV-1 PR, and its resilience to the effects of PI RAMs, provided evidence of a high genetic barrier to the development of resistance to DRV. Moreover DRV showed potent activity against the majority of PI-resistant SDMs, primary isolates, and recombinant clinical isolates. There was no evidence of antagonism between DRV and any of the current HIV-1 ARVs. Cobicistat, a structural analogue of RTV, was found to be a potent mechanism-based inhibitor of human hepatic microsomal CYP3A activity. COBI has no detectable antiviral activity against HIV-1 and does not antagonize the antiviral effect of DRV.

The clinical program for DRV/COBI FDC is based on the comprehensive development programs of the 2 individual compounds and on the pharmacokinetic bridging clinical program. The safety, pharmacokinetic, and efficacy results of the Week-24 analysis of the GS-US-216-0130 study support the use of DRV/COBI 800/150 mg once daily in ART-naïve and ART-experienced adult HIV-1 infected subjects with no DRV RAMs and with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L.

In the Week-24 analysis of study GS-US-216-0130 resistance development to DRV or other PIs and NRTIs was rare. Of the 313 subjects who received at least 1 dose of the study medication (DRV/COBI 800/150 mg once daily), 10 met the criteria for postbaseline resistance analysis (5 ART-naïve subjects: 1 SVR, 2 VR, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit and 5 ART-experienced subjects: 1 SVR, 2 VR, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One ART-experienced subject had developed a DRV RAM at position I84 as a mixture with WT (I84I/V). No phenotypic resistance to DRV or other PIs was observed. None developed any other primary or secondary PI RAMs. No subject developed NRTI resistance mutations (or phenotypic resistance) to their concomitant NRTI regimen.

The resistance profile of DRV/COBI FDC is driven by DRV. Due to its lack of antiviral activity, COBI does not select any HIV resistance mutations. The clinical resistance profile of DRV/rtv 800/100 mg once daily has been established in the ART-naïve study TMC114-C211 and ART-experienced TMC114-C229 study. Low levels of resistance development were observed in the DRV/rtv 800/100 mg once daily treatment arms of the TMC114-C211 ART-naïve study and the TMC114-C229 ART-experienced study (with 0 DRV RAMs). The comparable low levels of

resistance development in the GS-US-216-0130 study confirms the clinical resistance profile of DRV/rtv 800/100 mg once daily in ART-naïve and ART-experienced subjects with 0 DRV RAMs and the high genetic barrier of DRV, whether boosted with COBI or rtv.

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Janssen Research & Development

Summary of Clinical Pharmacology Studies Addendum

Physiologically-based Pharmacokinetic Modeling of Interactions of CYP3A4 Inhibitors with Cobicistat

DRV/COBI (darunavir/cobicistat)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ARV	antiretroviral
ATV	atazanavir
COBI	cobicistat
CYP	cytochrome P450
DRV	darunavir
EVG	elvitegravir (Vitekta®)
GSI	Gilead Sciences, Inc.
HIV(-1)	human immunodeficiency virus (type 1)
MRT	mean residence time
PAM	post authorization measure
PBPK	physiologically-based pharmacokinetic
P-gp	P-glycoprotein
QTc	QT interval duration corrected for heart rate
Vss	apparent steady state volume of distribution

1. BACKGROUND AND OVERVIEW

Cobicistat (COBI; developed by Gilead Sciences, Inc. [GSI]) is a mechanism-based cytochrome P450 (CYP) 3A inhibitor that enhances or "boosts" the exposure of antiretrovirals (ARVs) used in the treatment of human immunodeficiency virus type 1 (HIV-1) infection that are CYP3A substrates, eg, atazanavir (ATV; developed by Bristol Myers Squibb), darunavir (DRV; developed by Janssen), and elvitegravir (EVG; developed by GSI).

This submission fulfils a post authorization measure (PAM) for REZOLSTA® and an additional pharmacovigilance activity (Category 3) agreed in the REZOLSTA Risk Management Plan. This submission follows a similar PAM for Tybost® (COBI 150 mg tablet) and is based on data collected and analyses performed by GSI. The PAM committed to justify the assumption that CYP3A4 was largely responsible for the elimination of COBI, with a request to evaluate the potential effect of potent CYP3A4 inhibitors on COBI exposure using physiologically-based pharmacokinetic (PBPK) simulations to provide further information on drug-drug interactions with COBI.

This summary includes an analysis of data collected from multiple studies of COBI and the development of a PBPK model to identify the major mode of elimination of COBI and the effect of potent CYP3A4 inhibitors on COBI exposure (Module 5.3.2.2/AD-216-2113).

No new clinical pharmacology information is submitted.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

No new clinical pharmacology information is submitted.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

Report AD-216-2113 presents a summary of available clinical data regarding the role of CYP3A in COBI disposition and a PBPK model for COBI to investigate potential interactions with potent CYP3A4 inhibitors (Module 5.3.2.2/AD-216-2113).

The evaluation was made on intensively sampled clinical pharmacokinetic data from studies in which COBI was dosed alone or with other agents expected to have minimal effects on COBI absorption and disposition (Table 1).

Table 1: Clinical Studies With Cobicistat Providing Intensive Pharmacokinetic Data

Study	Brief Description	Cobicistat Dosing
GS-US-216-0101	Single- and multiple-dose with effects on midazolam pharmacokinetics	50, 100 and 200 mg single dose and once daily (14 d) 100 mg ritonavir single dose and once daily (14 d)
GS-US-216-0107	QT/QTc study	250 and 400 mg single dose
GS-US-216-0111	[^{14}C]COBI mass balance	150 mg once daily (7d: 6 d unlabeled + 1 d ^{14}C)
GS-US-216-0112	Probe drug interaction (digoxin, desipramine, efavirenz)	150 mg once daily (10 d)
GS-US-216-0113	Safety assessment	300 mg single dose and once daily (7 d), 400 mg single dose
GS-US-216-0116	Bioequivalence, with effects on midazolam and elvitegravir	150 mg once daily (2 x 10 d)
GS-US-216-0119	Darunavir and tipranavir interaction	150 mg twice daily (10 d)
GS-US-216-0121	Effects on glomerular filtration rate and creatinine clearance	150 mg once daily (7 d)

An evaluation of intensively-sampled pharmacokinetic data for COBI coadministered with ATV, a representative potent inhibitor of human CYP3A, was also performed (Table 2).

Table 2: Clinical Studies with Cobicistat and Atazanavir Providing Intensive Pharmacokinetic Data

Study	Brief Description	Cobicistat Dosing
GS-US-216-0110	Comparison of cobicistat and ritonavir as pharmacokinetic enhancers of 300 mg atazanavir	100 and 150 mg once daily (10 d)
GS-US-216-0114	Cobicistat + atazanavir (300 mg), emtricitabine and tenofovir disoproxil fumarate (Phase 3 study)	150 mg once daily (14 – 57 d)

3.1. Absorption

No new information is submitted.

3.2. Distribution

No new information is submitted.

3.3. Metabolism and Excretion

The clearance of COBI and probe drugs eliminated by known mechanisms was compared in order to explore the potential routes of elimination for COBI. Collectively the data were consistent with the in vitro studies on COBI metabolism, with no evidence for involvement of CYP2B6 elimination in COBI elimination, but with strong association with CYP3A activity and moderate association with CYP2D6 activity:

- CYP3A: In study GS-US-216-0101, the CYP3A probe substrate, midazolam, was dosed alone, or with COBI on the final dose of a 14 days once daily COBI dosing period. It was demonstrated that midazolam clearance is a suitable measure of CYP3A activity when dosed with 50 mg COBI. Under these conditions COBI clearance was highly correlated with that of midazolam, confirming involvement of CYP3A in the elimination of COBI. No correlation was seen at higher COBI doses due to the greater inhibition of CYP3A and consequent increased contribution of routes other than CYP3A metabolism to midazolam elimination (Module 5.3.4.1/GS-US-216-0101-CSR).
- CYP2D6: In study GS-US-216-0112, COBI 150 mg once daily clearance at steady state shows a weaker, but significant, correlation with the clearance of desipramine, a CYP2D6 substrate, either when desipramine is dosed alone or when co-dosed with COBI (Module 5.3.3.4/GS-US-216-0112-CSR).
- CYP2B6 and P-glycoprotein (P-gp): In study GS-US-216-0112, contrary to the results with CYP3A and CYP2D6, CYP2B6 and P-gp activity, no significant correlation was seen between the clearance of COBI and that of the probe substrate dosed alone or dosed with 150 mg COBI. Thus, CYP2B6 and P-gp activity are unlikely to affect COBI elimination (Module 5.3.3.4/GS-US-216-0112-CSR).

3.4. Clinical Pharmacokinetics

3.4.1. Pharmacokinetics of Cobicistat after Single-and Multiple-Dose Administration of Cobicistat in Healthy and Infected Subjects

All available single-dose and multiple dose intensively-sampled pharmacokinetic data for COBI were assessed, for studies where COBI was dosed alone or with agents expected to have minimal effects on COBI pharmacokinetics:

- Single-dose: Pharmacokinetic data were analyzed from study GS-US-216-0101 cohort 1 (50 mg), 2 (100 mg) and 3 (200 mg), study GS-US-216-0107 treatment group A (250 mg) and B (400 mg), and study GS-US-216-0113 visit 1 treatment group 1 (300 mg) and 2 (400 mg).
- Multiple-dose: Pharmacokinetic data analyzed were from subjects assumed to be at steady state and were from once daily regimens, unless noted otherwise. They were from study GS-US-216-0101 cohort 1 (50 mg), 2 (100 mg) and 3 (200 mg), study GS-US-216-0112 cohorts 1, 2 and 3 (150 mg), study GS-US-216-0113 treatment group 1 (300 mg, sampled on Day 4 and Day 7), study GS-US-216-0116 groups A and B (150 mg), study GS-US-216-0119 cohort 1 (150 mg twice daily) and study GS-US-216-0121 cohort 1 (150 mg) and 4 (150 mg to mild/moderate renally impaired).
- Additionally, available intensively sampled pharmacokinetic data were analyzed from study GS-US-216-0110 treatment A (100 mg COBI) and B (150 mg COBI), and study GS-US-216-0114 (150 mg COBI + Truvada) and in all cases COBI was dosed once daily with 300 mg ATV once daily, a potent inhibitor of CYP3A.

The results of these analyses are presented in Module 5.3.2.2/AD-216-2113.

Assessment of these data at steady state demonstrated that volume of distribution and clearance of COBI decrease with higher doses suggesting a dose non-linearity for COBI. Further decreases were seen with multiple doses exhibiting time-dependent pharmacokinetics, which are consistent

with COBI being a mechanism-based inhibitor of CYP3A. With the single doses of COBI, apparent clearance reaches a minimum, and mean residence time (MRT) reaches a maximum, at doses ≥200 mg whereas with multiples doses these were reached at dose ≥150 mg once daily with only modest changes at higher dose. When the COBI dose was 150 mg, addition of ATV had little effect, likely because the plateau in increased bioavailability and decreased clearance had already been reached.

Overall, COBI 150 mg was considered to maximally inhibit CYP3A. As such, further increases in dose of COBI or coadministration of other potent CYP3A inhibitor are unlikely to cause major effects on COBI pharmacokinetics.

3.4.2. Compartmental Analysis of Cobicistat Pharmacokinetics

A better mechanistic understanding of COBI absorption and disposition can be gained by the application of structural models. This had been previously explored in the population pharmacokinetics analyses for COBI (Module 5.3.3.5/COBI population PK report).

For the analysis described in Module 5.3.2.2, single-dose data were fit initially to a one-compartment open model (WinNonlin Classic PK3) and then to the same model but incorporating a lag period (WinNonlin Classic PK4).

The results of these analyses are presented in Module 5.3.2.2/AD-216-2113.

3.5. Pharmacokinetic-Pharmacodynamic Relationship for Efficacy Parameters

No new information is submitted.

3.6. Pharmacokinetic-Pharmacodynamic Relationship for Safety Parameters

No new information is submitted.

4. DEVELOPMENT OF A PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL FOR COBICISTAT

This section summarizes the key findings from a PBPK model that was developed with GastroPlus 8.5 in order to understand the potential effect of potent CYP3A4 inhibitors on COBI exposure. The focus was on steady-state pharmacokinetics of COBI at a dose of 150 mg once daily.

Details on the development of this model are presented in Module 5.3.2.2/AD-216-2113.

Development of the PBPK model was performed in multiple stages.

- First, a compartment model with fixed clearance (hepatic and renal) was developed to check performance of the solubility/gut physiology model. Representative concentration data were from study GS-US-216-0101 cohort 2. A single dose of 100 mg of COBI in the fasted state was modeled and the fit (r^2=0.77) was similar to the one seen using a conventional one compartmental method [GastroPlus Record 0101-100-SD]. GastroPlus predicted approximately 40% of the bioavailable dose would be absorbed through the caecum and colon.
- The next step was to switch from a fixed non-renal clearance to one dependent on CYP3A and CYP2D6 to identify initial enzyme kinetic parameters. The model first included CYP2D6 in the liver and intestine, then CYP3A was added to the liver and CYP3A4 to the intestine. Under the conditions applied to this model, CYP2D6 was determined to contribute to 6% of the metabolic clearance of COBI and CYP3A was responsible for the remainder (94%), in addition to the fixed renal clearance applied to the model.
- Then, the full PBPK model with enzyme-mediated metabolic clearance was developed to identify factors influencing distribution. The full PBPK model based on default PBPK parameters was found to give the best prediction of the volume of distribution of COBI. Under these conditions a predicted apparent steady state volume of distribution (V_{ss}) value of 92 L was obtained, close to the typical value of 77 L obtained through population pharmacokinetic analysis.
- This model was then adapted for use with multiple dosing (COBI 150 mg once daily). Representative concentration data were from study GS-US-216-0116 cohort 1. In order to approximately match the pharmacokinetic profile of COBI from study GS-US-216-0116, the activity of CYP3A4 was reduced by 75% [GastroPlus Record 0116-150-MD-PBPK]. This led to an increase in the relative contribution of CYP2D6 to COBI elimination from 6% for a single dose to 24% for multiple dosing, with still a predominant contribution from CYP3A of 76% in COBI elimination.

In summary, the PBPK model was developed in which the simulated COBI plasma concentrations approximately matched the ones measured in clinical settings. Using this approach it was estimated that CYP2D6 accounts for ≤25% of the clearance of COBI at steady state (150 mg once daily) in vivo with CYP3A being the major enzyme involved in this clearance.

5. REFERENCES

Not applicable

Janssen Research & Development

Summary of Clinical Pharmacology Studies Addendum

Cobicistat-containing Highly Active Antiretroviral Regimens in HIV-1 Infected Patients with Mild to Moderate Renal Impairment

DRV/COBI (darunavir/cobicistat)

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ABBREVIATIONS

abbreviation	description of abbreviated term
ARV	antiretroviral
ATV	atazanavir
COBI	cobicistat
CSR	clinical study report
DRV	darunavir
EVG	elvitegravir
FDC	fixed dose combination
FTC	emtricitabine
HIV (-1)	human immunodeficiency virus (type 1)
IN	integrase
INSTI	integrase strand transfer inhibitor
INSTI-R	integrase strand transfer inhibitor associated resistance
NNRTI	nonnucleoside reverse transcriptase inhibitor
NNRTI-R	nonnucleoside reverse transcriptase inhibitor associated resistance
NRTI	nucleoside reverse transcriptase inhibitor
NRTI-R	nucleoside reverse transcriptase inhibitor associated resistance
PAM	post-authorization measure
PI	protease inhibitor
PI-R	protease inhibitor resistance
RNA	ribonucleic acid
PR	protease
RAP	resistance analysis population
RMP	risk management plan
RT	reverse transcriptase
SD	standard deviation
STB	Stribild®, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated
TDF	tenofovir disoproxil fumarate
TFV	tenofovir

1. BACKGROUND AND OVERVIEW

This submission supports the provision of final efficacy and safety data (Week 96) from Phase 3 Study GS-US-236-0118 in fulfillment of a post-authorization measure (PAM) for REZOLSTA® (darunavir [DRV]/cobicistat [COBI] fixed dose combination [FDC]). The provision of the final clinical study report (CSR) is an additional pharmacovigilance activity (category 3) in the REZOLSTA risk management plan (RMP).

This summary presents virology resistance data using the final dataset, through Week 96, for Study GS-US-236-0118. This Phase 3 study evaluated the effect of COBI-containing regimens on parameters of renal function and assessed the safety and tolerability of these regimens in human immunodeficiency virus type 1 (HIV-1) infected antiretroviral (ARV) treatment-naïve and ARV treatment-experienced subjects with mild to moderate renal impairment (safety and efficacy results are summarized in Module 2.7.4/Section 1.1.1). The study contained a pharmacokinetic substudy that assessed the pharmacokinetics of COBI, emtricitabine (FTC), tenofovir (TFV), elvitegravir (EVG), atazanavir (ATV), and DRV at baseline and following once daily, multiple-dose administration of Stribild® (STB), COBI-boosted ATV (ATV/COBI) + 2 nucleoside reverse transcriptase inhibitors (NRTIs), or COBI-boosted DRV (DRV/COBI) + 2 NRTIs. These results were presented in the interim Week 48 CSR submitted previously. An analysis of the virology resistance data through Week 96 is provided in Section 4. No new clinical pharmacology information is submitted.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

No new information is submitted. A tabular summary of Study GS-US-236-0118 is provided in Module 2.7.4/Appendix 8.1.

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

No new clinical pharmacology information is submitted.

4. SPECIAL STUDIES

4.1. Virology Resistance Analysis in Study GS-US-236-0118

The following sections summarize the key findings from the virology resistance analyses that were conducted through the end of the study, Week 96, in Study GS-US-236-0118. A tabular summary of the study is provided in Module 2.7.4/Appendix 8.1.

4.1.1. Virology Resistance Assays

Analysis of resistance data is summarized below and is described in detail in the resistance analysis plan (Module 5.3.5.2/GS-US-236-0118 Final CSR/Appendix 16.1.10).

Pretreatment analysis of HIV-1 protease/reverse transcriptase (PR/RT) genotype was assessed at screening for all Cohort 1 (STB, ARV treatment-naïve) subjects using the GeneSeq™ assay (Monogram Biosciences, South San Francisco, CA, USA); this assay also determined the HIV-1 subtype. A retrospective analysis of HIV-1 integrase (IN) genotype was further assessed at

baseline for all Cohort 1 (STB) subjects in the resistance analysis population using the GeneSeq™ IN assay (Monogram Biosciences, South San Francisco, CA, USA).

For postbaseline resistance analyses, PR/RT genotyping and phenotyping assays were performed on subjects in both cohorts with virologic failure or failure to achieve plasma HIV-1 ribonucleic acid (RNA) <400 copies/mL at study discontinuation (at or after Week 8 and on study drugs). In the STB cohort, IN genotyping and phenotyping assays were also performed. The PhenoSense GT™, PhenoSense™ IN, and GeneSeq™ IN assays (Monogram Biosciences, South San Francisco, CA, USA) were used for these purposes.[1] The PhenoSense GT™ assay included genotypic and phenotypic data relevant to all currently approved NRTIs, nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs), with the exception of the NNRTI rilpivirine. The PhenoSense IN assay assessed both EVG and raltegravir phenotypes. No analyses of viral tropism were conducted in this study.

4.1.2. Pretreatment Virology Resistance Data

4.1.2.1. Screening Analysis of HIV-1 Subtype and PR/RT Genotype

HIV-1 genotyping of the PR/RT genes was conducted at screening to assess for preexisting resistance as part of the enrollment criteria for all Cohort 1 (STB) subjects who entered the study. As defined in the protocol, Cohort 1 (STB) subjects were to have genotypic sensitivity to FTC and tenofovir disoproxil fumarate (TDF). Consistent with the enrollment criteria, no subject with available data (32 of 33) had a K65R or M184V/I mutation at study entry. One subject did not have screening data available for PR/RT due to failure of both GeneSeq！ and GenoSure MG！ assays.

Primary PI resistance (PI-R) mutations were observed in 6.3% of Cohort 1 (STB) subjects, most commonly M46L (n=1) and V82A (n=1) in PR, but were considered fully sensitive to ATV. NRTI-associated resistance (NRTI-R) mutations were observed in 12.5% of subjects, most commonly M41L (n=1), V118I (n=2), and K219K/R (n=1) in RT. Primary NNRTI-associated resistance (NNRTI-R) mutations were observed in 6.3% of subjects, including K103N (n=1) and V90V/I+V106V/I+V108V/I (n=1) in RT (Module 5.3.5.2/GS-US-236-0118 Final CSR/ Appendix 16.2/Virology Listing 1).

The HIV-1 subtype was determined for all Cohort 1 (STB) subjects with available data (32 of 33) by the screening genotype. Most subjects had HIV-1 subtype B (90.6%) (Module 5.3.5.2/GS-US-236-0118 Final CSR/Appendix 16.2/Virology Listing 1).

4.1.2.2. Baseline Analysis of HIV-1 IN Genotype

Retrospective HIV-1 genotyping of the IN gene was conducted at baseline for all Cohort 1 (STB) subjects considered to have virologic failure (2 of 33). No subject was found to have primary or secondary integrase strand transfer inhibitor (INSTI) associated resistance (INSTI-R) mutations (Module 5.3.5.2/GS-US-236-0118 Final CSR/Appendix 16.2/Virology Listing 1).

4.1.3. Development of Resistance

4.1.3.1. Virologic Failure Definition and Resistance Analysis Population

The resistance analysis population (RAP) included subjects with either: 1) for Cohort 1: suboptimal virologic response: HIV-1 RNA >50 copies/mL and <1 log_{10} reduction from baseline at Week 8 that was confirmed and HIV-1 RNA ≥400 copies/mL at the subsequent visit; or 2) for Cohort 1: virologic rebound: HIV-1 RNA ≥400 copies/mL at any visit past week 8 after achieving HIV-1 RNA <50 copies/mL, that is confirmed and ≥400 copies/mL at the next scheduled or unscheduled visit; or 2 subsequent visits with >1 log_{10} increase in HIV-1 RNA from nadir; 3) for Cohort 2: virologic rebound: HIV-1 RNA ≥400 copies/mL at any visit that is confirmed and ≥400 copies/mL at the next scheduled or unscheduled visit; or 4) for both Cohort 1 and Cohort 2: Discontinuation from study with HIV-1 RNA ≥400 copies/mL at last visit (Last) past Week 8, while receiving study drugs (or within 72 hours of discontinuation). Subjects who discontinued the study before week 8 (Early DC; Cohort 1 only), or who were not receiving study drugs within 72 hours prior to virologic rebound (Off SD) were not analyzed for resistance.

Of the 106 enrolled and treated subjects, 4 (3.8%) met the virologic failure criteria and were included in the end of study RAP (2 Cohort 1 [STB] subjects and 2 Cohort 2 [PI/COBI] subjects; Table 2) (Module 5.3.5.2/GS-US-236-0118 Final CSR/Appendix 16.2/Virology Listing 2 and 3).

4.1.3.2. Development of Resistance in the Study Cohorts at End of Study

Cohort 1: STB

In the STB cohort, postbaseline genotypic and phenotypic PR, RT, and IN data were available for the 2 subjects analyzed for resistance development (Table 1). No subject developed resistance mutations in PR, RT, or IN and both subjects remained phenotypically susceptible to TDF, FTC, EVG, and ATV.

Cohort 2: PI/co

In the PI/COBI cohort, postbaseline genotypic and phenotypic PR and RT data were available for the 2 subjects analyzed for resistance development (Table 1). Both subjects did not develop any primary PI or NRTI-associated drug resistance mutations and both remained phenotypically susceptible to all drugs in their regimen (Table 1) (Module 5.3.5.2/GS-US-236-0118 Final CSR/ Appendix 16.2/Virology Listings 2 and 3).

Table 1: GS-US-236-0118: Summary of HIV-1 Genotypic Resistance at the End of the Study (RAP Analysis Set)

	Number of Subjects (% Subjects; %RAP)	
Resistance Development Category, n (%)	**STB (N=33)**	**PI/COBI + 2 NRTIs (N=73)**
Resistance Analysis Population	2 (6.1)	2 (2.7)
Subjects with Data	2	2
Developed Resistance Mutations to Study Drugs	0	0
No Resistance Mutations Observed[a]	2 (6.1; 100)	2 (2.7; 100)[b]
Any INSTI-R[c]	0	0
Any Primary PI-R[d]	0	0
Any NRTI- R[e]	0	0
M184V/I	0	0
K65R	0	0
Any NNRTI-R[f]	0	0

[a] No change from baseline at primary INSTI-R, PI-R, NRTI-R, or NNRTI-R sites.
[b] Baseline data not available for Cohort 2
[c] Primary integrase strand transfer inhibitor resistance (INSTI-R) mutations are T66I/A/K, E92Q/G, T97A, Y143C/H/R, S147G, Q148H/K/R, and N155H/S. Other INSTI-R mutations are H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K.
[d] Primary protease inhibitor resistance (PI-R) mutations are D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/T/S/L, I84V, N88S, and L90M in PR.
[e] Nucleoside/nucleotide reverse transcriptase inhibitor resistance (NRTI-R) mutations are M41L, E44D, A62V, K65R, D67N, T69D, T69 Insertions; K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, and K219Q/N/E/R in RT.
[f] Non-nucleoside reverse transcriptase inhibitor resistance (NNRTI-R) mutations are V90I, A98G, L100I, K101E/H/P, K103N, V106A/M/I, V108I, E138A, V179D/F/T, Y181C/I/V, Y188L/C/H, G190A/S, P225H, and M230L in RT.

Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Appendix 16.2/Virology Listing 2 and 3

Table 2: GS-US-236-0118: Details of Subjects in the End of Study (RAP Analysis Set)

Subject ID	Treatment Cohort	Time of Virology Analysis	Screening HIV-1 RNA (copies/mL)	HIV-1 subtype	Emergent Mutations				Drug Susceptibility (Fold-Change from WT)			
					INSTI[a]	PI-R[b]	NRTI[c]	NNRTI[d]	EVG	ATV/rtv	FTC	TFV
0986-1010	Cohort 1 STB	Week 8	66100	B	--	--	--	--	1.36	0.50	0.89	0.94
0433-1030	Cohort 1 STB	Week 48	12500	B	--	--	--	--	1.73	0.59	0.85	0.73
3672-2032	Cohort 2 PI/COBI+2NRTIs	Week 60	ND	B	--	--	--	--	ND	1.07	1.21	0.86
1480-2069	Cohort 2 PI/COBI+2NRTIs	Week 48	ND	B	--	--	--	--	ND	1.13	1.07	1.10

--, no mutations developed; ND = no data; /r = ritonavir boosted.

[a] Primary integrase strand transfer inhibitor resistance (INSTI-R) mutations are T66I/A/K, E92Q/G, T97A, Y143C/H/R, S147G, Q148H/K/R, and N155H/S. Other INSTI-R mutations are H51Y, L68I/V, V72A/N/T, L74M, Q95K/R, F121C/Y, A128T, E138A/K, G140A/C/S, P145S, Q146I/K/L/P/R, V151L/A, S153A/F/Y, E157K/Q, G163K/R, E170A, and R263K.

[b] Primary protease inhibitor resistance (PI-R) mutations are D30N, V32I, L33F, M46I/L, I47V/A, G48V, I50L/V, I54M/L, Q58E, T74P, L76V, V82A/F/T/S/L, I84V, N88S, and L90M in PR.

[c] Nucleoside/nucleotide reverse transcriptase inhibitor resistance (NRTI-R) mutations are M41L, E44D, A62V, K65R, D67N, T69D, T69 Insertions; K70E/R, L74V/I, V75I, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, and K219Q/N/E/R in RT.

[d] Non-nucleoside reverse transcriptase inhibitor resistance (NNRTI-R) mutations are V90I, A98G, L100I, K101E/H/P, K103N, V106A/M/I, V108I, E138A, V179D/F/T, Y181C/I/V, Y188L/C/H, G190A/S, P225H, and M230L in RT.

Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Appendix 16.2/Virology Listing 1, 2 and 3

4.1.3.3. Summary of Resistance Development

Resistance development to 1 or more components of STB or to 1 or more components of a PI/COBI + 2NRTIs-containing regimen did not occur in this study. Of the 106 enrolled and treated subjects, 4 subjects (3.8%) were analyzed for resistance development (STB: 2 of 33 subjects, 6.1%; PI/COBI: 2 of 73 subjects, 2.7%), with data available for all 4 subjects.

4.2. Results of Unplanned Analyses

None conducted.

REFERENCES

The following reference list is also provided in Module 2.7.5, and linked from that location to Module 5.4, where applicable.

1. Petropoulos CJ, Parkin NT, Limoli KL, Lie YS, Wrin T, Huang W, et al. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. Antimicrob Agents Chemother 2000;44:920-8.

Janssen Research & Development

Summary of Clinical Efficacy

Darunavir/Cobicistat 800/150 mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

Status: Approved
Date: 16 October 2013
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
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ABBREVIATIONS

3TC	lamivudine
AAG	alpha-1-acid glycoprotein
ABC	abacavir
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ANCOVA	analysis of covariance
ART	antiretroviral therapy
ARV	antiretroviral
ATV	atazanavir
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval tau
AZT	zidovudine
BMI	body mass index
C_{0h}	predose plasma concentration
CI	confidence interval
C_{max}	maximum plasma concentration
COBI	cobicistat
C_{tau}	plasma concentration at the end of the dosing interval tau
ddI	didanosine
DRV	darunavir
EFV	efavirenz
EVG	elvitegravir
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
GAM	generalized additive model
HBsAg	hepatitis B virus surface antigen
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus type 1
IAS	International AIDS Society
ITT	intent-to-treat; ITT population: all subject who received at least 1 dose of study medication
LOCF	last observation carried forward
LPV	lopinavir
M=E	missing equals excluded
M=F	missing equals failure
NA	not applicable
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI	non-nucleoside reverse transcriptase inhibitor
OBR	optimized background regimen
OP	on protocol
PI	protease inhibitor
PR	protease
qd	quaque die, once daily
RAM	resistance-associated mutation
RNA	ribonucleic acid
RT	reverse transcriptase
rtv	low-dose ritonavir
SCE	Summary of Clinical Efficacy
SD	standard deviation
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response
TMC114-C211	Study TMC114-C211, referred to as ARTEMIS
TMC114-C229	Study TMC114-TiDP31-C229, referred to as ODIN
VF	virologic failure

EXECUTIVE SUMMARY

The darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI). Cobicistat has recently been registered to be coadministered as a pharmacoenhancer of DRV and atazanavir (ATV). Comprehensive drug development programs have been conducted for the individual compounds DRV (in combination with low-dose ritonavir [rtv] as pharmacokinetic enhancer) and COBI.

The intended indication of the DRV/COBI 800/150 mg FDC is the same as the approved indication of the DRV/rtv 800/100 mg once daily regimen, ie, for the treatment of HIV-1 infection in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV resistance-associated mutations (RAMs), and with plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L. This is a so called 'substitution indication' of an already approved regimen, ie, the single agents have already been licensed for combined use at the same dose levels as in the FDC.

The comparable exposure to DRV (AUC_{24h}) after DRV/rtv 800/100 mg and after DRV/COBI 800/150 mg coadministered as single agents (study GS-US-216-0115) or as a FDC (study TMC114IFD1001) in healthy subjects allows the extrapolation of efficacy data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects. Bioequivalence of DRV/COBI 800/150 mg coadministered as single agents and the FDC tablet is demonstrated in study TMC114IFD1003, and allows extrapolation of data from studies with DRV and COBI coadministered as single agents to DRV/COBI FDC. A Phase 3b, open-label, single-arm study (GS-US-216-0130) was conducted to generate additional supportive safety data (primary objective) and efficacy and pharmacokinetic data (secondary objectives) on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects.

In support of the FDC tablet of DRV/COBI 800/150 mg once daily for the treatment HIV-1 infection, this Summary of Clinical Efficacy (SCE) includes:

- A brief summary of the virologic response and immunologic benefit of DRV/rtv 800/100 mg once daily as established in the historical studies TMC114-C211 (also referred to as ARTEMIS) in antiretroviral therapy (ART)-naïve HIV-1 infected adult subjects, and TMC114-C229 (also referred to as ODIN) in ART-experienced HIV-1 infected adult subjects with no DRV RAMs.
- A summary of the efficacy of DRV/COBI 800/150 mg once daily coadministered as single agents, as observed in the Week-24 primary analysis of the Phase 3b study GS-US-216-0130.
- A comparison of these DRV/COBI 800/150 mg Week-24 efficacy data with the Week-24 efficacy results in the historical DRV/rtv studies.

Study TMC114-C211 was a randomized controlled, open-label, 192-week, Phase 3 study in ART-naïve HIV-1 infected subjects, comparing DRV/rtv 800/100 mg once daily with LPV/rtv 800/200 daily dose (given once daily or 400/100 mg twice daily). Both arms used a fixed

background regimen consisting of TDF 300 mg once daily and FTC 200 mg once daily. Study TMC114-C211 demonstrated sustained virologic response and immunologic benefit of DRV/rtv 800/100 mg once daily in combination with other ARVs for the treatment of HIV-1 infection in 343 ART-naïve adults. The results of the Week-192 analysis confirmed noninferiority of DRV/rtv 800/100 mg once daily to lopinavir (LPV)/rtv 800/200 daily dose with regard to virologic response (confirmed plasma HIV-1 RNA <50 copies/mL) which was demonstrated at Week 48 and confirmed by the Week-96 and Week-192 analyses. Study TMC114-C229 was a randomized (1:1 ratio), open-label, 48-week, noninferiority study comparing DRV/rtv 800/100 mg once daily versus DRV/rtv 600/100 mg twice daily (both in combination with an individually selected optimized background regimen (OBR) of at least 2 nucleoside/nucleotide reverse transcriptase inhibitors [NRTIs]) in 294 ART-experienced HIV-1 infected subjects with no DRV RAMs. The benefit-risk balance for DRV was judged positive for the treatment of HIV-1 infection in ART-experienced adults with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL, and CD4+ cell count >$100x10^6$ cells/L.

In the open-label, single-arm, multicenter study GS-US-216-0130, 313 HIV-1 infected adult subjects (295 ART-naïve and 18 ART-experienced with no DRV RAMs) were treated with DRV/COBI 800/150 mg once daily coadministered as single agents plus 2 NRTIs. In the Food and Drug Administration (FDA)-defined snapshot analysis, 83.7% of treatment-naïve subjects and 61.1% of treatment-experienced subjects reached virologic response (HIV-1 RNA <50 copies/mL) at Week 24. The results of this efficacy parameter were supported by those of the other virologic parameters (change from baseline in log_{10} viral load, categorical analysis of viral load). The percentage of subjects with plasma HIV-1 RNA <50 copies/mL increased throughout the treatment period and had not reached a plateau by Week 24 (missing equals failure [M=F] analysis). In the time to loss of virologic response (TLOVR) analysis, where a response at 2 consecutive visits is required, 78.6% of treatment-naïve subjects and 44.4% of treatment-experienced subjects were responders at Week 24. At Week 24, the mean change from baseline in CD4+ cell count was +$133x10^6$ cells/L in the treatment-naïve subgroup, and +$88x10^6$ cells/L in the treatment-experienced subgroup (last observation carried forward [LOCF] analysis).

The efficacy results of study GS-US-216-0130 are compared with the results in the DRV/rtv 800/100 mg once daily treatment arm of the Week-24 analyses of 2 studies used as historical controls, TMC114-C211 in ART-naïve HIV-1 infected subjects and TMC114-C229 in treatment-experienced HIV-1 infected subjects with no DRV RAMs. Comparisons between studies are to be interpreted with caution given the inherent limitations associated with the use of historical data as control, and the small sample size of the treatment-experienced subgroup in study GS-US-216-0130. In treatment-naïve subjects, 83.7% of subjects reached virologic response at Week 24 with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130, and 81.6% of subjects with DRV/rtv 800/100 mg once daily in study TMC114-C211 (Week-24 snapshot analysis). In treatment-experienced subjects, 61.1% of subjects reached virologic response at Week 24 with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130, and 70.1% with DRV/rtv 800/100 mg once daily in study TMC114-C229 (Week-24 snapshot analysis).

The long-term efficacy of the DRV/rtv 800/100 mg once daily treatment regimen has been well established in the 192-week study TMC114-C211 and in the 48-week study TMC114-C229. Based on the comparable pharmacokinetics of DRV/rtv 800/100 mg once daily and DRV/COBI 800/150 mg once daily, and on the positive efficacy results of the supportive GS-US-216-0130 study, it is expected that treatment with DRV/COBI 800/150 mg once daily will lead to similar long-term efficacy results as obtained with DRV/rtv 800/100 mg once daily in the intended indication.

The resistance profile of DRV/COBI FDC is driven by DRV. Due to its lack of antiviral activity, COBI does not select any HIV resistance mutations. The clinical resistance profile of DRV/rtv 800/100 mg once daily has been established in the ART-naïve study TMC114-C211 and ART-experienced TMC114-C229 study. As was observed in the DRV/rtv 800/100 mg once daily treatment arms of TMC114-C211 and TMC114-C229, resistance development to DRV or other PIs, and to the background NRTIs was rare in study GS-US-216-0130, confirming the high genetic barrier to resistance of DRV, irrespective if coadministered with rtv or COBI. Of the 313 treated subjects, 10 met the criteria for postbaseline resistance analysis (5 treatment-naïve and 5 treatment-experienced). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One treatment-experienced subject with poor pill bottle returns, indicative of poor adherence, had developed a DRV RAM at position I84 as a mixture with wild-type (I84I/V). No phenotypic resistance to DRV or other PIs was observed. No subjects developed any other primary or secondary PI RAMs. No subjects developed an NRTI RAM (or phenotypic resistance) to their concomitant NRTI regimen.

In conclusion, the established antiviral and immunologic efficacy of DRV/rtv 800/100 mg once daily for the treatment of HIV-1 infection, the established primary pharmacodynamic properties of COBI 150 mg as a pharmacokinetic enhancer of DRV, the antiviral and immunologic efficacy of DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130, and the bioequivalence of the FDC tablet with DRV/COBI 800/150 mg coadministered as single agents, support the use of the FDC tablet once daily with food in the intended indication.

1. BACKGROUND AND OVERVIEW OF CLINICAL EFFICACY

1.1. Background

The DRV/COBI FDC tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved HIV-1 PI. Cobicistat has recently been registered to be coadministered as a pharmacokinetic enhancer of DRV. Comprehensive drug development study programs have been conducted for the individual compounds DRV (in combination with rtv as pharmacokinetic enhancer) and COBI. The development program of the FDC tablet is primarily based on these development programs.

Darunavir

Treatment with DRV/rtv 800/100 mg once daily in combination with other antiretroviral (ARV) treatments has been shown to provide substantial and durable efficacy in HIV-1 treatment, with a high genetic barrier to the development of resistance, helping preserve future therapeutic options.[6] The efficacy of this dose regimen is demonstrated by the 192-week study TMC114-C211 in 343 ART-naïve HIV-1 infected adult subjects, and by the 48-week study TMC114-C229 in 294 ART-experienced HIV-1 infected adult subjects without DRV RAMs[*].[1,6] In ART-naïve subjects, DRV/rtv 800/100 mg once daily was compared to a daily dose of LPV/rtv 800/200 mg, both treatments coadministered with a fixed background regimen of emtricitabine/tenofovir disoproxil fumarate (FTC/TDF) over a treatment period of 192 weeks. In the ART-experienced subjects, DRV/rtv 800/100 mg once daily was compared to DRV/rtv 600/100 mg twice daily, both in combination with an OBR of ≥2 NRTIs over a treatment period of 48 weeks. In both studies, noninferiority in virologic response was shown versus the comparator group (refer to Module 5.3.5.1/TMC114-C211-W192-CRR and Module 5.3.5.1/TMC114-C229-W48-CRR).

Cobicistat

Cobicistat is a new chemical entity developed by Gilead Sciences Inc. (Gilead) and recently licenced for use as a pharmacokinetic enhancer to increase systemic exposure of coadministered ARVs metabolized by cytochrome P450-3A enzyme, including the PIs DRV, ATV, and the integrase strand transfer inhibitor elvitegravir (EVG).[1] Cobicistat has no detectable antiviral activity against HIV-1. A single tablet regimen (STR) containing EVG, COBI, emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) or STRIBILD was FDA-approved on 27 August 2012, and approved in the European Union on 28 May 2013, for treatment of HIV-1 infection in adults aged 18 years and over who are ART-naïve, or who are infected with HIV-1 without known mutations associated with resistance to any of the 3 ARV agents in STRIBILD. The approval is based on efficacy and safety data up to 48 weeks in 1,408 subjects, including 701 treated with the STR EVG/COBI/FTC/TDF regimen.[8]

Cobicistat has been shown to provide DRV exposures comparable to those obtained with rtv. In the proof-of-concept study for the pharmacoenhancing effect of COBI 150 mg on DRV

[*] DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V[5]

(GS-US-216-0115), the pharmacokinetics and relative bioavailability of DRV/COBI 800/150 mg once daily, coadministered as single agents for 10 days, were compared with those of DRV/rtv 800/100 mg once daily, in 33 healthy subjects (refer to Module 5.3.1.2/ GS-US-216-0115-CSR). The 90% confidence intervals (CIs) of the pharmacokinetic parameters of DRV (area under the plasma concentration-time curve over the dosing interval [AUC_{tau}], maximum plasma concentration [C_{max}], and predose plasma concentration [C_{0h}]) were within 80.00-125.00% when coadministered with COBI 150 mg once daily compared to when DRV is coadministered with rtv 100 mg once daily. The values of DRV plasma concentration observed at the end of the dosing interval (C_{tau}) were lower with DRV/COBI compared to DRV/rtv (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2).

DRV/COBI FDC

The intended indication of the DRV/COBI FDC 800/150 mg is the same as the approved indication at the same dose level of the single agents, ie, for the treatment of HIV-1 infection in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100x10^6$ cells/L (substitution indication). The development of a FDC tablet of DRV with its pharmacokinetic enhancer in a once-daily regimen offers the option to simplify DRV-containing ARV regimens by reducing pill burden.

The clinical program for DRV/COBI FDC is primarily based on the comprehensive development programs of the 2 individual compounds and on the pharmacokinetic bridging clinical program. As the DRV/COBI FDC 800/150 mg is indicated as a 'substitution indication' of an already approved regimen, no comparative efficacy study was conducted. The DRV/COBI FDC development program in adult subjects consists of 3 studies:

(1) A Phase 1 study TMC114IFD1001, investigating the relative oral bioavailability of 2 FDC formulations (G003 and G004) of DRV/COBI 800/150 mg once daily and that of DRV/rtv 800/100 mg once daily coadministered as single agents under fed conditions (refer to Module 5.3.1.1/TMC114IFD1001-CSR).

(2) A Phase 1 study TMC114IFD1003, assessing the bioequivalence of DRV when coadministered with COBI either as the FDC (formulation G006) or the single agents under fed and fasted conditions (refer to Module 5.3.1.2/TMC114IFD1003-CSR).

(3) An ongoing Phase 3b, open-label, single-arm study GS-US-216-0130 assessing safety (primary objective), efficacy and pharmacokinetic parameters (secondary objectives) in HIV-1 infected adult subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents for at least 48 weeks (refer to Module 5.3.5.2/ GS-US-216-0130-W24-CSR).

In the Phase 1 study TMC114IFD1001, the FDC formulations G003 and G004 were investigated; the G003 and G004 formulation had the same concentration of active ingredients but there were minor differences in excipient combinations. Formulation G006, which matches the core tablet composition of formulation G004 and differs only in the color of the film coat, was used in bioequivalence study TMC114IFD1003 and has been chosen as the proposed

commercial formulation (refer to the Summary of Biopharmaceutical Studies and Associated Analytical Methods in Module 2.7.1).

The comparable exposures to DRV (AUC_{24h}) with DRV/rtv 800/100 mg and DRV/COBI 800/150 mg coadministered as single agents (study GS-US-216-0115) or as FDC (study TMC114IFD1001) in healthy subjects allow the extrapolation of efficacy data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects. The DRV C_{tau} was lower with DRV/COBI relative to DRV/rtv. Based on pharmacokinetic/pharmacodynamic analyses on the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229, the lower DRV C_{tau} is not expected to be clinically relevant (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2/Section 3.4). The bioequivalence of DRV/COBI 800/150 mg coadministered as single agents and the FDC is further demonstrated in study TMC114IFD1003. The Phase 3b, open-label, single-arm study GS-US-216-0130 was conducted to generate additional supportive safety data (primary objective) and efficacy and pharmacokinetic data (secondary objectives) on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects.

1.2. Overview

A summary of the results of individual clinical studies is presented in Section 2. In Section 2.1 of this SCE, a summary is given of the studies establishing the efficacy of DRV/rtv 800/100 mg once daily treatment in ART-naïve and ART-experienced HIV-1 infected adult subjects.

A brief statement on the antiviral profile of COBI 150 mg is given in Section 2.2.

In Section 2.3, the results of the Week-24 efficacy analysis of the Phase 3b study GS-US-216-0130 are presented in support of the FDC tablet of DRV/COBI 800/150 mg once daily for the treatment of HIV-1 infected ART-naïve adult subjects and HIV-1 infected ART-experienced adult subjects with no DRV RAMs. In this open-label, single-arm, multicenter, Phase 3b study, 313 HIV-1 infected adult subjects (295 ART-naïve and 18 ART-experienced) were treated with DRV/COBI 800/150 mg once daily coadministered as single agents plus 2 fully active NRTIs. The efficacy results of the Week-24 analysis include data up to the cut-off date for the primary analysis, [redacted], when the last subject had his/her Week-24 visit or discontinued prematurely.

In Section 3, a historical comparison between the Week-24 results of study GS-US-216-0130 and those of the Phase 3 studies that investigated DRV/rtv 800/100 mg once daily in combination with other ARVs in treatment-naïve HIV-1 infected adults (TMC114-C211) and in treatment-experienced adults with no DRV RAMs (TMC114-C229) is presented.

All the clinical information relevant to dosing is summarized and analyzed in Section 4.

Information regarding persistence of efficacy is summarized in Section 5.

2. SUMMARY OF RESULTS OF INDIVIDUAL STUDIES

2.1. Summary of Efficacy Results of Studies With DRV/rtv Once Daily

The evidence of efficacy of DRV/rtv 800/100 mg once daily is based on the analyses of study TMC114-C211 in 343 ART-naïve HIV-1 infected adult subjects, and study TMC114-C229 in 294 ART-experienced HIV-1 infected adult subjects.

2.1.1. Study TMC114-C211

Study TMC114-C211 was a randomized controlled, open-label, 192-week, Phase 3 study in ART-naïve HIV-1 infected subjects with a viral load ≥5,000 HIV-1 RNA copies/mL at screening, comparing DRV/rtv 800/100 mg once daily with LPV/rtv 800/200 daily dose (given once daily or 400/100 mg twice daily). Both arms used a fixed background regimen consisting of TDF 300 mg once daily and FTC 200 mg once daily. Lopinavir/rtv was chosen as comparator as it has proven efficacy and safety in treatment-naïve HIV-1 infected subjects. The primary objective of the study was to demonstrate noninferiority in virologic response (defined as a confirmed plasma HIV-1 RNA <50 copies/mL, intent-to-treat [ITT] population, TLOVR) of DRV/rtv versus LPV/rtv treatment at Week 48, when administered in combination with a fixed TDF/FTC background regimen. Analyses were also performed at Week 96 (when all subjects had reached 96 weeks or discontinued earlier) and at Week 192, in support of the long-term use of DRV/rtv versus LPV/rtv in treatment-naïve HIV-1 infected subjects. For further information on study design, refer to Module 5.3.5.1/TMC114-C211-W192-CRR.

At baseline, the median time since diagnosis of HIV-1 infection was 1.1 years, the mean $\log_{10}$ viral load for all subjects was 4.85 $\log_{10}$ copies/mL; less than 20% of subjects had a baseline viral load <20,000 copies/mL and approximately one third had a baseline viral load ≥100,000 copies/mL. The median baseline CD4+ cell count for all subjects was 225×10^6 cells/L; approximately 60% of subjects had a baseline CD4+ cell count ≥200×10^6 cells/L and 15.5% had a baseline CD4+ cell count <100×10^6 cells/L.

The main results of the Week-48 and Week-96 efficacy analyses of study TMC114-C211 are summarized in Table 1.

Table 1: Efficacy Summary – TMC114-C211 Week-48 and Week-96 Analyses

Parameter	Week 48[a]			Week 96[b]		
	DRV/rtv 800/100 mg once daily N=343	LPV/rtv 800/200 mg daily dose N=346	Treatment Difference (95% CI of Difference)[d]	DRV/rtv 800/100 mg once daily N=343	LPV/rtv 800/200 mg daily dose N=346	Treatment Difference (95% CI of Difference)[d]
Virologic Response						
HIV-1 RNA <50 Copies/mL[c] All Subjects,% (n/N)	83.7% (287/343)	78.3% (271/346)	5.3% (-0.5; 11.2)	79.0% (271/343)	70.8% (245/346)	8.2% (1.7; 14.7)
Baseline HIV-1 RNA <100,000 Copies/mL[c]	85.8% (194/226)	84.5% (191/226)	1.3% (-5.2; 7.9)	80.5% (182/226)	75.2% (170/226)	5.3% (-2.3; 13.0)
Baseline HIV-1 RNA ≥100,000 Copies/mL[c]	79.5% (93/117)	66.7% (80/120)	12.8% (1.6; 24.1)	76.1% (89/117)	62.5% (75/120)	13.6% (1.9; 25.3)
Baseline CD4+ Cell Count <200 Cells/L	79.4% (112/141)	70.3% (104/148)	9.2% (-0.8; 19.2)	78.7% (111/141)	64.9% (96/148)	13.9% (3.5; 24.2)
Baseline CD4+ Cell Count ≥200 Cells/L	86.6% (175/202)	84.3% (167/198)	2.3% (-4.6; 9.2)	79.2% (160/202)	75.3% (149/198)	4.0% (-4.3; 12.2)
Immunologic Change						
Median (Range) Change in CD4+ Cell Count, x10^6 Cells/L[e]	+137 (-182; 725)	+141 (95; 684)		+171 (-278; 921)	+188 (-179; 782)	

N=total number of subjects; n=number of observations.
[a] Data based on analyses at Week 48.
[b] Data based on analyses at Week 96.
[c] Imputations according to the TLOVR algorithm.
[d] Based on normal approximation to the difference in % response.
[e] Noncompleter is failure imputation: subjects who discontinued prematurely are imputed with a change equal to 0.
Source: Module 5.3.5.1/TMC114-C211-W48-CRR and TMC114-C211-W96-CRR.

In the Week-48 analysis, noninferiority in virologic response, defined as the percentage of subjects with plasma HIV-1 RNA <50 copies/mL, of DRV/rtv 800/100 mg once daily was demonstrated (at the predefined 12% noninferiority margin) for both ITT and On Protocol (OP) populations. These results were confirmed in the Week-96 analysis, and sustained up to 192 weeks of treatment of study TMC114-C211. Virologic response at Week 192 was achieved in 68.8% of subjects in the DRV/rtv group and 57.2% in the LPV/rtv group (ITT, TLOVR; refer to Module 5.3.5.1/TMC114-C211-W192-CRR). The lower limit of the 95% CI of the difference between the treatment groups was >-12% (ie, delta, the maximum allowable difference). The estimated difference [95% CI] between the treatment groups was 11.6% [4.4; 18.8] and was statistically significant, thereby demonstrating noninferiority (p-value <0.001). The lower limit of the 95% CI for the difference in virologic response was above 0, and the secondary objective to test for superiority of DRV/rtv over LPV/rtv showed a statistically significant difference between the treatments, thus superiority of DRV/rtv over LPV/rtv in this patient population could be concluded (p=0.002). The results were robust, as shown by different sensitivity analyses performed. Of the DRV/rtv subjects with a confirmed virologic response of <50 copies/mL (undetectable) at Week 48, 81.3% remained undetectable at Week 192 versus 68.5% with LPV/rtv. When comparing the Week-96 and Week-192 results, 87.7% of DRV/rtv subjects and 80.0% of LPV/rtv subjects remained undetectable at Week 192 if they were undetectable at Week 96. Immunologic response was similar in the DRV/rtv and LPV/rtv treatment groups. The

mean change from baseline in CD4+ cell count at Week 192 was 266 and 269x10^6 cells/L in the DRV/rtv and LPV/rtv group.

In the Week-192 analysis, there were more virologic failures (VF) in the LPV/rtv group (20.5%) than in the DRV/rtv group (16.0% using the TLOVR non-VF censored algorithm). Of the virologic failures with paired baseline/endpoint genotypes, 4 DRV/rtv subjects and 9 LPV/rtv subjects with developing PI RAMS at endpoint were identified. None of the developing PI RAMs were primary (major) PI mutations and all virologic failures remained susceptible to DRV, LPV, amprenavir, ATV, indinavir, saquinavir and tipranavir after treatment.

At Week 48, no apparent relationship was observed between the DRV pharmacokinetic parameters (AUC_{24h} and C_{0h}) and change from baseline in $\log_{10}$ viral load or virologic response (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2).

In conclusion, DRV/rtv 800/100 mg once daily was shown to be noninferior to LPV/rtv 800/200 mg daily dose at Week 48, Week 96 and Week 192, with respect to the percentage of subjects showing virologic response (plasma HIV-1 RNA <50 copies/mL, ITT, TLOVR). The efficacy of DRV/rtv 800/100 mg once daily in terms of the virologic and immunologic response is well sustained for at least 192 weeks in treatment-naïve HIV-1 infected adult subjects.

2.1.2. Study TMC114-C229

TMC114-C229 was a Phase 3, randomized, open-label, 48-week study comparing DRV/rtv 800/100 mg once daily versus DRV/rtv 600/100 mg twice daily in ART-experienced HIV-1 infected subjects with screening genotype resistance testing showing no DRV RAMs and with a viral load >1,000 HIV-1 RNA copies/mL and a CD4+ cell count >50x10^6 cells/L at screening. Both arms used an OBR of at least 2 NRTIs. Since the study was not blinded, several sensitivity analyses were performed. For further information on study design, refer to Module 5.3.5.1/ TMC114-C229-W48-CRR.

At baseline, the mean duration of HIV-1 infection was 8.5 years; the mean log viral load was 4.16 $\log_{10}$ copies/mL; 86.7% of the subjects had a viral load <100,000 copies/mL. The median CD4+ cell count was 228x10^6 cells/L; 57.5% of subjects had a baseline CD4+ cell count ≥200x10^6/L and 16.7% had a baseline CD4+ <100x10^6 cells/L.

At Week 48, virologic response, defined as the percentage of subjects with plasma HIV-1 RNA <50 copies/mL, with DRV/rtv 800/100 mg once daily was demonstrated to be noninferior (at the predefined 12% noninferiority margin) compared to DRV/rtv 600/100 mg twice daily for the ITT and OP populations of treatment-experienced subjects carrying 0 DRV RAMs (Table 2). The results of the primary efficacy parameter were supported by the secondary virologic parameters (viral load <400 copies/mL, change in $\log_{10}$ viral load from baseline, time to virologic response, and time to loss of virologic response), as well as the immunologic response (change in CD4+ cell count from baseline).

Table 2: Efficacy Summary – TMC114-C229 Week-48 Analysis

Parameter	DRV/rtv 800/100 mg Once Daily N=294	DRV/rtv 600/100 mg Twice Daily N=296	Treatment Difference (95% CI of Difference)[b]
Virologic Response[a], % (n/N)			
HIV-1 RNA <50 Copies/mL	72.1% (212/294)	70.9% (210/296)	1.2% (-6.1; 8.5)
All Subjects,% (n/N)			
Baseline HIV-1 RNA			
<100,000 Copies/mL	77.6% (198/255)	73.2% (194/265)	4.4% (-3.0; 11.9)
≥100,000 Copies/mL	35.9% (14/39)	51.6% (16/31)	-15.7% (-39.2; 7.7)
Baseline CD4+ Cell Count			
≥100 x10^6 Cells/L	75.1% (184/245)	72.5% (187/258)	2.6% (-5.1; 10.3)
<100 x10^6 Cells/L	57.1% (28/49)	60.5% (23/38)	-3.4% (-24.5; 17.8)
HIV-1 Clade			
Type B	70.4% (126/179)	64.3% (128/199)	6.1% (-3.4; 15.6)
Type AE	90.5% (38/42)	91.2% (31/34)	-0.7% (-14.0, 12.6)
Type C	72.7% (32/44)	78.8% (26/33)	-6.1% (-2.6, 13.7)
Other[c]	55.2% (16/29)	83.3% (25/30)	-28.2% (-51.0, -5.3)
Immunologic Change			
Median Change in CD4+ Cell Count, x10^6 Cells/L[e]	+108	+112	-5 (-25; 16)[d]

N=total number of subjects; n=number of observations.
[a] Imputations according to the TLOVR algorithm.
[b] Based on a normal approximation of the difference in % response.
[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX.
[d] Difference in means.
[e] Last Observation Carried Forward imputation.
Source: Module 5.3.5.1/TMC114-C229-W48-CRR.

The virologic failure rate (HIV-1 RNA ≥50 copies/mL TLOVR non-VF-censored) was similar in the DRV/rtv once daily group (65/294, 22.1%) and DRV/rtv twice daily group (54/296, 18.2%). Development of resistance was infrequent among virologic failures in both treatment groups. Of all virologic failures with matching baseline/endpoint genotypes, only 1 subject (DRV/rtv once daily) developed primary (major) PI mutations, including DRV RAMs, and lost susceptibility to DRV. The proportion of virologic failure subjects who retained susceptibility to all currently available PIs was 96.6% for the DRV/rtv once daily group and 100% for the DRV/rtv twice daily group. In the DRV/rtv once daily group, 7/59 (11.9%) virologic failures, with available phenotypes at baseline and endpoint, lost susceptibility to an NRTI in the background regimen, compared to 4/41 (9.8%) in the DRV/rtv twice daily group.

At Week 48, no relevant relationship was observed between DRV C_{0h} and the decrease from baseline in $\log_{10}$ viral load in either treatment group. In the DRV/rtv once daily group, the decrease from baseline in $\log_{10}$ viral load tended to be smaller in subjects with higher AUC_{24h} values, while no relevant relationship was observed between AUC_{24h} and the change in $\log_{10}$ viral load in the DRV/rtv twice daily group (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2).

In conclusion, the virologic response with DRV/rtv 800/100 mg once daily was demonstrated to be noninferior to the response with DRV/rtv 600/100 mg twice daily in the Week-48 analysis of study TMC114-C229. The results show robust virologic and immunologic benefits of DRV/rtv

800/100 mg once daily in combination with an OBR of ≥2 NRTIs in treatment-experienced, HIV-1 infected adult subjects with 0 DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100x10^6 cells/L.

2.2. Cobicistat 150 mg

Cobicistat is devoid of antiviral activity in vitro (refer to the Summary of Virology in Module 2.7.2).

The Gilead proof-of-concept study (GS-US-216-0115) and the pharmacokinetic bridging studies TMC114-IFD1001 and TMC114IFD1003 provide evidence of the primary pharmacodynamic properties of COBI as a pharmacokinetic enhancer of DRV (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2).

2.3. Summary of Efficacy Results With DRV/COBI Once Daily

2.3.1. Study Design of Study GS-US-216-0130

Study GS-US-216-0130 is a Phase 3b open-label, single-arm, multicenter study in HIV-1 infected, ART-naïve adult subjects or ART-experienced adult subjects with no DRV RAMs. The primary objective is to evaluate the safety and tolerability of DRV/COBI 800/150 mg plus 2 NRTIs in the studied population through 24 weeks of treatment. The secondary objectives are to assess the safety and tolerability of the regimen through 48 weeks of treatment, to assess the efficacy of the regimen as determined by a virologic response of HIV-1 RNA <50 copies/mL at Weeks 24 and 48 of treatment, and to assess the change from baseline in CD4+ cell count at Weeks 24 and 48. After 48 weeks of treatment, subjects were given the option to participate in an open-label rollover extension of the study to receive COBI, DRV, and investigator-selected NRTIs, and attend study visits every 12 weeks until COBI becomes commercially available, or until Gilead elects to terminate development of COBI. Subjects who completed the Week-48 visit and did not wish to participate in the rollover part of the study were required to complete a follow-up visit 30 days after the Week-48 visit.

A total of 314 subjects were enrolled, and 313 subjects received at least 1 dose of study medication DRV/COBI 800/150 mg once daily coadministered as single agents. Of these 313 subjects, 295 (94.2%) were ART-naïve and 18 (5.8%) were ART-experienced. Subjects were considered treatment-naïve if they had never received treatment with an approved or investigational ARV drug. Subjects were considered treatment-experienced if they had been on a stable ARV regimen for at least 12 weeks prior to screening. For further details on inclusion and exclusion criteria, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 7.3.

Subjects were scheduled to receive DRV/COBI 800/150 mg once daily coadministered as single agents plus 2 fully active investigator-selected NRTIs selected after resistance testing at screening. All treatments were to be administered orally under fed conditions for a treatment period of at least 48 weeks. In subjects with the M184V/I reverse transcriptase mutation present at screening, FTC or lamivudine (3TC) could be included as a third (not-fully active) NRTI for the purpose of maintaining the M184V mutation.

The primary Week-24 analysis (safety, efficacy, and resistance analyses) was performed when all subjects had been treated for 24 weeks or discontinued earlier (cut-off date [redacted]). The subject's medical condition, any adverse events (AEs), laboratory evaluations for efficacy and safety, and study medication adherence were monitored and documented at screening, at baseline, and at all subsequent study visits. A blood sample for population pharmacokinetics of DRV was taken at every visit from Week 2 onwards. For more details on the timing of treatment and assessments, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 7.5.1. A pharmacokinetic substudy was performed in a subset of subjects at selected study sites; the substudy included intensive pharmacokinetic sampling. The data of this substudy were used to develop the population pharmacokinetic modeling of COBI-boosted DRV (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2).

Efficacy assessments included plasma HIV-1 RNA and CD4+ cell count. The primary efficacy endpoint was the proportion of subjects who reached HIV-1 RNA <50 copies/mL at Week 24 using the snapshot analysis. Other efficacy analyses were the proportion of subjects who reached HIV-1 RNA <50 copies/mL at Week 24 using other imputation methods, the change in viral load over time, and the change from baseline in CD4+ cell count at Week 24 and over time.

The HIV-1 protease/reverse transcriptase (PR/RT) genotype was analyzed at screening. The development of genotypic and phenotypic resistance was assessed: baseline and postbaseline HIV-1 PR/RT genotype/phenotype was obtained for subjects showing virologic failure during treatment, ie, subjects with suboptimal virologic response or virologic rebound, as defined in the protocol, and subjects with HIV-1 RNA ≥400 copies/mL at study discontinuation after Week 8 who did not meet virologic failure criteria (refer to Module 5.3.5.2/GS-US-216-0130-CTP-v2).

Subjects could be withdrawn from the study for lack of efficacy and had to be withdrawn if they experienced an unacceptable toxicity.

2.3.2. Study Population

2.3.2.1. Subject Disposition

Of the 397 subjects screened, 314 were enrolled in the study at 56 sites in the United States of America. The ITT population comprised 313 subjects who received at least 1 dose of both study medications DRV and COBI. Of the 313 subjects, 295 were ART-naïve and 18 were ART-experienced (Table 3). All the data presented in this document are data on the ITT population unless otherwise specified.

In the treatment-naïve subgroup, 36 subjects (12.2%) discontinued study medication prior to the Week-24 analysis cut-off date (Table 3). The most common reasons (>2% of subjects) for premature discontinuation of study medication were AE(s) (15 subjects, 5.1%), lost to follow-up (9 subjects, 3.1%), and subject noncompliance (6 subjects, 2.0%).

In the treatment-experienced subgroup, 3 of the 18 subjects (16.7%) discontinued study medication prior to the Week-24 analysis cut-off date: 2 subjects (11.1%) were lost to follow-up, and 1 subject (5.6%) withdrew consent.

Table 3: Premature Discontinuation of Study Medication – GS-US-216-0130 Week-24 Analysis

Premature Discontinuation of Study Medication, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Subjects Prematurely Discontinuing Study Medication	36 (12.2)	3 (16.7)	39 (12.5)
Reasons for Discontinuing Study Medication			
Adverse Event	15 (5.1)	0	15 (4.8)
Investigator's Discretion	1 (0.3)	0	1 (0.3)
Lost to Follow-up	9 (3.1)	2 (11.1)	11 (3.5)
Protocol Violation	1 (0.3)	0	1 (0.3)
Subject Noncompliance	6 (2.0)	0	6 (1.9)
Withdrew Consent	4 (1.4)	1 (5.6)	5 (1.6)

N=total number of subjects; n=number of observations.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-2.

2.3.2.2. Extent of Exposure

The overall median (range) duration of exposure to study medication was 31.4 weeks (0.1 to 42.4 weeks), with a median exposure of 31.9 weeks in the treatment-naïve subjects and a median exposure of 26.6 weeks in treatment-experienced subjects. A total of 281 subjects (89.8%) had received the study medication for at least 24 weeks prior to the cut-off date for the Week-24 analysis, 89.8% of the treatment-naïve subjects and 88.9% of the treatment-experienced subjects (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.1).

2.3.2.3. Treatment Adherence

Adherence to DRV and COBI was measured by pill count, ie, the ratio of the number of pills taken (dispensed minus returned) over the number of prescribed pills for the period the subject was in the study.

Up to Week 24, adherence to the prescribed DRV/COBI 800/150 mg was 99.2% in treatment-naïve subjects and 97.3% in treatment-experienced subjects (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 8.4). An adherence rate of ≥95% up to the Week-24 visit was recorded in 94.6% of the treatment-naïve subjects and in 77.8% of the treatment-experienced subjects.

2.3.2.4. Demographic and Baseline Disease Characteristics

Demographic data and baseline disease characteristics are summarized in Table 4 and Table 5, respectively.

The majority of subjects in the treatment-naïve subgroup were male (90.2%), their median age was 34 years (range 18 to 72 years); most were white (59.7%) or black (34.2%), and their ethnicity was most often not Hispanic or Latino (78.3%). The median baseline body mass index (BMI) was 25.9 kg/m^2 (range 16.5 to 45.3 kg/m^2).

In the treatment-experienced subgroup, 13 of 18 subjects (72.2%) were male, the median age was 48 years (range 22 to 69 years); they were white (61.1%) or black (38.9%), and most were not Hispanic or Latino (77.8%). The median BMI was 24.3 kg/m^2 (range 18.0 to 43.0 kg/m^2).

Table 4: Demographic Data – GS-US-216-0130 Week-24 Analysis

Parameter	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Age (Years)			
Median (Range)	34 (18 - 72)	48 (22 - 69)	35 (18 - 72)
Sex, n (%)			
Male	266 (90.2)	13 (72.2)	279 (89.1)
Female	29 (9.8)	5 (27.8)	34 (10.9)
Race, n (%)			
White	176 (59.7)	11 (61.1)	187 (59.7)
Black or African Heritage	101 (34.2)	7 (38.9)	108 (34.5)
American Indian or Alaska Native	4 (1.4)	0	4 (1.3)
Asian	4 (1.4)	0	4 (1.3)
Native Hawaiian or Pacific Islander	2 (0.7)	0	2 (0.6)
Other	8 (2.7)	0	8 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	64 (21.7)	4 (22.2)	68 (21.7)
Not Hispanic or Latino	231 (78.3)	14 (77.8)	245 (78.3)
Height (cm)			
Median (Range)	175.3 (149.9 - 210.8)	175.3 (152.4 - 185.4)	175.3 (149.9 - 210.8)
BMI (kg/m^2)			
Median (Range)	25.9 (16.5 - 45.3)	24.3 (18.0 - 43.0)	25.7 (16.5 - 45.3)

N=total number of subjects; n=number of observations.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-4.

In the treatment-naïve subgroup, the mean baseline $\log_{10}$ HIV-1 RNA value was 4.8 copies/mL, the mean baseline CD4+ cell count was $378x10^6$ cells/L, and the mean baseline CD4+ cell percentage was 22.6%. The CD4+ cell count was $\leq 200x10^6$ cells/L in 47 subjects (15.9%). The majority of subjects (81.7%) had asymptomatic HIV-1 infection, 26 subjects (8.8%) had symptomatic HIV-1 infection, and 28 (9.5%) were diagnosed with acquired immunodeficiency syndrome (AIDS). At screening, 5 subjects (1.7%) were hepatitis B virus surface antigen (HBsAg) positive, and 7 (2.4%) were hepatitis C virus (HCV) seropositive.

In the treatment-experienced subgroup, the mean baseline $\log_{10}$ HIV-1 RNA value was 4.8 copies/mL, the mean baseline CD4+ cell count was $198x10^6$ cells/L, and the mean CD4+ cell percentage was 11.9%. The CD4+ cell count was $\leq 200x10^6$ cells/L in 12 subjects (66.7%). The median number of years since HIV diagnosis was 8.5 years (range 2 to 24 years). Ten subjects (55.6%) had asymptomatic HIV-1 infection, 2 subjects (11.1%) had symptomatic HIV-1 infection, and 6 (33.3%) were diagnosed with AIDS. At screening, none of the subjects were HBsAg positive, and 1 subject (5.6%) was HCV seropositive.

Table 5: Disease Characteristics – GS-US-216-0130 Week-24 Analysis

Disease Characteristics	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Baseline HIV-1 RNA, log_{10} Copies/mL			
Mean (SD)	4.8 (0.76)	4.8 (1.04)	4.8 (0.78)
Median (Range)	4.8 (2.6 – 7.0)	5.0 (2.7 – 6.8)	4.8 (2.6 – 7.0)
Baseline HIV-1 RNA Category, n (%)			
≤100,000 Copies/mL	173 (58.6)	9 (50.0)	182 (58.1)
>100,000 Copies/mL	122 (41.4)	9 (50.0)	131 (41.9)
Baseline CD4+ Cell Count, $x10^6$ Cells/L			
Mean (SD)	378.2 (199.94)	197.8 (214.30)	367.8 (204.79)
Median (Range)	370.0 (6 – 1473)	107.0 (5 – 643)	361.0 (5 – 1473)
Baseline CD4+ Cell Count Category, n (%)			
≤$50x10^6$ Cells/L	17 (5.8)	5 (27.8)	22 (7.0)
51 to $200x10^6$ Cells/L	30 (10.2)	7 (38.9)	37 (11.8)
201 to $350x10^6$ Cells/L	85 (28.8)	2 (11.1)	87 (27.8)
351 to $500x10^6$ Cells/L	94 (31.9)	1 (5.6)	95 (30.4)
>$500x10^6$ Cells/L	69 (23.4)	3 (16.7)	72 (23.0)
CD4+ Cell %			
Mean (SD)	22.6 (9.99)	11.9 (10.25)	21.9 (10.29)
Median (Range)	23.8 (0.8 – 47.4)	7.8 (0.8 – 30.6)	23.2 (0.8 – 47.4)
Years Since HIV Diagnosis			
Mean (SD)	NA	10.8 (7.13)	NA
Median (Range)	NA	8.5 (2.0 - 24.0)	NA
HIV Disease Status, n (%)			
Asymptomatic	241 (81.7)	10 (55.6)	251 (80.2)
Symptomatic	26 (8.8)	2 (11.1)	28 (8.9)
AIDS	28 (9.5)	6 (33.3)	34 (10.9)
HBsAg Status, n (%)			
Positive	5 (1.7)	0	5 (1.6)
Negative	289 (98.0)	18 (100.0)	307 (98.1)
Undetermined	1 (0.3)	0	1 (0.3)
HCV Antibody Status, n (%)			
Positive	7 (2.4)	1 (5.6)	8 (2.6)
Negative	288 (97.6)	17 (94.4)	305 (97.4)

N=total number of subjects; n=number of observations; NA=not applicable; SD=standard deviation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-5.

2.3.2.5. Baseline Genotypic Resistance

The PR/RT resistance mutations used for this analysis are defined according to the definitions of the International AIDS Society (IAS USA November 2011)[4] as well as any additional PR/RT resistance mutations reported by the GenoSure™ MG assay algorithm (refer to Module 5.3.5.2/ GS-US-216-0130-SAP-W24-Virology). The baseline resistance mutations are shown in Table 6. According to the GenoSure MG assay, most study subjects (96.2%) had subtype B HIV-1 virus.

As expected in the treatment-naïve subjects, only 9 subjects (3.1%) had 1 primary PI RAM, with the M46I/L and Q58E mutation found in 3 and 4 subjects, respectively. One or more secondary PI RAMs were found in 95.9% of subjects, reflecting the strong polymorphic nature of these mutations. One or more non-nucleoside reverse transcriptase inhibitor (NNRTI) RAMs were found in 25.1% of subjects, and 12.2% of subjects had NRTI RAMs. The most prevalent RAM found at baseline was the K103N and/or S NNRTI RAM mutation (11.2%), indicating transmitted resistance (K103N is a major NNRTI RAM with a potential to reduce nevirapine and

efavirenz [EFV] susceptibility). All other NNRTI RAMs were present at a frequency <5% (E138A/G/R was observed in 4.1% of the treatment-naïve baseline samples). Two subjects in the treatment-naïve subgroup also had the M184V mutation, also suggesting some transmitted resistance (M184V is a major NRTI RAM with a potential to reduce 3TC and FTC susceptibility). NRTI RAM M41L was observed in 2% of the treatment-naïve baseline samples.

In the treatment-experienced subjects, 1 subject (5.6%) had 2 primary PI-associated mutations (M46I/L and I54V), the other 17 subjects had none. One or more secondary PI-associated mutations were found in 17 of the 18 subjects (94.4%). Nearly three-quarters (72.2%) of the subjects had 1 or more NNRTI RAMs, K103N being the most prevalent (44.4%). The M184V and/or I mutation was the most prevalent NRTI RAM (33.3%, 6 of 18 subjects); one or more NRTI RAMs were found in 38.9% of subjects. The presence of these mutations is often correlated with prior use of ARV agents. For further details refer to Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Table 9-3.

As a result of the screening criteria, no enrolled subjects had HIV-1 harboring any of the DRV RAMs, and all were fully active to DRV as well as to the 2 NRTIs in their background regimen based on genotypic assessment.

Table 6: HIV-1 Subtype and Baseline Mutations – GS-US-216-0130 Week-24 Analysis

Subtype of HIV-1 Infection, n (%) Mutations[a] at Baseline, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
B HIV-1 Subtype	**284 (96.3)**	**17 (94.4)**	**301 (96.2)**
Non-B HIV-1 Subtype	**11 (3.7)**	**1 (5.6)**	**12 (3.8)**
Number of Subjects With ≥1 RAM			
DRV RAMs	0	0	0
Primary PI RAMs	9 (3.1)	1 (5.6)	10 (3.2)
Secondary PI RAMs	283 (95.9)	17 (94.4)	300 (95.8)
NNRTI RAMs	74 (25.1)	13 (72.2)	87 (27.8)
NRTI RAMs	36 (12.2)	7 (38.9)	43 (13.7)
Number of RAMs, Average[b]			
Primary PI RAMs	1.0	2.0	1.1
Secondary PI RAMs	3.2	3.6	3.2
NNRTI RAMs	1.1	1.7	1.2
NRTI RAMs	1.1	1.3	1.2

N=total number of subjects; n=number of subjects with observation.
[a] IAS-USA 2011 list[4] and additional PR/RT resistance mutations reported by the Genosure MG assay algorithm.
[b] Average calculated based on the number of subjects with at least 1 RAM at baseline.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-3.

2.3.2.6. Prior and Concomitant Medication

All except 2 subjects, 1 who was treatment-naïve and 1 who was treatment-experienced, received TDF-based ARV medication during the study (Table 7). The most commonly administered background regimen was FTC/TDF: 292 treatment-naïve subjects (99.0%), and 11 treatment-experienced subjects (61.1%). One treatment-experienced subject had a switch in background therapy during the study (discontinuation of zidovudine [AZT] from a background regimen of AZT+FTC/TDF), refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 8.3.

For prior ARV medications of the treatment-experienced subjects, please refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Listing 3.4. For non-ARV therapy administered during the study, please refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 3.4.1.

Table 7: Antiretroviral Background Regimens – GS-US-216-0130 Week-24 Analysis

ARV Medication During the Study n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
TDF-based Regimen	294 (99.7)	17 (94.4)	311 (99.4)
Other Regimens	1 (0.3)	1 (5.6)	2 (0.6)
FTC/TDF	292 (99.0)	11 (61.1)	303 (96.8)
AZT+FTC/TDF	0	4 (22.2)	4 (1.3)
ABC+TDF	2 (0.7)	1 (5.6)	3 (1.0)
ABC+FTC/TDF	0	1 (5.6)	1 (0.3)
ABC/3TC	1 (0.3)	0	1 (0.3)
ddI+FTC	0	1 (5.6)	1 (0.3)

N=total number of subjects; n=number of observations; ABC=abacavir; ddI=didanosine.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 3.1.2.

2.3.3. Efficacy Results

2.3.3.1. Primary Efficacy Parameter

The main efficacy parameter was virologic response defined as the percentage of subjects with plasma viral load <50 copies/mL in the FDA-defined snapshot analysis.

In the treatment-naïve subgroup, virologic response was reached at Week 24 by 247 subjects (83.7%). There were 29 subjects (9.8%) with virologic failure at Week 24, and 19 subjects (6.4%) had no virologic data in the Week-24 window (Table 8). The reasons for virologic failure and the absence of virologic data in the Week-24 window are presented in Table 8. All but 1 of the 17 subjects with virologic failure due to HIV-1 RNA #50 copies/mL had a baseline viral load >100,000 copies/mL. Fourteen of the 17 subjects with virologic failure were still in the study at Week 36. Ten of these 14 had HIV-1 RNA levels available at the cut-off date for this Week-24 analysis; 6 of these 10 had a HIV-1 RNA level <50 copies/mL (Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Listing 4.1).

Of the 18 treatment-experienced subjects, virologic response was reached at Week 24 by 11 subjects (61.1%). There were 7 subjects (38.9%) with virologic failure at Week 24, including 2 subjects (11.1%) that had discontinued with their last available HIV-1 RNA ≥50 copies/mL (Table 8 and Figure 1).

Table 8: Proportion of Subjects With HIV-1 RNA Levels <50 Copies/mL at Week 24 (Snapshot Analysis) – GS-US-216-0130 Week-24 Analysis

HIV-1 RNA Category, Number of Subjects, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Virologic Response at Week 24, 95% CIs[a]	**247 (83.7)**	**11 (61.1)**	**258 (82.4)**
HIV-1 RNA <50 Copies/mL	79.0 to 87.8	35.7 to 82.7	77.8 to 86.5
Virologic Failure at Week 24	**29 (9.8)**	**7 (38.9)**	**36 (11.5)**
HIV-1 RNA ≥50 Copies/mL	17 (5.8)	5 (27.8)	22 (7.0)
Discontinued due to Lack of Efficacy	0	0	0
Discontinued due to Other Reasons and Last Available HIV-1 RNA ≥50 Copies/mL	12 (4.1)	2 (11.1)	14 (4.5)
No Virologic Data in Week 24 Window[b]	**19 (6.4)**	**0**	**19 (6.1)**
Discontinued due to AE/Death	14 (4.7)	0	14 (4.5)
Discontinued due to Other Reasons and Last Available HIV-1 RNA <50 Copies/mL	3 (1.0)	0	3 (1.0)
Missing Data During Window but on Study Medication	2 (0.7)	0	2 (0.6)

N=total number of subjects; n=number of observations.
[a] 95% CI is the 2-sided exact 95% CI for binomial proportions.
[b] Window 20-30 weeks.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-1.

2.3.3.2. Other Efficacy Parameters

2.3.3.2.1. Virologic Response

Four additional virological response parameters were analyzed: confirmed virologic response (<50 copies/mL, TLOVR), virologic response (<50 copies/mL) with M=F, a missing equals excluded (M=E), and an LOCF method (Table 9). These sensitivity analyses demonstrated that the results for virologic response defined as plasma viral load <50 copies/mL were generally consistent across the different imputation methods used (Table 9).

Table 9: Sensitivity Analyses for the Proportion of Subjects With HIV-1 RNA Levels <50 Copies/mL at Week 24 – GS-US-216-0130 Week-24 Analysis

Analysis/Imputation Method Number (%) of Responders HIV-1 RNA Levels <50 Copies/mL	Treatment-naïve		Treatment-experienced		All Subjects	
TLOVR	N=295	232 (78.6)	N=18	8 (44.4)	N=313	240 (76.7)
Missing=Excluded	N=267	250 (93.6)	N=16	11 (68.8)	N=283	261 (92.2)
Missing=Failure	N=295	250 (84.7)	N=18	11 (61.1)	N=313	261 (83.4)
Last Observation Carried Forward	N=282	253 (89.7)	N=17	11 (64.7)	N=299	264 (88.3)

N=total number of subjects, n=number of responders.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-2, Tables 4.4.1.1, 4.4.1.2, 4.4.1.3, and 4.4.1.4.

In the TLOVR analysis (Table 10), 78.6% of treatment-naïve subjects reached and maintained confirmed HIV-1 RNA !50 copies/mL through Week 24 and were considered responders; 10.2% of subjects were classified as virologic failures (9.5% due to no viral suppression through Week 24, 0.7% due to virologic rebound, and no discontinuations due to lack of efficacy or death), 5.1% of subjects discontinued due to AE(s), and 6.1% due to other reasons. Fifteen subjects (5.1%) were defined as nonresponders due to drug discontinuation due to AE(s),

and 18 subjects (6.1%) were nonresponders due to drug discontinuation due to other reasons. No subjects were considered nonresponders as a result of drug discontinuation due to lack of efficacy or death.

In the treatment-experienced subgroup, 8 subjects (44.4%) reached and maintained confirmed HIV-1 RNA !50 copies/mL through Week 24 and were considered responders (TLOVR). Seven subjects (38.9%) were classified as virologic failure. The only reason for virologic failure was no viral suppression through Week 24. Three subjects (16.7%) discontinued due to other reasons (lost to follow-up, subject withdrawal, protocol noncompliance, protocol violation and other reasons).

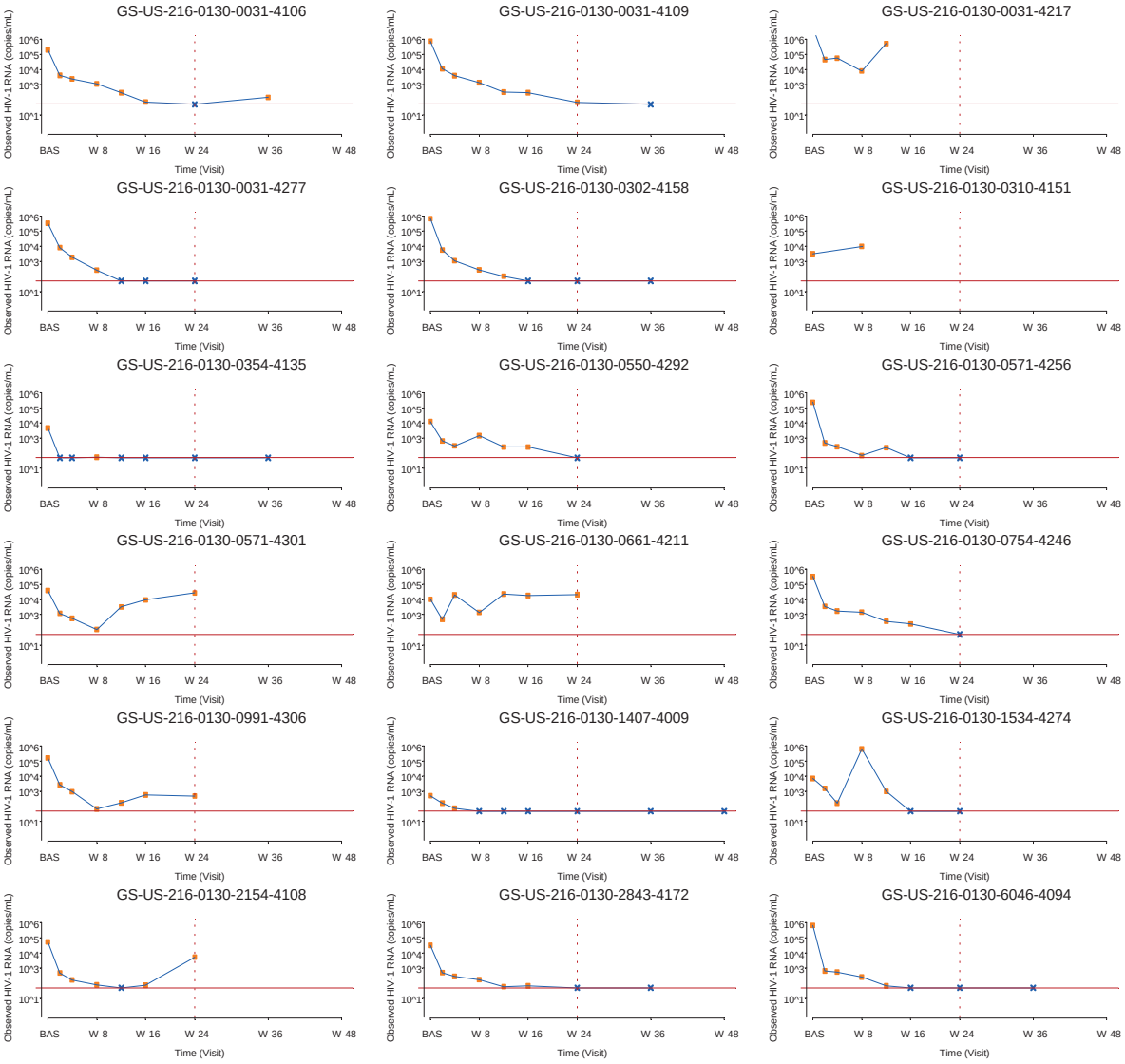
The viral load over time of each of the 18 treatment-experienced subjects is presented individually in Figure 1.

Table 10: Virologic Outcome (TLOVR Analysis) and Immunologic Outcome at Week 24 – GS-US-216-0130 Week-24 Analysis

HIV-1 RNA Category, Number of Subjects, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Responder[a]	**232 (78.6)**	**8 (44.4)**	**240 (76.7)**
95% CI	73.5 to 83.2	21.5 to 69.2	71.6% to 81.2
Virologic Failure[b]	**30 (10.2)**	**7 (38.9)**	**37 (11.8)**
Rebound	2 (0.7)	0	2 (0.6)
Never Suppressed Through Week 24	28 (9.5)	7 (38.9)	35 (11.2)
Discontinued due to Lack of Efficacy	0	0	0
Drug Discontinuation due to AE(s)	**15 (5.1)**	**0**	**15 (4.8)**
Drug Discontinuation due to Other Reasons[c]	**18 (6.1)**	**3 (16.7)**	**21 (6.7)**
Mean (SD) HIV-1 RNA Change From Baseline, $\log_{10}$ Copies/mL	**-3.00 (0.788)**	**-2.56 (1.459)**	**-2.98 (0.842)**
Mean (SD) CD4+ Cell Count Change From Baseline[d]**,** $x10^6$ Cells/L	**+133 (135.4)**	**+88 (155.4)**	**+131 (136.8)**

[a] A responder reached and maintained confirmed HIV-1 RNA <50 copies/mL through Week 24.
[b] Virologic failure includes confirmed rebound and failure to reach confirmed HIV-1 RNA <50 copies/mL through Week 24.
[c] Other reasons include lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.
[d] LOCF imputation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-2.

Figure 1: Individual Viral Load Over Time of the 18 Treatment-experienced Subjects - GS-US-216-0130 Week-24 Analysis



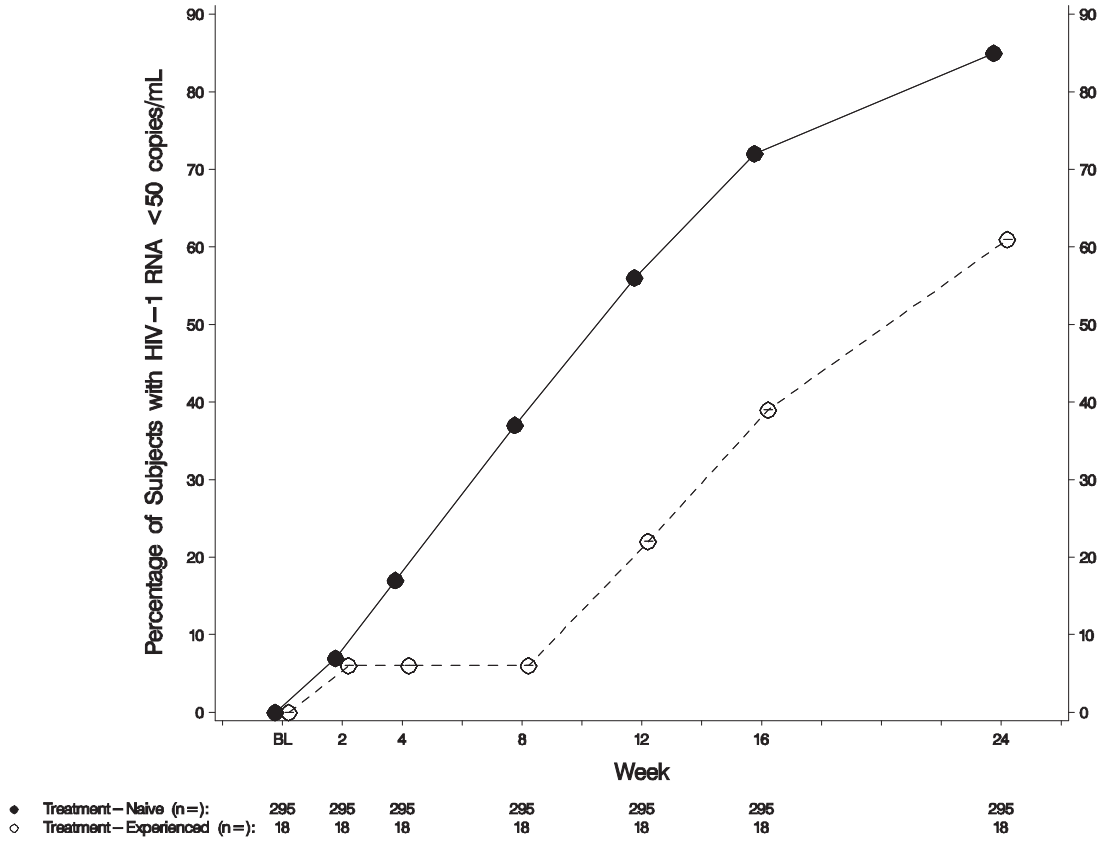
X-axis: Time (visit) with dotted vertical line marking Week 24;
Y-axis: HIV-1 RNA (copies/mL) with horizontal line marking HIV-1 RNA=50 copies/mL.
Square marks above the horizontal line: HIV-1 RNA ≥50 copies/mL; x-marks on the horizontal line: HIV-1 RNA <50 copies/mL.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Listing 4.1.

The percentage of responders over time (M=F) is presented in Figure 2. The percentage of subjects with HIV-1 RNA levels <50 copies/mL continued to increase with continued treatment and had not reached a plateau by Week 24.

In the treatment-naïve subgroup, the percentage of subjects with HIV-1 RNA levels <50 copies/mL at Week 24 was 93.6% using the M=E method, 89.7% using LOCF analysis, and 84.7% using the M=F method.

In the treatment-experienced subgroup, the percentage of subjects with HIV-1 RNA levels <50 copies/mL at Week 24 was 68.8% using the M=E method, 64.7% using LOCF analysis, and 61.1% using the M=F method.

Figure 2: Percentage of Subjects With Plasma HIV-1 RNA <50 Copies/mL Over Time (M=F) - GS-US-216-0130 Week-24 Analysis

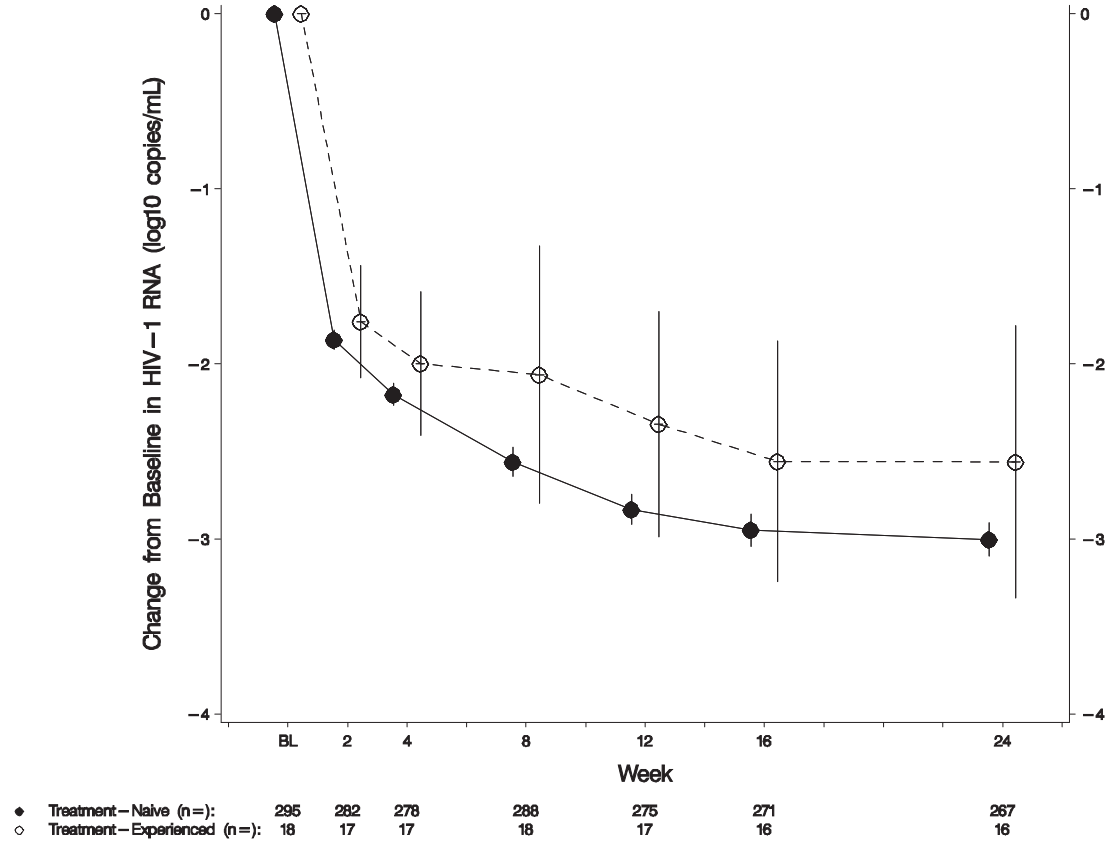


Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Figure 9-1.

The change from baseline in plasma HIV-1 RNA levels is presented in Figure 3. In the treatment-naïve subgroup, the mean (standard deviation [SD]) baseline $\log_{10}$ HIV-1 RNA level was 4.8 (0.76) copies/mL. HIV-1 RNA levels decreased during DRV/COBI treatment, with a steep drop in the first 2 weeks of treatment, followed by a continued gradual decrease up to Week 24. At Week 24, the mean (SD) change from baseline in $\log_{10}$ HIV-1 RNA was –3.0 (0.79) copies/mL.

In the treatment-experienced subgroup, the mean (SD) baseline $\log_{10}$ HIV-1 RNA level was 4.8 (1.04) copies/mL. During DRV/COBI treatment, HIV-1 RNA levels followed a similar trend as observed in the treatment-naïve subgroup. At Week 24, the mean (SD) change from baseline in $\log_{10}$ HIV-1 RNA was –2.6 (1.46) copies/mL.

Figure 3: Mean (95% CIs) Change From Baseline in HIV-1 RNA (log_{10} Copies/mL) Over Time (M=E) - GS-US-216-0130 Week-24 Analysis



Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Figure 9-2.

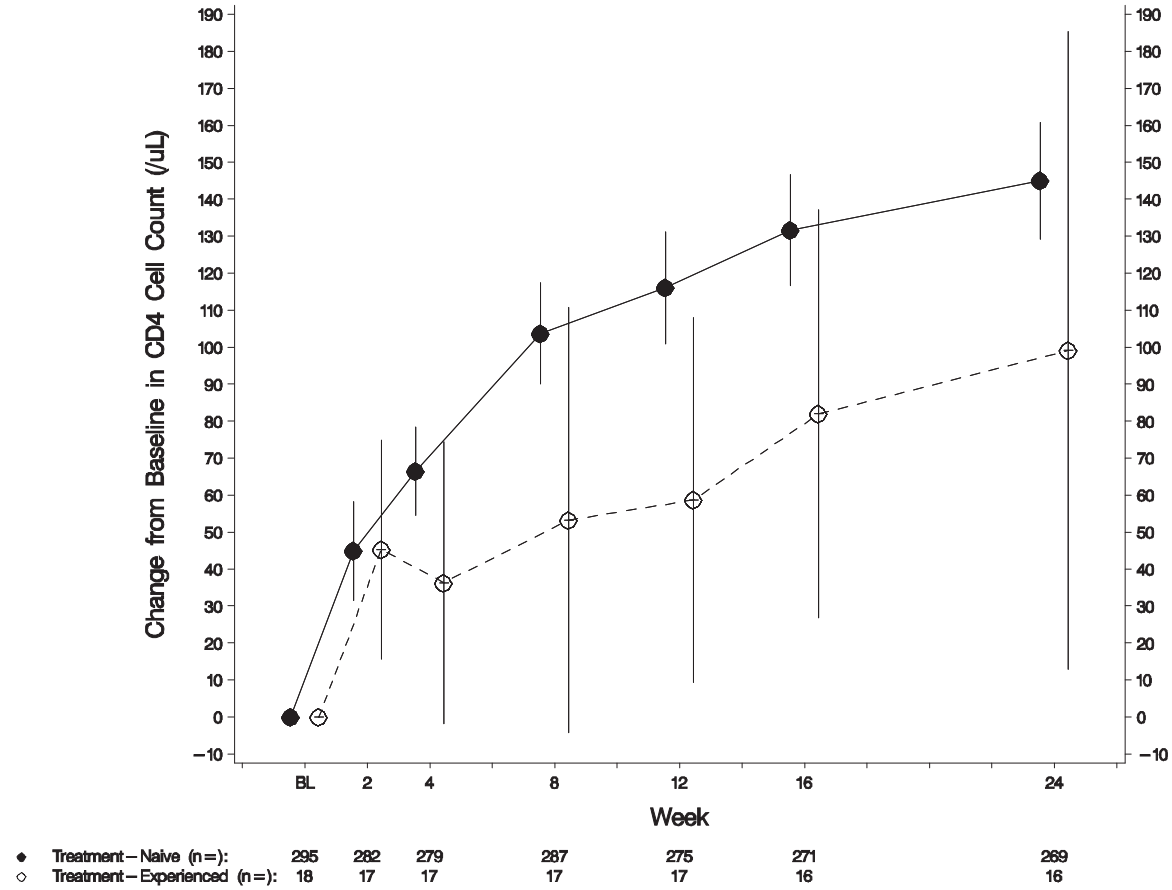
2.3.3.2.2. Immunologic Response

A graphical presentation of the mean change from baseline in CD4+ cell count over time is provided in Figure 4.

In the treatment-naïve subgroup, the mean (SD) baseline CD4+ cell count was 378 (199.9)x10^6 cells/L. The CD4+ cell counts increased steadily throughout treatment. At Week 24, the mean (SD) change from baseline in CD4+ cell count was +145 (131.6)x10^6 cells/L (observed data), and +133 (135.4)x10^6 cells/L (LOCF).

In the treatment-experienced subgroup, the mean (SD) CD4+ cell count at baseline was 198 (214.3) x10^6 cells/L. At Week 24, the mean change from baseline in CD4+ cell count was +99 (161.9) x10^6 cells/L (observed data), and +88 (155.4) x10^6 cells/L (LOCF).

Figure 4: Mean (95% CIs) Change From Baseline in CD4+ Cell Count Over Time (M=E) – GS-US-216-0130 Week-24 Analysis



Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Figure 9-3.

2.3.3.3. Conclusions on Efficacy Data of Study GS-US-216-0130

In the FDA-defined snapshot analysis, 83.7% treatment-naïve subjects and 61.1% of treatment-experienced subjects reached virologic response at Week 24. The percentage of subjects reaching HIV-1 RNA levels <50 copies/mL increased throughout the treatment period and had not reached a plateau by Week 24 (M=F analysis). These efficacy results were supported by those of the other virologic parameters (change from baseline in $\log_{10}$ viral load, categorical analysis of viral load). In the TLOVR analysis, where a response at 2 consecutive visits is required, 78.6% of treatment-naïve subjects and 44.4% of treatment-experienced subjects were responders. At Week 24, the mean increase from baseline in CD4+ cell count was $133x10^6$ cells/L in the treatment-naïve subgroup, and $88x10^6$ cells/L in the treatment-experienced subgroup (LOCF). The small sample size of the treatment-experienced subgroup (n=18) limits the relevance of these subgroup analyses.

2.3.4. Resistance Determinations of Study GS-US-216-0130

The baseline PR/RT genotypic analysis is described in Section 2.3.2.5.

2.3.4.1. Influence of Baseline Genotype on Response

The effect of 5 baseline genotype characteristics on treatment response was explored: HIV-1 subtype, presence of NNRTI resistance mutations, presence of the K103N and/or S mutation, presence of NRTI resistance mutations, and presence of the M184V and/or I mutation. In both the treatment-naïve and treatment-experienced subjects, none of these 5 characteristics had an impact on treatment response (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/ Section 9.2.2).

2.3.4.2. Development of Resistance

Of the 313 treated subjects, 10 met the criteria for postbaseline PR/RT genotype and phenotype analysis (see Section 2.2), 5 treatment-naïve subjects (1 subject with suboptimal virologic response, 2 subjects with virologic rebound, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit), and 5 treatment-experienced subjects (1 subject with suboptimal virologic response, 2 subjects with virologic rebound, and 2 discontinuations with HIV-1 RNA ≥400 copies/mL at last visit). Nine of these 10 subjects were virologic failures at Week 24 according to the snapshot analysis (7 subjects with HIV-1 RNA ≥50 copies/mL and 2 subjects discontinued study medication due to other reasons and their last available HIV-1 RNA was ≥50 copies/mL). One subject had confirmed virologic rebound at Week 12 followed by confirmed virologic suppression <50 copies/mL.

For the details of the genotypic and phenotypic analyses, refer to Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Table 9-5. Of the 10 subjects who met the criteria for postbaseline PR/RT genotype and phenotype analysis, 1 treatment-experienced subject developed a resistance mutation in PR as a mixture with wild-type (DRV RAM I84I/V); no phenotypic resistance to DRV or other PIs was observed. The subject had poor pill bottle returns, indicative of poor adherence. Another treatment-experienced subject developed 2 RT mutations: NRTI RAM L74I/L and NRTI RAM P225H/P, which are known to be associated with resistance to didanosine (ddI) and abacavir (ABC), and EFV, respectively. The subject's background regimen consisted of FTC+TDF+AZT, and these mutations were not associated with the development of phenotypic resistance to the NRTIs in the background regimen. The phenotypic resistance to FTC that was observed in this subject was associated with the presence of the M184V/I at baseline and postbaseline. No other instances of resistance development were observed.

2.3.4.3. Resistance Conclusions

Baseline genotype characteristics were not seen to have an impact on treatment response in the treatment-naïve or treatment-experienced subjects with no DRV RAMS at screening.

Resistance development to DRV or other PIs, and to the background NRTIs was rare in this study. Of the 313 treated subjects, 10 met the criteria for postbaseline resistance analysis (5 treatment-naïve and 5 treatment-experienced). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One treatment-experienced subject with poor pill bottle returns indicative of poor adherence had developed a DRV RAM at position I84 as a mixture with wild-type (I84I/V). No phenotypic resistance to DRV or other PIs was observed.

No subjects developed any other primary or secondary PI RAMs. No subjects developed an NRTI RAM (or phenotypic resistance) to their concomitant NRTI regimen.

2.3.5. Pharmacokinetics/Pharmacodynamics

There was no clinically relevant relationship between the exposure to DRV when coadministered with COBI and the decrease in viral load at Week 24 (from baseline) or virologic response (HIV-1 RNA <50 copies/mL) at Week 24 in treatment-naïve HIV-1 infected subjects. The sample size of treatment-experienced HIV-1-infected subjects is too small to reliably evaluate the relationship between DRV exposure and efficacy in this subgroup (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2).

3. COMPARISON AND ANALYSES OF RESULTS ACROSS STUDIES

Given that the efficacy and resistance profiles of DRV have been established in the DRV/rtv development program, and the Phase 1 studies GS-US-216-0115 and TMC114IFD1001 demonstrated comparable pharmacokinetics of DRV/rtv and DRV/COBI, a comparison of the results of study GS-US-216-0130 with historical controls is presented in this section. Comparisons between studies are to be interpreted with caution given the inherent limitations associated with the use of historical data as control. The small sample size of the treatment-experienced subgroup further limits the interpretation of this historical comparison in this subgroup.

The Week-24 results of the 295 treatment-naïve HIV-1 infected adults in the GS-US-216-0130 study were compared with the Week-24 results of the treatment-naïve HIV-1 infected adults treated with DRV/rtv 800/100 mg once daily of the Phase 3b study TMC114-C211. The Week-24 results of the 18 treatment-experienced HIV-1 infected adults with no DRV RAMs in the GS-US-216-0130 study were compared with the Week-24 results of the DRV/rtv 800/100 mg once daily treatment group of the Phase 3b study TMC114-C229, which included adult treatment-experienced subjects with no DRV RAMs at baseline. For the analysis methods used in these comparisons, refer to Module 5.3.5.2/GS-US-216-0130-SAP-W24-Addendum.

The sex, age, main baseline disease characteristics, and baseline resistance data of the treatment-naïve and treatment-experienced subgroups in GS-US-216-0130, the DRV/rtv 800/100 mg once daily arm in study TMC114-C211, and the DRV/rtv 800/100 mg once daily arm in study TMC114-C229 are summarized in Table 11.

The treatment-naïve subject populations of TMC114-C211 and GS-US-216-0130 are similar with respect to demographic data and baseline disease and resistance characteristics. The treatment-experienced subjects of study GS-US-216-0130 are somewhat older (median age was 48 years, while it was 40 years in TMC114-C229), and the median number of years (range) since HIV diagnosis was 8.5 years (range 2 to 24 years) in the GS-US-216-0130 study, while it was 1.1 years (range 0 to 22 years) in study TMC114-C229. The treatment-experienced subjects in study GS-US-216-0130 also have a slightly higher baseline viral load (mean $\log_{10}$ viral load was 4.8 copies/mL) than those in study TMC114-C229 (mean $\log_{10}$ viral load 4.2 copies/mL), and a lower CD4+ cell count (mean cell count 198×10^6 cells/L) than those in study TMC114-C229

(mean cell count 250x10^6 cells/L). The percentage of subjects with HIV-1 RNA ≥100,000 copies/mL was 50.0% in study GS-US-216-0130, and 13.3% in study TMC114-C229.

Table 11: Main Demographics, Disease Characteristics, and Baseline Resistance – Week-24 Analyses of GS-US-216-0130, DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229

	Treatment–naïve Subjects		Treatment–experienced Subjects	
Demographic Parameter or Disease Characteristics	**TMC114-C211 DRV/rtv 800/100 mg qd N=343**	**GS-US-216-0130 DRV/COBI Single Agents 800/150 mg qd N=295**	**TMC114-C229 DRV/rtv 800/100 mg qd N=294**	**GS-US-216-0130 DRV/COBI Single Agents 800/150 mg qd N=18**
Sex, n (%)				
Female	104 (30.3)	29 (9.8)	115 (39.1)	5 (27.8)
Male	239 (69.7)	266 (90.2)	179 (60.9)	13 (72.2)
Age (Years)				
Median (Range)	34 (18 - 70)	34 (18 - 72)	40 (18 - 70)	48 (22 – 69)
Log_{10} Viral Load (Copies/mL)				
Mean (SD)	4.9 (0.64)	4.8 (0.76)	4.2 (0.81)	4.8 (1.04)
Median (Range)	4.9 (2.9 - 6.8)	4.8 (2.6 - 7.0)	4.2 (1.7 - 6.4)	5.0 (2.7 - 6.8)
Viral Load (Copies/mL), n (%)				
≤100,000 [a]	226 (65.9)	173 (58.6)	255 (86.7)	9 (50.0)
>100,000 [a]	117 (34.1)	122 (41.4)	39 (13.3)	9 (50.0)
CD4+ Cell Count (x10^6 Cells/L)				
Mean (SD)	245 (148.8)	378 (199.9)	250 (164.4)	198 (214.3)
Median (Range)	228 (4 - 750)	370 (6 – 1473)	219 (24 - 1306)	107 (5 – 643)
Number of Mutations [b]				
Median (Range)				
DRV RAMs	0 (0 - 2)	0 (0 - 0)	0 (0 - 2)	0 (0 – 0)
Primary PI mutations	0 (0 - 3)	0 (0 – 1)	0 (0 - 5)	0 (0 – 2)
PI RAMs [c]	3 (0 - 11)	3 (0 – 9)	3 (0 - 13)	3.5 (0 - 7)
NRTI RAMs	0 (0 - 5)	0 (0 – 3)	1 (0 - 7)	0 (0 – 2)
NNRTI RAMs	0 (0 – 3)	0 (0 – 3)	2 (0 - 5)	1 (0 – 3)

N=total number of subjects; n=number of observations; qd=once daily.

[a] The categories are <100.000 and ≥100.000 copies/mL in TMC114-C211 and TMC114-C229, they are ≤100,000 and >100,000 copies/mL in GS-US-216-0130.

[b] For GS-US-216-0130: IAS-USA 2011 list[4] and additional PR/RT resistance mutations reported by the Genosure MG assay algorithm; For TMC114-C211: IAS-USA 2006 list;[3] For TMC114-C229: IAS-USA 2008 list.[2]

[c] Includes all primary and secondary mutations.

Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-4, Table 8-5 and Table 9-3;
Module 5.3.5.1/TMC114-C211-W48-CRR/Table 6, Table 7, Table 9 and Display GEN.11;
Module 5.3.5.1/TMC114-C229-W48-CRR/Table 7, Table 8, Table 11 and Display GEN.11.

The efficacy results at Week 24 of the GS-US-216-0130, TMC114-C211, and TMC114-C229 studies are summarized in Table 12. In treatment-naïve subjects, the efficacy of treatment with DRV/rtv 800/100 mg once daily in study TMC114-C211 is similar to that seen with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130. The percentage of subjects reaching virologic response at Week 24 (snapshot analysis) was 81.6% in the historical study TMC114-C211, and 83.7% in the treatment-naïve subgroup of study GS-US-216-0130. The change from baseline in log_{10} viral load at Week 24 was -3.11 copies/mL with DRV/rtv 800/100 mg once daily, and -3.00 copies/mL with DRV/COBI 800/150 mg once

daily. The change from baseline in CD4+ cell count at Week 24 was +142x10^6 cells/L and +145x10^6 cells/L with DRV/rtv and DRV/COBI, respectively.

In treatment-experienced subjects (n=18), the percentage of subjects reaching virologic response at Week 24 was 70.1% in the historical study TMC114-C229, and 61.1% in the treatment-experienced subgroup of study GS-US-216-0130. The decrease in log_{10} viral load at Week 24 was -2.09 copies/mL with DRV/rtv 800/100 mg once daily, and -2.56 copies/mL with DRV/COBI 800/150 mg once daily. The change from baseline in CD4+ cell count was +83x10^6 cells/L and +99x10^6 cells/L with DRV/rtv and DRV/COBI, respectively.

Resistance development to DRV or other PIs, and to the background NRTIs was rare in the Week-24 analysis of study GS US-216-0130. These low levels of resistance development were comparable to those observed in the DRV/rtv 800/100 mg once daily arm of TMC114-C211 and TMC114-C229, confirming the clinical resistance profile of DRV/rtv 800/100 mg once daily in ART-naïve subjects and ART-experienced subjects with no DRV RAMs and the high genetic barrier of DRV whether boosted with COBI or rtv (refer to the Summary of Virology in Module 2.7.2).

Table 12: Virologic Responses and Change From Baseline in CD4+ Cell Count – Week-24 Analyses of Studies GS-US-216-0130, DRV/rtv 800/100 mg once daily arm of TMC114-C211 and TMC114-C229

	Treatment–naïve Subjects		Treatment–experienced Subjects	
Efficacy Parameter	**TMC114-C211 DRV/rtv 800/100 mg qd N=343**	**GS-US-216-0130 DRV/COBI Single Agents 800/150 mg qd N=295**	**TMC114-C229 DRV/rtv 800/100 mg qd N=294**	**GS-US-216-0130 DRV/COBI Single Agents 800/150 mg qd N=18**
Virologic Response (Snapshot)				
HIV-1 RNA <50 Copies/mL	280 (81.6)	247 (83.7)	206 (70.1)	11 (61.1)
Virologic Response (TLOVR)				
HIV-1 RNA <50 Copies/mL	273 (79.6)	232 (78.6)	201 (68.4)	8 (44.4)
Log_{10} Viral Load (Copies/mL) [a]				
Mean (SD) Change From Baseline	-3.11 (0.67)	-3.00 (0.79)	-2.09 (1.08)	-2.56 (1.46)
CD4+ Cell Count (x10^6 cells/L) [a]				
Mean (SD) Change From Baseline	+142 (113)	+145 (131.6)	+83 (123)	+99 (161.9)

N=total number of subjects, qd=once daily.
[a] Observed case analysis at Week 24.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-1, Table 9-2;.
For data of study TMC114-C211 and TMC114-C229: data on file.

4. ANALYSIS OF CLINICAL INFORMATION RELEVANT TO DOSING RECOMMENDATIONS

The individual substances of the DRV/COBI 800/150 mg FDC have already been licensed for combined use at the same dose levels as in the combination. The intended indication of the FDC is the same as the approved indication of the DRV/rtv 800/100 mg once daily regimen, ie, for the treatment of HIV-1 infection in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV resistance-associated mutations (RAMs), and with plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count ≥100x10^6 cells/L. This is also called 'substitution indication' of an already approved regimen.

The efficacy of treatment with DRV/rtv 800/100 mg once daily in combination with other ARVs is demonstrated by the 192-week study TMC114-C211 in 343 ART-naïve HIV-1 infected adult subjects, and by the 48-week study TMC114-C229 in 294 ART-experienced HIV-1 infected adult subjects without DRV RAMs. In both studies, noninferiority in virologic response was shown versus the comparator group.

The efficacy of COBI 150 mg as a pharmacokinetic enhancer of DRV is provided by the Gilead-sponsored proof-of-concept Phase 1 study GS-US-216-0115. In this study, the pharmacokinetics and relative bioavailability of DRV/COBI 800/150 mg once daily coadministered as single agents were compared with those of DRV/rtv 800/100 mg once daily administered for 10 days in 33 healthy subjects. The results demonstrate that the DRV pharmacokinetic parameters AUC_{tau}, C_{max} and C_{0h} are similar following repeated dosing of DRV 800 mg once daily under fed conditions, whether coadministered with 100 mg rtv once daily or 150 mg COBI once daily. The results of this study are supported by those of the bioavailability study TMC114IFD1001, designed to compare 2 FDC test formulations of DRV/COBI 800/150 mg once daily with DRV/rtv 800/100 mg once daily in healthy subjects following repeated dosing under fed conditions. The results of these 2 studies allow the bridging of the pharmacokinetic data of the proposed DRV/COBI FDC with the existing DRV/rtv data. The DRV C_{tau} was lower with DRV/COBI relative to DRV/rtv. Based on pharmacokinetic/pharmacodynamic analyses on the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229, the lower DRV C_{tau} is not expected to be clinically relevant.

The demonstration of comparable DRV exposures after DRV/rtv 800/100 mg and DRV/COBI 800/150 mg allows the extrapolation of efficacy data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected ART-naïve adult subjects and ART-experienced adult subjects with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L. The efficacy results of the Week-24 analysis of study GS-US-216-0130 further support the use of DRV/COBI 800/150 mg once daily in this population.

In the Week-24 FDA-defined snapshot analysis of study GS-US-216-0130, 83.7% of treatment-naïve subjects and 61.1% of treatment-experienced subjects reached virologic response. These results were supported by the other efficacy parameters (other imputation methods, change from baseline in $\log_{10}$ viral load, categorical analysis of viral load) and the immunologic response (change in CD4+ cell count). Historical comparisons showed that, in treatment-naïve subjects, the percentage of subjects reaching virologic response at Week 24 with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130 (83.7%, Week-24 snapshot analysis) is similar to that seen with DRV/rtv 800/100 mg once daily in study TMC114-C211 (81.6%, Week-24 snapshot analysis). The small sample size of the treatment-experienced subgroup in study GS-US-216-0130 (n=18) limits the interpretation of any historical comparison for this subgroup.

The clinical resistance profile of DRV/rtv 800/100 mg once daily has been established in studies TMC114-C211 and TMC114-C229 in ART-naïve and ART-experienced subjects, respectively.

As was observed in the DRV/rtv 800/100 mg once daily treatment arms of TMC114-C211 and TMC114-C229, resistance development to DRV or resistance development to DRV or other PIs, and to the background NRTIs was rare in study GS-US-216-0130, confirming the high genetic barrier to resistance of DRV, irrespective if coadministered with rtv or COBI. Of the 313 treated subjects in study GS-US-216-0130, 10 met the criteria for postbaseline resistance analysis (5 treatment-naïve and 5 treatment-experienced). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One treatment-experienced subject with poor pill bottle returns, indicative of poor adherence, had developed a DRV RAM at position I84 as a mixture with wild-type (I84I/V). The mutation was not associated with phenotypic resistance to DRV or any other PI in that subject. No subjects developed an NRTI RAM (or phenotypic resistance) to their concomitant NRTI regimen.

5. PERSISTANCE OF EFFICACY AND/OR TOLERANCE EFFECTS

The long-term efficacy of the DRV/rtv 800/100 mg once daily treatment regimen has been well established in the 192-week study TMC114-C211 in treatment-naïve HIV-1 infected subjects, and in the 48-week study TMC114-C229 in treatment-experienced HIV-1 infected subjects with no DRV RAMs. In study TMC114-C211, the virologic response rate (HIV-1 RNA <50 copies/mL) was 83.7% at Week 48, and 68.8% at Week 192 in the DRV/rtv 800/100 mg once daily arm (ITT, TLOVR). The mean increase from baseline in CD4+ cell count was $154x10^6$ cells/L at Week 48, and $266x10^6$ cells/L at Week 192 (ITT, M=F). Of the DRV/rtv-treated subjects with a confirmed virologic response of <50 copies/mL at Week 48, 81% remained undetectable at Week 192. The efficacy response observed in subjects receiving DRV/rtv 800/100 mg once daily provides evidence of the durable potency of a DRV/rtv-containing regimen in the treatment-naïve population (refer to Module 5.3.5.1/ TMC114-C211-W192-CRR). In study TMC114-C229, the virologic response (HIV-1 RNA <50 copies/mL) was 72.1% at Week 48 (ITT, TLOVR), and the mean increase from baseline in CD4+ cell count was $108x10^6$ cells/L in the DRV/rtv 800/100 mg once daily arm (ITT, LOCF) (refer to Module 5.3.5.1/TMC114-C229-W48-CRR).

Based on the comparable pharmacokinetics of DRV/rtv 800/100 mg once daily and DRV/COBI 800/150 mg once daily, and on the positive efficacy results of the supportive GS-US-216-0130 study, it is expected that treatment with DRV/COBI 800/150 mg once daily will lead to similar long-term efficacy results as obtained with DRV/rtv 800/100 mg once daily in the intended indication.

6. CONCLUSION

The established antiviral and immunologic efficacy of DRV/rtv 800/100 mg once daily for the treatment of HIV-1 infection, the established primary pharmacodynamic properties of COBI 150 mg as a pharmacokinetic enhancer of DRV, the antiviral and immunologic efficacy of DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130, and the bioequivalence of the FDC tablet with DRV/COBI 800/150 mg coadministered as single agents, support the use of the FDC tablet once daily with food in the intended indication.

REFERENCES

The following reference list is also provided in Module 2.7.5. All literature references are considered supportive but have been included for the convenience of the reviewer.

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Janssen Research & Development

Summary of Clinical Safety

Darunavir/Cobicistat 800/150 mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

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ABBREVIATIONS

ADR	adverse drug reaction
AE	adverse event
AEOI	adverse event of interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the plasma concentration-time curve over the dosing interval tau
BMI	body mass index
C_{0h}	predose plasma concentration
CCDS	company core data sheet
CIOMS	Council for International Organizations of Medical Sciences
C_{max}	maximum plasma concentration
COBI	cobicistat
CSR	clinical study report
C_{tau}	plasma concentration at the end of the dosing interval tau
CTP	clinical trial protocol
CYP	cytochrome P450
DBP	diastolic blood pressure
DRV	darunavir
ECG	electrocardiogram
EF_{PO4}	fractional excretion of phosphate
eGFR	estimated glomerular filtration rate
$eGFR_{CC}$	eGFR calculated by cystatin C clearance
$eGFR_{CG}$	eGFR calculated using the Cockcroft-Gault method
$eGFR_{MDRD}$	eGFR calculated using the Modification of Diet in Renal Disease method
EVG	elvitegravir
FDC	fixed dose combination
FTC	emtricitabine
GSI	Gilead Sciences Incorporated
HBsAg	hepatitis B surface antigen
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
ICF	informed consent form
IgM	immunoglobulin M
ITT	intent-to-treat; ITT population: all subject who received at least 1 dose of the study medication
LDL	low-density lipoprotein
LPV	lopinavir
LS	least square
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
PI	protease inhibitor
PSUR	periodic safety update report
qd	quaque in die, once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula[1]: $QTc=QT \times (1000/RR)^b$ with b=1/2
QTcF	QT interval corrected for heart rate using Fridericia's formula[5]: $QTc=QT \times (1000/RR)^b$ with b=1/3
RAM	resistance associated mutation
RNA	ribonucleic acid
rtv	low-dose ritonavir
SAE	serious adverse event
SAP	statistical analysis plan
SCS	Summary of Clinical Safety
SD	standard deviation

SOC	system organ class
STR	single tablet regimen
TDF	tenofovir disoproxil fumarate
TMC	Tibotec Medicinal Compound
TMC114-C211	Study TMC114-C211, also referred to as ARTEMIS
TMC114-C229	Study TMC114-TiDP31-C229, also referred to as ODIN
ULN	upper limit of normal

EXECUTIVE SUMMARY

The darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI). Cobicistat has recently been registered to be coadministered as a pharmacokinetic enhancer of atazanavir (ATV) and DRV. Comprehensive drug development programs have been conducted for the individual compounds DRV (in combination with low-dose ritonavir [rtv] as pharmacokinetic enhancer) and COBI.

The intended indication of the DRV/COBI 800/150 mg FDC is the same as the approved indication of the DRV/rtv 800/100 mg once daily regimen, ie, for the treatment of HIV-1 infection in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV resistance-associated mutations (RAMs), and with plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L. This is a so called 'substitution indication' of an already approved regimen, ie, the single agents have already been licensed for combined use at the same dose levels as in the FDC.

In support of the FDC tablet of DRV/COBI 800/150 mg once daily for the treatment of HIV-1 infection, this Summary of Clinical Safety (SCS) provides:

- A brief summary of the safety of DRV/rtv 800/100 mg once daily as established in the historical studies TMC114-C211 (also referred to as ARTEMIS) in ART-naïve HIV-1 infected adult subjects, and TMC114-C229 (also referred to as ODIN) in ART-experienced HIV-1 infected adult subjects with no DRV RAMs.
- A brief summary of the key clinical safety studies that investigated the effects of COBI on the renal tubular secretion of creatinine and on QTc, and the effects of DRV on QTc.
- A summary of all the safety data with DRV/COBI 800/150 mg once daily from the DRV/COBI FDC development program.

The safety findings of studies TMC114-C211 and TMC114-C229 with DRV/rtv demonstrated that DRV/rtv 800/100 mg once daily was generally safe and well tolerated in HIV-1 infected subjects.

Darunavir and COBI have no impact on QTc; COBI showed a modest effect on the PR interval similar to what is seen with rtv. Cobicistat was seen to inhibit the renal tubular secretion of creatinine without apparent effect on the actual glomerular filtration.

The DRV/COBI FDC development program in adult subjects consists of 3 clinical studies: a relative oral bioavailability study (TMC114IFD1001), a pivotal bioequivalence study (TMC114IFD1003), and a single-arm, open-label, Phase 3b safety study (GS-US-216-0130). The comparable pharmacokinetics (AUC_{24h} and C_{max}) of DRV/rtv 800/100 mg and DRV/COBI 800/150 mg coadministered as single agents (study GS-US-216-0115) or as the FDC (study TMC114IFD1001) in healthy subjects allow the extrapolation of safety data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects. The bioequivalence of the FDC tablet to DRV/COBI 800/150 mg coadministered as single agents is further demonstrated in study TMC114IFD1003. The Phase 3b, open-label, single-arm study (GS-US-216-0130) was conducted to generate additional safety data (primary objective) and

efficacy and pharmacokinetic data (secondary objectives) on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with other ARVs in HIV-1 infected subjects.

The Phase 1 study TMC114IFD1001 assessed the relative oral bioavailability in healthy subjects of 2 FDC formulations (G003 and G004) of DRV/COBI 800/150 mg once daily and to that of DRV/rtv 800/100 mg once daily coadministered as single agents under fed conditions. The G003 and G004 formulation had the same concentration of active ingredients but there were minor differences in excipient combinations. Of the 36 randomized and treated subjects, 30 received treatment as planned, 6 subjects (16.7%) dropped out before study completion (5 due to adverse events [AEs], 1 due to withdrawal of consent). All 36 subjects experienced one or more AEs in the course of the study. The most common AEs by system organ class (SOC) (reported in at least 20% of subjects) were Nervous System Disorders (80.6%), Gastrointestinal Disorders (75.0%), Skin and Subcutaneous Tissue Disorders (66.7%), and General Disorders and Administration Site Conditions (63.9%). The most frequently reported AEs by preferred term (in at least 25% of subjects) were headache (72.2%), fatigue (61.1%), diarrhea (30.6%), nausea (27.8%), skin irritation (27.8%) and pruritus (25.0%). No deaths or other serious AEs (SAEs) were reported. No relevant differences between the 3 treatments were observed in incidence or severity of AEs. Five subjects (13.9%) discontinued the study medication prematurely due to an AE: 2 subjects in the DRV/rtv treatment phase (both rash), 2 subjects in the DRV/COBI G003 treatment phase (rash and maculo-papular rash) and 1 subject in the DRV/COBI G004 treatment phase (maculo-papular rash). These AEs leading to permanent discontinuation were grade 2 or grade 3. Mean changes in laboratory parameters, electrocardiogram (ECG) and vital signs parameters were generally small and not considered clinically relevant. None of the laboratory, ECG or vital signs abnormalities were reported as an AE. In conclusion, the safety results demonstrated that treatment with DRV/COBI 800/150 mg as FDC tablets G003 and G004 for 10 days in healthy adult subjects was generally safe and well tolerated. No safety signals were detected during treatment with DRV/COBI 800/150 mg in adult healthy subjects.

The Phase 1 study TMC114IFD1003 in healthy subjects assessed the bioequivalence of DRV when coadministered with COBI either as the FDC (formulation G006) or as single agents, under fed or fasted conditions. Formulation G006, the proposed commercial formulation, matches the core tablet composition of formulation G004 and differs only in the color of the film coat. Of the 133 randomized and treated subjects, 130 received treatments as planned, ie, 2 single administrations of DRV/COBI 800/150 mg, once as an FDC tablet (G006) and once coadministered as single agents under fed or fasted conditions, with a 7-day washout between the 2 administrations. Three subjects (2.3%) dropped out before study completion, 2 due to withdrawal of consent and 1 due to a protocol violation. Sixty-four subjects (48.1%) experienced 1 or more AEs. The most common AEs by SOC (reported in at least 10% subjects) were Nervous System Disorders (33.1%), Gastrointestinal Disorders (19.5%), and Musculoskeletal and Connective Tissue Disorders (13.5%). The most frequently reported AEs by preferred term (in at least 5% of subjects) were headache (30.1%), muscle spasms (9.0%), and diarrhea (8.3%). All AEs were grade 1 (42.1%) or grade 2 (6.0%) in severity. No deaths or other SAEs were observed, and there were no premature study discontinuations due to an AE. Mean changes in laboratory parameters and vital signs parameters were generally small and not considered

clinically relevant. None of the laboratory or vital signs abnormalities were reported as an AE. In conclusion, the safety results of study TMC114IFD1003 demonstrated that a single administration of DRV/COBI 800/150 mg as FDC tablet G006 or coadministered as single agents under fed or fasted conditions in healthy adult subjects was generally safe and well tolerated. No safety signals were detected during treatment with DRV/COBI 800/150 mg in adult healthy subjects.

Study GS-US-216-0130 is an ongoing, Phase 3b, open-label, single-arm, multicenter study in 313 HIV-1 infected, antiretroviral therapy (ART)-naïve (n=295) and ART-experienced (n=18) adult subjects with no DRV RAMs. The primary objective of this study was to evaluate, after 24 weeks of treatment, the safety and tolerability of DRV/COBI 800/150 mg once daily coadministered as single agents, plus 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The secondary objectives are to assess the safety and tolerability of the regimen through 48 weeks of treatment, to assess the efficacy of the regimen as determined by a virologic response of HIV-1 RNA <50 copies/mL at Week 24 and 48 of treatment, and to assess the change from baseline in CD4+ cell counts at Week 24 and Week 48. After Week 48, subjects are given the option to participate in an open-label extension of the study.

The median exposure in the 313 subjects in the intent-to-treat (ITT) population was 31.4 weeks through the cut-off for the Week-24 analysis ([redacted]). In the Week-24 analysis (primary endpoint), 5.8% of subjects experienced at least 1 grade 3 (5.1%) or grade 4 (0.6%) AE. All grade 3 or 4 AEs had an incidence of 0.3% (1 subject), except for hypersensitivity (1.0%, 3 subjects) and maculo-papular rash (0.6%, 2 subjects). There were 2 grade 4 AEs in 1 subject each, idiopathic thrombocytopenic purpura and hypersensitivity; neither were assessed as drug-related by the investigator. Five subjects (1.6%) experienced at least 1 grade 3 AE that was study drug-related. Overall, 87.9% of subjects experienced at least 1 AE. The incidence of AEs was highest (in >15% of all subjects) in the SOCs Gastrointestinal Disorders (52.4%), Infections and Infestations (48.9%), Skin and Subcutaneous Tissue Disorders (28.1%), Nervous System Disorders (19.8%), and General Disorders and Administration Site Conditions (15.3%). By preferred term, the most frequently occurring AEs (in >5% of all subjects) were diarrhea (24.9%), nausea (21.4%), upper respiratory tract infection (9.9%), headache (9.3%), rash (preferred term, 8.6%), vomiting (8.3%), fatigue (6.4%) flatulence (6.1%), nasopharyngitis (5.8%), and sinusitis (5.4%). Fifteen subjects (4.8%) experienced one or more SAEs, including 3 subjects (1.0%) who had 1 SAE considered by the investigator to be related to the study medication (immune reconstitution syndrome, rash, and maculo-papular rash). Treatment was permanently discontinued in 15 subjects (4.8%) because of 1 or more AEs. Most AEs leading to discontinuation were in the SOC of Skin and Subcutaneous Tissue Disorders (7 subjects, 2.2%). All but 2 AEs that led to discontinuation were considered to be study drug-related. Overall, 39.3% of subjects experienced at least 1 AE that was considered related to DRV/COBI. Diarrhea (14.7%) and nausea (14.4%) were the only AEs considered to be study drug-related in more than 5% of subjects, most drug-related AEs were recorded in 1 or 2 subjects.

In the analysis of AEs of interest to DRV/COBI, rash (grouped term, 16.3%), lipid abnormalities (2.9%) and severe skin reactions (2.6%) were the AE-of-interest clinical entities with incidences greater than 2%. Overall, 23.6% of subjects experienced at least 1 AE of interest.

In the laboratory safety analysis, the estimated glomerular filtration rate (eGFR) based on cystatin clearance ($eGFR_{CC}$) was stable over time, whereas an increase in creatinine level and a modest decrease in eGFR based on creatinine clearance (using the Cockcroft-Gault method [$eGFR_{CG}$] and the Modification of Diet in Renal Disease method [$eGFR_{MDRD}$]) were noted from Week 2 onwards: the mean change in creatinine was +0.09 mg/dL and the mean change in $eGFR_{CG}$ was !9.6 mL/min at Week 2. These changes stabilized and remained more or less constant through Week 24: the mean change in creatinine was +0.12 mg/dL and the mean change in $eGFR_{CG}$ was !11.5 mL/min at Week 24. There were no grade 3 or 4 abnormalities in creatinine. There were no laboratory abnormalities suggestive of proximal renal tubular dysfunction. Renal laboratory assessments showed changes consistent with the inhibitory effects of COBI on renal tubular creatinine secretion. An increase in serum creatinine due to the COBI inhibitory effect generally does not exceed 0.4 mg/dL from baseline. There were no clinically relevant changes from baseline in the Week-24 analysis in mean values of the other clinical chemistry parameters, hematology parameters, or lipid parameters (fasting high-density lipoprotein [HDL] cholesterol, fasting low-density lipoprotein [LDL] cholesterol, fasting total cholesterol to HDL cholesterol ratio, or fasting glucose), or in the liver-related laboratory tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin [direct, indirect and total]). The majority of grade 3 or 4 clinical laboratory abnormalities were associated with changes in creatine kinase (5.8%) and ALT (2.3%). All other grade 3 or 4 abnormalities occurred in less than 2% of subjects. All laboratory-related AEs were grade 1, not serious, and did not lead to treatment discontinuation. The most frequently reported laboratory-related AEs, hypercholesterolemia and hypertriglyceridemia, were recorded in 4 subjects (1.3%) each.

No clinically relevant safety observations were made in a review of body weight values, concomitant medication uses, reports of study drug overdoses, pregnancies, and ECG findings.

Most adverse drug reactions (ADRs, as defined per company's assessment) to DRV/COBI treatment were mild in severity. The most frequent (≥2%) ADRs of grade 2 or more were rash (grouped term, 5.8%), diarrhea (5.1%), and nausea (3.2%). The most frequent (≥2 subjects, 0.6%) ADRs of grade 3 or 4 were maculo-papular rash and hypersensitivity (0.6% each). All other grade 3 or 4 ADRs were reported in 1 subject (0.3%). Twelve subjects (3.8%) discontinued treatment due to 1 or more ADRs. The ADR profile of DRV/COBI 800/150 mg once daily coadministered as single agents is consistent with the safety profile of the single agents DRV and COBI, though with a higher incidence of mild to moderate rash.

The review of the safety data of the Week-48 analysis of study GS-US-216-0130, and of the SAEs reported with DRV/COBI during the ongoing studies and received until the cut-off date for this SCS of [redacted], did not identify any safety concerns associated with DRV/COBI 800/150 mg treatment.

No subgroup analyses were performed in special groups or situations.

In conclusion, DRV/COBI 800/150 mg once daily coadministered as single agents was generally well tolerated in 313 treatment-naïve and treatment-experienced HIV-1 infected adult subjects in study GS-US-216-0130. The reported AEs and DRV/COBI ADRs were consistent with those

expected in the subject population and the known safety profiles of the single agents. The results of the safety analyses of the Phase 1 studies and of the Week-24 safety analysis of the Phase 3b study GS-US-216-0130 support the use of DRV/COBI 800/150 mg once daily in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV RAMs.

1. INTRODUCTION

1.1. Background

The DRV/COBI FDC tablet is a combination of 2 single agents: DRV, an HIV-1 PI, and COBI, a pharmacokinetic enhancer which has recently been registered to be concurrently administered. Comprehensive drug development programs have been conducted for the individual compounds DRV (in combination with rtv as pharmacokinetic enhancer) and COBI. The development program of the FDC tablet is primarily based on these development programs.

Darunavir Safety Profile

The DRV company core data sheet (CCDS) provides the safety information of DRV in combination with rtv in HIV-1 infected adults and pediatric subjects (aged 3 to less than 18 years).[9] The safety findings from the clinical studies demonstrate that treatment with all studied dose regimens of DRV/rtv was generally safe and well tolerated in healthy subjects and HIV-1 infected subjects. Treatment with DRV/rtv 800/100 mg once daily in combination with other ARTs has been shown to provide substantial and durable efficacy in HIV-1 treatment, with a high genetic barrier to the development of resistance, helping preserve future therapeutic options. The safety of this dose regimen is supported by the 192-week study TMC114-C211 in 343 ART-naïve HIV-1 infected adult subjects, by the 48-week study TMC114-C229 in 294 ART-experienced HIV-1 infected adult subjects without DRV RAMs[*], and by postmarketing experience.[2,8]

Cobicistat Safety Profile

Cobicistat is a new chemical entity developed by Gilead Sciences Inc. (Gilead) recently licensed for use as a pharmacokinetic enhancer (booster) to increase systemic exposure of coadministered antiretrovirals (ARVs) metabolized by cytochrome P450 (CYP)-3A enzymes, including the PIs DRV and ATV, and the integrase strand transfer inhibitor elvitegravir (EVG).[11] A single tablet regimen (STR) containing EVG, COBI, emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF) or STR EVG/COBI/FTC/TDF was FDA-approved on 27 August 2012, and approved in the European Union on 28 May 2013, based on efficacy and safety data up to 48 weeks in 1,408 subjects (including 701 treated with the STR EVG/COBI/FTC/TDF regimen).[10]

Cobicistat has been shown to provide DRV exposures similar to those obtained with rtv. In the proof-of-concept study for the pharmacoenhancing effect of COBI 150 mg on DRV (GS-US-216-0115), the pharmacokinetics and relative bioavailability of DRV/COBI 800/150 mg coadministered as single agents once daily for 10 days, were compared with those of DRV/rtv 800/100 mg once daily for 10 days, in 33 healthy subjects (refer to Module 5.3.1.2/GS-US-216-0130-CSR). The 90% confidence intervals (CIs) of the pharmacokinetic parameters of DRV (area under the plasma concentration-time curve over the dosing interval [AUC_{tau}], maximum plasma concentration [C_{max}], and predose plasma concentration [C_{0h}]) were within 80.00 to 125.00% when boosted by COBI compared to when boosted by rtv. The values of DRV

[*] DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V[6]

plasma concentration observed at end of the dosing interval (C_{tau}) were lower in the COBI group compared to the rtv group.

DRV/COBI FDC Safety Profile

The intended indication of the DRV/COBI FDC 800/150 mg is the same as the approved indication at the same dose level of the single agents, ie, for the treatment of HIV-1 infection in HIV-1 infected treatment-naïve adult subjects and treatment-experienced adult subjects with no DRV RAMs, plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100x10^6$ cells/L (substitution indication). The development of a FDC tablet of DRV with its pharmacokinetic enhancer in a once-daily regimen offers the option to simplify DRV-containing ARV regimens by reducing pill burden.

The clinical program for DRV/COBI FDC is primarily based on the comprehensive development programs of the 2 individual compounds and on the pharmacokinetic bridging clinical program. As the DRV/COBI FDC 800/150 mg is indicated as a 'substitution indication' of an already approved regimen, no comparative efficacy study was conducted. The DRV/COBI FDC development program in adult subjects consists of 3 studies:

(1) A Phase 1 study TMC114IFD1001, investigating the relative oral bioavailability of 2 FDC formulations (G003 and G004) of DRV/COBI 800/150 mg once daily and that of DRV/rtv 800/100 mg once daily coadministered as single agents under fed conditions (refer to Module 5.3.1.1/TMC114IFD1001-CSR).

(2) A Phase 1 study TMC114IFD1003, assessing the bioequivalence of DRV when coadministered with COBI either as the FDC (formulation G006) or the single agents under fed and fasted conditions (refer to Module 5.3.1.2/TMC114IFD1003-CSR).

(3) An ongoing Phase 3b, open-label, single-arm study GS-US-216-0130 assessing safety (primary objective), efficacy and pharmacokinetic parameters (secondary objectives) in HIV-1 infected adult subjects treated with DRV/COBI 800/150 mg once daily coadministered as single agents for at least 48 weeks (refer to Module 5.3.1.2/ GS-US-216-0130-W24-CSR).

In the Phase 1 study TMC114IFD1001, the FDC formulations G003 and G004 were investigated; the G003 and G004 formulation had the same concentration of active ingredients but there were minor differences in excipient combinations. Formulation G006, which matches the core tablet composition of formulation G004 and differs only in the color of the film coat, was used in bioequivalence study TMC114IFD1003 and has been chosen as the proposed commercial formulation (refer to the Summary of Biopharmaceutical Studies and Associated Analytical Methods in Module 2.7.1).

The comparable pharmacokinetics (AUC_{24h} and C_{max}) of DRV/rtv 800/100 mg and DRV/COBI 800/150 mg coadministered as single agents (study GS-US-0216-0115) or FDC (study TMC114IFD1001) in healthy subjects allow the extrapolation of safety data from DRV/rtv 800/100 mg once daily to DRV/COBI 800/150 mg once daily in HIV-infected subjects. The bioequivalence between DRV/COBI 800/150 mg coadministered as single agents and the FDC is

further demonstrated in study TMC114IFD1003. A Phase 3b, open-label, single-arm study (GS-US-216-0130) was conducted to generate additional safety data (primary objective) and efficacy and pharmacokinetic data (secondary objectives) on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in HIV-1 infected subjects.

1.2. Overview of the Summary

In Section 2, the safety data are presented of the relevant Phase I studies in healthy subjects, with DRV/rtv, with COBI, and with DRV/COBI.

The safety data in HIV-1 infected subjects are presented in Section 3. In Section 3.1, the safety data with DRV/rtv 800/100 mg once daily are briefly summarized. A short statement on the safety of COBI is given in Section 3.2. In Section 3.3, the safety data with DRV/COBI 800/150 mg once daily are presented, ie, the results of the Week-24 primary analysis of study GS-US-216-0130 including data up to the primary analysis cut-off date ([redacted]), when the last subject had his/her Week-24 visit or discontinuation visit. The AEs in the Week-24 analysis of the GS-US-216-0130 study were reviewed by medical experts for identification of ADRs associated with DRV/COBI, they are reported in Section 3.3.10. In Section 3.3.11, this ADR profile of DRV/COBI 800/150 mg once daily is compared with that of DRV/rtv 800/100 mg once daily, taken from historical control studies. In Section 3.4, a summary is presented of the available Week-48 safety data of the ongoing study GS-US-216-0130, and of the SAEs considered by the investigator to be related to DRV/COBI reported during ongoing studies with DRV/COBI and received up until the cut-off date of [redacted] for this SCS.

In Section 4, safety data in special groups (eg, subjects coinfected with hepatitis B or C virus) and situations (eg, pregnancy) are presented.

In Section 5 postmarketing data are provided.

Overall conclusions on the safety data in this SCS are presented in Section 6.

1.3. Safety Assessments and Statistical Methods

Details on the safety assessments can be found in the clinical trial protocol (CTP) and the clinical study report (CSR) of each study, details on the statistical methods are described in the statistical analysis plan (SAP) of each study. Two differences across the studies are noteworthy.

In the studies conducted by the Applicant, the relationship between an AE and the study medication was assessed by the investigator as not related, doubtful, possible, probable, or very likely. In the statistical analysis, the latter 3 were grouped as ‘at least possibly related’. In the studies conducted by Gilead, the relationship between an AE and the study medication was assessed by the investigator as either ‘not related’ or ‘related’.

In the studies conducted by the Applicant and in the ADR analyses of the Phase 3 studies GS-US-216-0130, TMC114-C211 and TMC114-C229, abnormalities in clinical laboratory data were determined using the criteria defined by the division of acquired immunodeficiency syndrome (AIDS) or DAIDS Table for Grading (refer to Module 5.3.5.2/GS-US-216-0130-W24-

SAP/Attachment 3). In the studies conducted by Gilead, laboratory abnormalities were graded using the Gilead Sciences Incorporated (GSI) Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Module 5.3.5.2/GS-US-216-0130-CTP-v2/Appendix 4). The GSI grading scale does not define toxicity grades for the parameter of LDL cholesterol, while the DAIDS table specifies limits for grade 1 to 3 abnormal LDL cholesterol values. In the GSI grading scale, creatinine levels are defined as >1.5 to 2.0 mg/dL for grade 1, and >2.0 to 3.0 mg/dL for grade 2. In the DAIDS grading system, abnormal creatinine levels are defined relative to the upper limit of normal (ULN) of the analyzing laboratory[*]. For all other laboratory parameters, the differences between the DAIDS and GSI grading tables are limited to small numerical differences in the boundaries of the ranges for the different grades.

2. SAFETY DATA IN HEALTHY SUBJECTS

In this section of the SCS, the key pharmacoclinical Phase 1 studies investigating specific safety aspects of DRV/rtv (Section 2.1), and COBI (Section 2.2) are briefly described. In Section 2.3, the safety information from 2 Phase 1 studies with DRV/COBI conducted by Gilead is briefly summarized, and the new safety data generated in the Phase 1 studies performed by the Applicant during the FDC development plan are presented.

2.1. Safety Data With DRV/rtv 800/100 mg in Study TMC114-C153

In the open-label, randomized, placebo- and active-controlled, 4-way crossover thorough QT study TMC114-C153, 40 healthy subjects were administered supratherapeutic doses of DRV/rtv 1600/100 mg once daily and 800/100 mg twice daily for 7 days. At the mean maximum DRV concentration of 6599 ng/mL observed in this study, the mean increase in QTcF was 2.2 ms with a 90% two-sided confidence interval (CI) of -2.0 to 6.3 ms. When evaluating the 2-sided 90% CI on the time-matched mean changes in QTcF versus placebo control, the upper bounds of both DRV/rtv groups never exceeded the 10 ms boundary. In the setting of this study and according to the E14 ICH Guidelines, DRV/rtv did not appear to prolong the QTc interval. The maximum mean difference in PR interval versus placebo with the supratherapeutic doses of DRV/rtv 800/100 mg twice daily (6.3 ms) and DRV/rtv 1600/100 mg once daily (4.9 ms) are not considered clinically significant. For more information on this study, refer to Module 5.3.4.1/TMC114-C153-CSR.

2.2. Safety Data With COBI 150 mg

2.2.1. Effect on Electrocardiogram, Study GS-US-216-0107

The effect on QTc interval of a single dose of COBI 250 mg and 400 mg, providing exposures approximately 2- and 4-fold above the recommended therapeutic dose, was evaluated in the randomized, placebo- and active-controlled (moxifloxacin 400 mg) 4-period crossover thorough QT study GS-US-216-0107 in 48 healthy subjects. In a study with demonstrated ability to detect

[*] In the DAIDS table, creatinine levels are defined as 1.1 to 1.3 xULN for grade 1, and >1.3 to 1.8xULN for grade 2. There were 4 different ULN for creatinine in the GS-US-216-0130 dataset, resulting in the following definitions:
ULN 1.14 mg/dL has grade 1: >1.254 to 1.482 mg/dL and grade 2: >1.482 to 2.052 mg/dL.
ULN 1.24 mg/dL has grade 1: >1.364 to 1.612 mg/dL and grade 2: >1.612 to 2.232 mg/dL.
ULN 1.35 mg/dL has grade 1: >1.485 to 1.755 mg/dL and grade 2: >1.755 to 2.43 mg/dL.
ULN 1.55 mg/dL has grade 1: >1.705 to 2.015 mg/dL and grade 2: >2.015 to 2.79 mg/dL.

small effects, the upper bound of the one-sided 95% CI for the largest placebo-adjusted, baseline-corrected QTc based on individual correction method (QTc) was below 10 ms, the threshold for regulatory concern. The dose of 400 mg COBI is expected to cover the high exposure clinical scenario. Prolongation of the PR interval was noted in subjects receiving COBI. The maximum mean (95% upper confidence bound) difference in PR from placebo after baseline-correction was 9.5 (12.1) ms for COBI 250 mg and 20.2 (22.8) ms for COBI 400 mg and is not considered to be clinically significant. For more information on this study, refer to Module 5.3.4.1/GS-US-216-0107-CSR.

2.2.2. Effect on Cardiac Function, Study GS-US-216-0116

In study GS-US-216-0116, ECGs and echocardiograms were collected at baseline and once at steady state, 3.5-6 hours postdose between Days 14-19 of dosing with 150 mg COBI daily. All subjects had normal absolute PR (<210 ms) and QTcF (<450 ms) intervals. The ECHO assessments showed that the three measures of left ventricular function were normal. Echocardiograms performed in Study GS-US-216-0116 at baseline and at steady-state COBI exposures indicated no clinically significant change in LV function. For more information on this study, refer to Module 5.3.4.1/GS-US-216-0116-CSR.

2.2.3. Effects on Serum Creatinine, Studies GS-US-216-0121, GS-US-216-0124, and GS-US-236-0130

In study GS-US-216-0121, the effect of COBI on serum creatinine was investigated in HIV-1-negative subjects with normal renal function (estimated glomerular filtration rate [eGFR] ≥80 mL/min, N=12) and HIV-negative subjects with mild-to-moderate renal impairment (eGFR 50-79 mL/min, N=18). A statistically significant change of eGFR, calculated by Cockcroft-Gault method ($eGFR_{CG}$) from baseline, was observed after 7 days of treatment with COBI 150 mg in subjects with normal renal function (mean ±SD change from baseline: -9.9 ±13.1 mL/min) and in subjects with mild-to-moderate renal impairment (mean ±SD change from baseline -11.9 ±7.0 mL/min). No statistically significant changes in $eGFR_{CG}$ were observed compared to baseline in both subject groups 7 days after COBI was discontinued. The actual GFR, as determined by the clearance of probe drug iohexol, was not altered from baseline following COBI treatment in subjects with normal renal function or in subjects with mild-to-moderate renal impairment, indicating that COBI inhibits tubular secretion of creatinine, reflected as a reduction in $eGFR_{CG}$, without affecting the actual GFR. For more information on this study, refer to Module 5.3.3.3/GS-US-216-0121-CSR.

In study GS-US-216-0124, the pharmacokinetics of COBI were investigated in HIV-1-negative subjects with severe renal impairment (estimated creatinine clearance <30 mL/min). Estimated GFR ($eGFR_{CG}$ and $eGFR_{MDRD}$) values were slightly lower at Day 7 than at baseline in subjects with severe renal impairment and in matched control subjects with normal renal function. The decreases were reversible, and had returned to baseline by Day 14. The findings are consistent with those observed in previous clinical studies, attributed to inhibition by COBI of the proximal tubular secretion of creatinine, and not considered clinically relevant. For more information on this study, refer to Module 5.3.3.3/GS-US-216-0124-CSR.

Study GS-US-236-0130 was a randomized, double-blind, placebo-controlled, multiple-dose, parallel design study in healthy adult subjects. The study examines the effect of 5 treatments (COBI, TDF, COBI+TDF, EVG/COBI/FTC/TDF and placebo) when given once daily for 30 days in the fed state at the proposed or approved doses on renal function. Subjects were then followed for a further 30 days to document the reversibility of any effects observed. Mean plasma concentrations of COBI when given alone were similar to those for subjects receiving COBI+TDF and slightly lower versus dosing with EVG/COBI/FTC/TDF. There was the expected effect on eGFR for COBI-containing regimens. The on-treatment (Day 15 and Day 30) aGFR (Iohexol Plasma Clearance) data showed decreases from baseline and versus placebo for COBI alone and for COBI+TDF. The 90% CI around ratios versus placebo did not fall within 80.00 to 125.00% except for COBI+TDF at Day 15. Similar analyses based on Day 15 and 30 versus Day 0 within each treatment group gave 90% CI around the ratios that just fell within 80.00 to 125.00% except for Day 15 in the COBI group. The study could not rule out the possibility that COBI alone does have a small effect of aGFR but the effect of coadministration of COBI+TDF was not consistently greater than the effect of COBI alone (or TDF alone). For more information on this study, refer to GS-US-236-0130-CSR.[4]

2.3. Safety Data With DRV/COBI 800/150 mg

2.3.1. Safety Data in Phase 1 Studies GS-US-216-0119 and GS-US-216-0115

Study GS-US-216-0119 was an open-label, partially randomized, multiple-dose, crossover, multiple-cohort study evaluating the pharmacokinetics and safety of twice-daily administration of COBI alone, DRV/COBI, DRV/rtv, and of tipranavir (TPV)/COBI and TPV/rtv. Each treatment was administered with food for 10 days. Treatment with DRV/COBI 600/100 mg twice daily coadministered as single agents was not associated with increased adverse safety findings versus rtv-boosted DRV. For more information on this study, refer to GS-US-216-0119-CSR.[7]

Study GS-US-216-0115 was an open-label, randomized, multiple-dose, 2-sequence, 2-period crossover study in healthy subjects evaluating the pharmacokinetics and safety of the once-daily administration of DRV/rtv 800/100 mg or DRV/COBI 800/150 mg coadministered as single agents. Each treatment was administered with food for 10 days. Both treatments were generally well tolerated. No SAEs occurred. One subject discontinued DRV/COBI on Day 8 due to maculo-papular rash (drug-related, grade 2); the rash resolved by Day 15. No clinically significant changes in vital signs or ECG results were observed. For more information on this study, refer to Module 5.3.1.2/GS-US-216-0115-CSR.

2.3.2. Safety Data in the FDC Development Program

Three different FDC tablet formulations were used in the Phase 1 studies where DRV/COBI 800/150 mg was administered to healthy subjects TMC114IFD1001 and TMC114IFD1003. Each formulation had the same concentration of active ingredients but with minor differences in excipient combinations. Formulation G003 contained microcrystalline cellulose while formulation G004 did not; formulation G004 contained more silicified microcrystalline cellulose. For commercial reasons, the non-functional coating color of the DRV/COBI G004 tablet was changed from white to pink, yielding the G006 tablet formulation which was selected as the

proposed commercial formulation. The DRV/COBI G004 and G006 formulations are identical, except for the non-functional coating color.

2.3.2.1. Safety Data in Study TMC114IFD1001

2.3.2.1.1. Study Design of TMC114IFD1001

In the open-label, randomized, 3-way crossover Phase 1 study TMC114IFD1001, 36 healthy subjects between the ages of 18 and 55 years with a body mass index (BMI) of 18.5 to 30.0 kg/m^2 were randomized and treated in order to assess, under fed and steady-state conditions, the rate and extent of DRV absorption following administration of the 2 FDC concept tablets of DRV/COBI (G003 and G004) relative to coadministration of DRV and rtv as single agents.

During 3 consecutive treatment sessions, each subject received 3 treatments according to a classical 6-sequence, 3-period Williams design, ie, Treatment A (reference treatment) DRV/rtv 800/100 mg once daily coadministered as single agents, Treatment B (test 1) DRV/COBI 800/150 mg once daily administered as FDC tablet G003, and Treatment C (test 2) DRV/COBI 800/150 mg once daily administered as FDC tablet G004. All treatments were administered for 10 days under fed conditions. There was a washout period of at least 7 days between subsequent treatment sessions.

On Day 10 of all treatment sessions, full pharmacokinetic profiles of DRV, COBI and rtv (as applicable) were determined over 24 hours. Safety and tolerability were monitored and documented throughout the study. Subjects were seen at regular visits during which the investigator assessed the subject's medical condition, any AEs, laboratory safety, and study medication adherence. All analyses were performed on the ITT population. For details on the timing and a description of the safety assessments as well as the methods used for the statistical analysis for AEs, clinical laboratory parameters, ECGs and vital signs, physical examinations including body weight and height, and pharmacokinetic analyses, refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 3.6.

For further details on the design of the TMC114IFD1001 study, refer to Module 5.3.1.1/TMC114IFD1001-CSR. Refer to Section 2.3.2.1.7 and Section 6 of this document for a summary and the conclusions of the safety results. For the pharmacokinetic results of this study, refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2.

2.3.2.1.2. Extent of Exposure

In study TMC114IFD1001, 36 subjects were randomized and treated (ITT population). Thirty subjects received treatment as planned. Six subjects (16.7%) dropped out before study completion, 2 subjects discontinued during or after having completed the first session, 1 subject discontinued during the second session and 3 subjects during the third session. Five subjects discontinued early because of an AE (see Section 2.3.2.1.4), and 1 subject withdrew consent. The extent of exposure of the 6 subjects who dropped out early is summarized in Table 1.

Table 1: Extent of Exposure for Subjects Who Discontinued Prematurely – TMC114IFD1001

Subject ID	Reason for Discontinuation	Treatment Sequence	Study Medication Intakes
1001-0015	Withdrawal of consent	A/B/C	DRV/rtv qd for 10 days DRV/COBI G003 qd for 10 days DRV/COBI G004 for 6 days
1001-0033	Adverse event	A/B/C	DRV/rtv qd for 10 days DRV/COBI G003 for 2 days
1001-0006	Adverse event	B/C/A	DRV/COBI G003 qd for 10 days DRV/COBI G004 qd for 10 days DRV/rtv qd for 8 days
1001-0009	Adverse event	B/C/A	DRV/COBI G003 qd for 9 days
1001-0034	Adverse event	C/A/B	DRV/COBI G004 qd for 10 days
1001-0036	Adverse event	C/B/A	DRV/COBI G004 qd for 10 days DRV/COBI G003 qd for 10 days DRV/rtv qd for 7 days

qd=once daily.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 6.

2.3.2.1.3. Demographic and Other Characteristics of Study Population

The demographic data of the ITT population are summarized in Table 2. The majority of subjects were female (83.3%) and all but one were white (97.2%). The median age was 46.5 years (range 20 to 55 years) and median BMI was 24.25 kg/m^2 (range 20.6 to 29.5 kg/m^2).

No relevant differences in demographic and baseline characteristics among the randomization groups were observed. At screening, all subjects had a nonreactive HIV serology test and negative hepatitis A antibody immunoglobulin M (IgM), hepatitis B surface antigen (HBsAg), and hepatitis C antibody tests. Serum pregnancy tests at screening were negative for all female subjects. Urine drug tests for amphetamines, barbiturates, benzodiazepine, cocaine, opiates, methadone, tetrahydrocannabinol, and propoxyphene were negative for all subjects. None of the subjects had a history of drug allergy. Nine subjects had a medical history condition related to dermatological or allergic/immunologic disorders (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 4.2). For 3 of these subjects, the medical history of dermatologic or allergic/immunologic disorders was considered a major protocol deviation (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 4.4).

Table 2: Demographic Data – TMC114IFD1001

Parameter	Randomization Group A/B/C N=6	B/C/A N=6	C/A/B N=6	C/B/A N=6	B/A/C N=6	A/C/B N=6	All Subjects N=36
Age, years							
Median	38.0	43.5	48.5	47.5	45.5	47.0	46.5
(Range)	(22-55)	(20-54)	(22-52)	(21-55)	(31-54)	(32-52)	(20-55)
Sex, n (%)							
Male	0	0	2 (33.3)	0	1 (16.7)	3 (50.0)	6 (16.7)
Female	6 (100.0)	6 (100.0)	4 (66.7)	6 (100.0)	5 (83.3)	3 (50.0)	30 (83.3)
Height, cm							
Median	167.5	165.0	167.0	161.5	164.5.0	165.0	165.0
(Range)	(161-169)	(157-169)	(160-183)	(154-170)	(159-181)	(158-180)	(154-183)
BMI, kg/m^2							
Median	23.45	24.25	23.95	23.80	25.55	24.95	24.25
(Range)	(21.4-25.5)	(22.4-27.2)	(20.6-27.2)	(20.7-29.5)	(21.8-26.8)	(22.0-27.6)	(20.6-29.5)
Race, n (%)							
White	6 (100.0)	6 (100.0)	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	35 (97.2)
Black	0	0	1 (16.6)	0	0	0	1 (2.8)
Ethnic Origin, n (%)							
Hispanic/Latino	1 (16.7)	0	0	0	0	0	1 (2.8)[a]
Not Hispanic/Latino	5 (83.3)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	35 (97.2)[a]

[a] Data were incorrectly reported as 0 (0.0) and 6 (100.0) in the source document.
N=total number of subjects with data; n=number of subjects with demographic characteristic.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 5.

Sixteen subjects (44.4%) used one or more concomitant medications during the study. The most frequently used concomitant medications were cetirizine, paracetamol and ibuprofen. Paracetamol and ibuprofen were used by 7 subjects (19.4%) and 3 subjects (8.3%), respectively, mainly to treat headache. Seven subjects (19.4%) used (levo)cetirizine to treat rashes and skin irritations (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 4.3). Three subjects received a concomitant therapy during the study that was disallowed per protocol (acyclovir, miconazole, raloxifene). These deviations were not considered to have had an impact on the study outcome.

2.3.2.1.4. Adverse Events

Unless specified otherwise, 1) the AEs presented below are those with onset during the treatment phase, 2) AEs are reported by preferred term, 3) drug relatedness to study medication (DRV, unless otherwise specified) is as assessed by the investigator, and 4) AE tables are listed by SOC and by preferred term, both ordered alphabetically. All AEs were mapped according to the Medical Dictionary for Regulatory Activities (MedDRA) version 14.

Summary of Adverse Events

A summary of the AEs in study TMC114IFD1001 is presented in Table 3. All 36 subjects (100.0%) experienced at least 1 AE during the study. No deaths or other SAEs were reported. Five subjects (13.9%) discontinued study medication prematurely due to an AE: 2 subjects during intake of DRV/rtv (both rash), 2 subjects during intake of DRV/COBI G003 (rash and maculo-papular rash), and 1 subject during intake of DRV/COBI G004 (maculo-papular rash).

Most AEs were grade 1 or grade 2 in severity. No grade 4 AEs were reported. Grade 3 AEs were reported for 3 subjects (8.3%), 1 subject during each treatment phase. The reported grade 3 AEs

were fatigue during intake of DRV/rtv, and maculo-papular rash during both sessions with DRV/COBI G003 and G004.

The most frequently reported AEs (in at least 25% of all subjects) were headache (72.2%), fatigue (61.1%), diarrhea (30.6%), nausea (27.8%), skin irritation (27.8%), and pruritus (25.0%).

No relevant differences between treatments were observed with respect to incidence of AEs.

Table 3: Summary of Adverse Events – TMC114IFD1001

n (%) of Subjects Experiencing	DRV/rtv N=34	DRV/COBI G003 N=35	DRV/COBI G004 N=34	Overall[a] N=36
Summary of all AEs				
≥1 AE	30 (88.2)	31 (88.6)	27 (79.4)	36 (100.0)
≥1 Grade 3 or 4 AE	1 (2.9)	1 (2.9)	1 (2.9)	3 (8.3)
≥1 AE at Least Possibly Related to DRV	22 (64.7)	2 (5.7)	1 (2.9)	24 (66.7)
≥1 AE at Least Possibly Related to DRV/COBI	1 (2.9)	23 (65.7)	20(58.8)	28 (77.8)
≥1 SAE	0	0	0	0
≥1 AE Leading to Permanent Discontinuation	2 (5.9)	2 (5.7)	1 (2.9)	5 (13.9)
Most Frequently Reported AEs[b]				
Diarrhoea	5 (14.7)	5 (14.3)	5 (14.7)	11 (30.6)
Fatigue	11 (32.4)	11 (31.4)	15 (44.1)	22 (61.1)
Headache	14 (41.2)	18 (51.4)	18 (52.9)	26 (72.2)
Nausea	4 (11.8)	3 (8.6)	5 (14.7)	10 (27.8)
Pruritus	4 (11.8)	3 (8.6)	3 (8.8)	9 (25.0)
Skin irritation	3 (8.8)	5 (14.3)	3 (8.8)	10 (27.8)

N=total number of subjects with data; n=number of subjects with observation.
[a] Includes the screening and follow-up periods.
[b] AEs reported in at least 25% of all subjects.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 12, Table 13, and Module 5.3.1.1/TMC114IFD1001-Anal-Saf-AE/Display SAF.1, Display SAF.5, and Display SAF.6.

Common Adverse Events

The incidence of AEs reported in more than 2 subjects during treatment by SOC or preferred term is summarized in Table 4.

The incidence of AEs was highest in the SOCs Nervous System Disorders (80.6%), Gastrointestinal Disorders (75.0%), Skin and Subcutaneous Tissue Disorders (66.7%), and General Disorders and Administration Site Conditions (63.9%). By preferred term, the most frequently reported AEs (reported by at least 25% of subjects) were headache (72.2%), fatigue (61.1%), diarrhea (30.6%), nausea (27.8%), skin irritation (27.8%) and pruritus (25.0%).

Table 4: Incidence of Adverse Events Reported in More Than 2 Subjects Overall by System Organ Class and Preferred Term – TMC114IFD1001

System Organ Class Preferred Term, n (%)	DRV/rtv N=34	DRV/COBI G003 N=35	DRV/COBI G004 N=34	Overall[a] N=36
Any Adverse Event	***30 (88.2)***	***31 (88.6)***	***27 (79.4)***	***36 (100.0)***
Eye Disorders	**2 (5.9)**	**1 (2.9)**	**1 (2.9)**	**4 (11.1)**
Conjunctival Irritation	1 (2.9)	1 (2.9)	1 (2.9)	3 (8.3)
Gastrointestinal Disorders	**14 (41.2)**	**15 (42.9)**	**15 (44.1)**	**27 (75.0)**
Abdominal Discomfort	0	1 (2.9)	3 (8.8)	4 (11.1)
Abdominal Pain	2 (5.9)	2 (5.7)	2 (5.9)	6 (16.7)
Abdominal Pain Upper	1 (2.9)	2 (5.7)	0	3 (8.3)
Constipation	1 (2.9)	1 (2.9)	1 (2.9)	3 (8.3)
Diarrhoea	5 (14.7)	5 (14.3)	5 (14.7)	11 (30.6)
Flatulence	4 (11.8)	1 (2.9)	1 (2.9)	6 (16.7)
Nausea	4 (11.8)	3 (8.6)	5 (14.7)	10 (27.8)
Regurgitation	1 (2.9)	1 (2.9)	1 (2.9)	3 (8.3)
General Disorders and Administration Site Conditions	**11 (32.4)**	**14 (40.0)**	**16 (47.1)**	**23 (63.9)**
Fatigue	11 (32.4)	11 (31.4)	15 (44.1)	22 (61.1)
Infections and Infestations	**4 (11.8)**	**2 (5.7)**	**2 (5.9)**	**7 (19.4)**
Nasopharyngitis	2 (5.9)	2 (5.7)	1 (2.9)	5 (13.9)
Metabolism and Nutrition Disorders	**2 (5.9)**	**2 (5.7)**	**2 (5.9)**	**5 (13.9)**
Decreased Appetite	2 (5.9)	2 (5.7)	2 (5.9)	5 (13.9)
Musculoskeletal and Connective Tissue Disorders	**2 (5.9)**	**2 (5.7)**	**1 (2.9)**	**4 (11.1)**
Nervous System Disorders	**17 (50.0)**	**20 (57.1)**	**20 (58.8)**	**29 (80.6)**
Dizziness	5 (14.7)	4 (11.4)	3 (8.8)	8 (22.2)
Headache	14 (41.2)	18 (51.4)	18 (52.9)	26 (72.2)
Somnolence	0	0	3 (8.8)	3 (8.3)
Renal and Urinary Disorders	**2 (5.9)**	**2 (5.7)**	**2 (5.9)**	**6 (16.7)**
Pollakiuria	1 (2.9)	2 (5.7)	2 (5.9)	5 (13.9)
Respiratory, Thoracic and Mediastinal Disorders	**2 (5.9)**	**2 (5.7)**	**2 (5.9)**	**6 (16.7)**
Oropharyngeal Pain	2 (5.9)	1 (2.9)	0	3 (8.3)
Skin and Subcutaneous Tissue Disorders	**12 (35.3)**	**8 (22.9)**	**14 (41.2)**	**24 (66.7)**
Acne	0	1 (2.9)	1 (2.9)	3 (8.3)
Hyperhidrosis	3 (8.8)	0	3 (8.8)	5 (13.9)
Pruritus	4 (11.8)	3 (8.6)	3 (8.8)	9 (25.0)
Rash	3 (8.8)	1 (2.9)	0	4 (11.1)
Skin Irritation	3 (8.8)	5 (14.3)	3 (8.8)	10 (27.8)
Vascular Disorders	**2 (5.9)**	**0**	**4 (11.8)**	**5 (13.9)**
Hot Flush	1 (2.9)	0	2 (5.9)	3 (8.3)

N=total number of subjects with data; n=number of subjects with observation.
[a] Includes the screening and follow-up periods.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 12.

Most AEs were grade 1 or grade 2 in severity. No grade 4 AEs were reported. A grade 3 AE was reported in 3 subjects (8.3%), 1 during each treatment session: fatigue during intake of DRV/rtv and maculo-papular rash during both sessions with DRV/COBI G003 and G004.

Adverse events considered at least possibly related to DRV or to DRV/COBI were mainly Nervous System Disorders, Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Table 13 and Table 14). Adverse events considered very likely related to

the study medication were reported for 4 subjects (11.1%); 2 subjects during DRV/rtv (1 rash, and 1 rash and pruritus), 1 subject during DRV/COBI G003 (maculo-papular rash), and 1 subject during DRV/COBI G004 (maculo-papular rash) (refer to Module 5.3.1.1/ TMC114IFD1001-CSR/Section 6.1.1).

Deaths, Serious Adverse Events and Other Significant Adverse Events

No death or other SAEs were reported in study TMC114IFD1001 (refer to Module 5.3.1.1/ TMC114IFD1001-CSR/Section 6.1.2).

Five subjects discontinued treatment prematurely due to an AE. Two subjects experienced rash during intake of DRV/rtv, 2 subjects experienced either rash or maculo-papular rash during intake of DRV/COBI G003, and 1 subject experienced maculo-papular rash during intake of DRV/COBI G004. All these events leading to permanent discontinuation were grade 2 or 3 in severity and considered probably or very likely related to the study medication (either DRV/rtv or DRV/COBI)[*] (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 6.1.2). More details on the subjects who had an AE leading to discontinuation are provided in Module 5.3.1.1/TMC114IFD1001-CSR/Supporting Data Display 1.

One subject suffered from fatigue (grade 3, possibly related to DRV/rtv). This AE started on Day 2 and lasted 6 days. No dose adjustments were made, the subject completed the study (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 6.1.2).

Narratives

Criteria for the generation of narratives in study TMC114IFD1001 were: AEs with fatal outcome, other SAEs, and AEs leading to discontinuation. Narratives are provided in Module 5.3.1.1/TMC114IFD1001-CSR/Supporting Data Display 1.

2.3.2.1.5. Clinical Laboratory Evaluations

Only treatment-emergent abnormalities are reported, ie, those abnormalities that emerged or worsened during treatment compared to the pretreatment reference value. The laboratory reports had to be interpreted for clinical significance by the investigator. Any clinically relevant change observed from signing the informed consent form (ICF) onwards had to be reported as an AE.

Descriptive statistics of the actual values of the laboratory parameters measured in study TMC114IFD1001 are provided in Module 5.3.1.1/TMC114IFD1001-Anal-Saf-Lab/ Display SAF.9. Descriptive statistics for the within-subject changes versus baseline are provided in Module 5.3.1.1/TMC114IFD1001-Anal-Saf-Lab /Display SAF.10. Overviews of the graded and nongraded laboratory abnormalities in study TMC114IFD1001 are provided in Module 5.3.1.1/TMC114IFD1001-Anal-Saf-Lab /Display SAF.11 and Module 5.3.1.1/ TMC114IFD1001-Anal-Saf-Lab /Display SAF.12, respectively.

[*] The rash of Subject 1001-0033 is grade 1 in the analysis tables and listings but is considered as grade 2 in severity in the CSR based on the available data.

Laboratory Values Over Time

In study TMC114IFD1001, laboratory values were inspected for obvious trends in change over time. No consistent or clinically relevant changes in blood chemistry or hematology were observed (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 6.2.1).

Incidence of Laboratory Abnormalities

The incidence of treatment-emergent graded laboratory abnormalities observed in at least 1 subject in any treatment phase is presented in Table 5. For the incidence of treatment-emergent nongraded laboratory abnormalities, refer to Module 5.3.1.1/TMC114IFD1001-CSR/Table 18.

No relevant differences in incidence of the graded or nongraded abnormalities between the treatment groups were obvious. The most frequent graded abnormalities were increased cholesterol levels, both LDL cholesterol and total cholesterol.

There was 1 subject with a grade 4 treatment-emergent laboratory abnormality (hyperkalemia) and 4 subjects with a grade 3 treatment-emergent laboratory abnormality: 1 subject with decreased lymphocyte count and 3 subjects with increased LDL cholesterol levels. For more details on these events, refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 6.2.1.

No laboratory abnormalities were reported as AEs.

Table 5: Incidence of Treatment-emergent Graded Laboratory Abnormalities – TMC114IFD1001

Laboratory Parameter Grouping **Laboratory Parameter** Grade[a], n (%)	**DRV/rtv** **N=34**	**DRV/COBI** **G003** **N=35**	**DRV/COBI** **G004** **N=34**
General Clinical Chemistry			
Hyperkalaemia			
Grade 1	0	0	1 (2.9)
Grade 4	0	0	1 (2.9)
Hypernatraemia			
Grade 1	3 (8.8)	2 (5.7)	1 (2.9)
Hyperuricaemia			
Grade 1	2 (5.9)	3 (8.6)	2 (5.9)
Hypocalcaemia (adjusted)			
Grade 1	2 (5.9)	2 (5.7)	2 (5.9)
Pancreatic Lipase			
Grade 1	1 (2.9)	1 (2.9)	1 (2.9)
Grade 2	0	0	1 (2.9)
General Hematology			
Hemoglobin			
Grade 1	1 (2.9)	2 (5.7)	1 (2.9)
Grade 2	1 (2.9)	0	0
Hematology Differential Counts			
Absolute Lymphocyte Count			
Grade 3	0	1 (2.9)	0
Neutrophils			
Grade 1	0	1 (2.9)	1 (2.9)
Lipids and Glucose			
Cholesterol			
Grade 1	8 (23.5)	7 (20.0)	10 (29.4)
Grade 2	8 (23.5)	14 (40.0)	11 (32.4)
LDL Cholesterol			
Grade 1	6 (17.6)	8 (22.9)	8 (23.5)
Grade 2	8 (23.5)	8 (22.9)	7 (20.6)
Grade 3	1 (2.9)	1 (2.9)	2 (5.9)
Liver Function			
Hyperbilirubinaemia			
Grade 1	0	0	1 (2.9)

N=total number of subjects with data; n=number of subjects with observation.
[a] DAIDS grades.
Source: Module 5.3.1.1/TMC114IFD1001-CSR/Table 17.

2.3.2.1.6. Electrocardiogram, Vital Signs, and Physical Examination

Electrocardiogram

Descriptive statistics of the actual measurements and the changes from reference are provided in Module 5.3.1.1/TMC114IFD1001-Anal-Saf-AE/Display SAF.13 and Display SAF.14, respectively. Changes in median ECG parameters were generally minor (refer to Module 5.3.1.1/TMC114IFD1001-CSR/Section 6.3.1). The QT values were corrected for heart rate using the Bazett (QTcB) and Fridericia (QTcF) formulae.[1,5]

Treatment-emergent abnormalities and changes in ECG parameters are presented in Module 5.3.1.1/TMC114IFD1001-CSR/Section 6.3.2. No relevant differences were observed in the incidence of ECG abnormalities between the treatment phases or treatment groups. The most frequent ECG abnormality was abnormally low heart rate, which was observed in 4 subjects

(12.5%) in the DRV/rtv treatment phase, in 5 subjects (14.7%) in the DRV/COBI G003 treatment phase, and in 5 subjects (14.7%) in the DRV/COBI G004 treatment phase.

At least 1 QTcF value >450 ms was observed in 3 subjects: in 2 subjects (6.3%) during DRV/rtv treatment and in 1 subject (2.9%) during DRV/COBI G003 and DRV/COBI G004 treatment. No QTcF values above 500 ms were recorded. Three QTcF abnormalities were <480 ms, the QTcF abnormality in the DRV/COBI G004 treatment phase was above 480 ms (ie, 488 ms). The QTcF abnormal values recorded during DRV/COBI G003 and DRV/COBI G004 treatment were the result of an increase from baseline between 30 to 60 ms. The abnormal QTcF values during DRV/rtv treatment were the result of increases from baseline <30 ms and were isolated observations (not confirmed at any other time point).

No ECG-related abnormalities were reported as AEs.

Vital Signs

Descriptive statistics of the actual measurements and the changes from reference are provided in Module 5.3.1.1/TMC114IFD1001-Anal-Saf-AE/Display SAF.17 and Display SAF.18, respectively. Median changes in vital signs parameters were generally small, and none of the changes were considered clinically relevant (refer to Module 5.3.1.1/ TMC114IFD1001-CSR/Section 6.3.1).

Treatment-emergent vital signs abnormalities are presented in Module 5.3.1.1/ TMC114IFD1001-CSR/Section 6.4.1. No relevant differences were observed in the incidence of vital signs abnormalities between the treatment phases or treatment groups.

The most frequent vital signs abnormality was abnormally low supine pulse, which was observed in 5 subjects (14.7%) in the DRV/rtv treatment phase, in 5 subjects (14.3%) in the DRV/COBI G003 treatment phase, and in 6 subjects (17.6%) in the DRV/COBI G004 treatment phase. All blood pressure abnormalities were grade 1 increased, except for 2 subjects with a grade 3 increased standing diastolic blood pressure (DBP) in the DRV/COBI G003 or G004 treatment phase (both on Day 10, 3 hours postdose).

Physical Examination

Abnormal new findings (ie, not present at screening) in physical examination were noted in 4 subjects. These findings were all reported as AEs (see Section 2.3.2.1.4).

2.3.2.1.7. Summary and Conclusions for Safety Data in Study TMC114IFD1001

The safety results of study TMC114IFD1001 demonstrated that administration of DRV/COBI 800/150 mg as FDC tablets G003 and G004 for 10 days under fed conditions in healthy adult subjects was generally safe and well tolerated.

Of the 36 randomized and treated subjects, 30 received treatment as planned, ie, DRV/rtv 800/100 mg once daily, DRV/COBI 800/150 mg once daily (G003 FDC tablet), and DRV/COBI 800/150 mg once daily (G004 FDC tablet); 6 subjects (16.7%) dropped out before study completion.

All 36 subjects experienced one or more AEs in the course of the study. The most common AEs by SOC (reported in at least 20% subjects) were Nervous System Disorders (80.6%), Gastrointestinal Disorders (75.0%), Skin and Subcutaneous Tissue Disorders (66.7%), and General Disorders and Administration Site Conditions (63.9%). The most frequently reported AEs by preferred term (in at least 25% of subjects) were headache (72.2%), fatigue (61.1%), diarrhea (30.6%), nausea (27.8%), skin irritation (27.8%) and pruritus (25.0%). Adverse events considered at least possibly related to DRV or to DRV/COBI were mainly Nervous System Disorders, Gastrointestinal Disorders, General Disorders and Administration Site Conditions, and Skin and Subcutaneous Tissue Disorders. Four subjects (11.1%) experienced an AE considered very likely related to the study medication, 2 subjects during DRV/rtv (1 rash, and 1 rash and pruritus), 1 subject during DRV/COBI G003 (maculo-papular rash), and 1 subject during DRV/COBI G004 (maculo-papular rash).

No deaths or other SAEs were reported. No relevant differences between treatments in incidence or severity of AEs were observed. Five subjects (13.9%) discontinued study medication prematurely due to an AE: 2 subjects in DRV/rtv treatment phase (both rash), 2 subjects in the DRV/COBI G003 treatment phase (rash and maculo-papular rash) and 1 subject in the DRV/COBI G004 treatment phase (maculo-papular rash). The AEs leading to permanent discontinuation were grade 2 or grade 3 in severity.

Median changes in laboratory parameters, ECG and vital signs parameters were generally small and not considered clinically relevant. None of the laboratory, ECG or vital signs abnormalities were reported as AEs.

In conclusion, administration of DRV/COBI as FDC tablets G003 and G004 was generally safe and well tolerated in healthy adult subjects. No safety signals were detected during treatment with DRV/COBI 800/150 mg in adult healthy subjects.

2.3.2.2. Safety Data in Study TMC114IFD1003

2.3.2.2.1. Study Design of TMC114IFD1003

In the open-label, randomized, 3-panel, single-center, single-dose, crossover Phase 1 study TMC114IFD1003, 133 healthy subjects between the ages of 18 and 60 years with a BMI of 18.5 to 30.0 kg/m^2 were randomized and treated to assess the bioequivalence of DRV when coadministered with COBI as either a FDC tablet (G006, pink-coated tablet with DRV/COBI 800/150 mg) or as single agents under fed and fasted conditions.

There were 2 treatment sessions for each of the 3 panels, with a washout period of at least 7 days between the 2 treatments sessions.

In Panel 1, 74 healthy subjects were randomly assigned to treatment sequence AB or BA (n=37 each). In Treatment A (Reference), a single dose of DRV 800 mg and COBI 150 mg were administered as single agents under fasted conditions. In Treatment B (Test), a single dose of DRV/COBI 800/150 mg was administered as FDC tablet G006 under fasted conditions.

In Panel 2, 40 healthy subjects were randomly assigned to treatment sequence CD or DC (n=20 each). In Treatment C (Reference), a single dose of DRV 800 mg and COBI 150 mg were administered as single agents under fed conditions (standardized breakfast). In Treatment D (Test), a single dose of DRV/COBI 800/150 mg was administered as a FDC tablet G006 under fed conditions (standardized breakfast).

In Panel 3, 19 healthy subjects were randomly assigned to treatment sequence EF (n=9) or FE (n=10). In Treatment E (Reference), a single dose of DRV/COBI 800/150 mg was administered as a FDC tablet G006, under fasted conditions. In Treatment F (Test), a single dose of DRV/COBI 800/150 mg was administered as a FDC tablet G006 under fed conditions (high-fat breakfast).

Full pharmacokinetic profiles of DRV and COBI were determined up to 72 hours after administration. Safety and tolerability were monitored and documented throughout the study. Subjects were seen at regular visits during which the investigator assessed the subject's medical condition, any AEs, laboratory safety, and study medication adherence.

All analyses were performed on the ITT population, defined as all subjects who received at least 1 dose of study medication (DRV or COBI), regardless of their adherence to the study protocol. For details on the timing and a description of the safety assessments as well as the methods used for the statistical analysis for AEs, clinical laboratory parameters, vital signs, physical examinations including body weight and height, and pharmacokinetic analyses, refer to Module 5.3.1.2/TMC114IFD1003-CSR/Section 3.9.

For further details on the design of the TMC114IFD1003 study, refer to the study report Module 5.3.1.2/TMC114IFD1003-CSR. For details on the statistical analysis of the safety data, refer to Module 5.3.1.2/TMC114IFD1003-SAP. Refer to Section 2.3.2.2.7 and Section 6 of this SCS for a summary and the conclusions of the safety results of the TMC114IFD1003 study. For the pharmacokinetic results of the study, refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2.

2.3.2.2.2. Overall Extent of Exposure

In study TMC114IFD1003, 133 subjects were randomized and treated. One hundred and thirty subjects completed the study as planned, 3 subjects dropped out before study completion. Reasons for early discontinuation were protocol violation for 1 subject in Panel 1 (Treatment sequence BA) during Treatment B in Session 1, and withdrawal by subjects for 2 subjects in Panel 2 (Treatment sequence DC) during Treatment D in Session 1. There were no discontinuations in Panel 3.

2.3.2.2.3. Demographic and Other Characteristics of Study Population

Demographic data are summarized in Table 6. No relevant differences were observed in demographic and baseline characteristics among the 3 panels.

Approximately half of the subjects were male (55.6%). The median age was 46.0 years (range 19 to 60 years) and the median BMI was 25.2 kg/m^2 (range 19 to 30 kg/m^2). All but 2 subjects were white, and all but 1 subject were not Hispanic or Latino.

All subjects had a nonreactive HIV serology test and negative hepatitis A antibody IgM, HBsAg, and hepatitis C antibody tests at screening. Serum pregnancy tests were negative for all female subjects. All subjects had negative alcohol breath tests and urine drug tests (amphetamines, barbiturates, benzodiazepine, cocaine, tetrahydrocannabinol [cannabinoids], opiates, methadone), at the last available test prior to the first study medication administration.

Table 6: Demographic Data – TMC114IFD1003

Parameter	Panel 1 N=74	Panel 2 N=40	Panel 3 N=19	All Subjects N=133
Age (Years)				
Mean (SD)	43.6 (10.56)	41.9 (13.65)	43.6 (11.06)	43.1 (11.58)
Median (Range)	46.0 (19 - 60)	43.0 (19 - 60)	46.0 (22 - 59)	46.0 (19 - 60)
Sex, n (%)				
Female	34 (45.9)	17 (42.5)	8 (42.1)	59 (44.4)
Male	40 (54.1)	23 (57.5)	11 (57.9)	74 (55.6)
Height (cm)				
Mean (SD)	171.8 (8.75)	173.6 (9.63)	173.7 (10.94)	172.6 (9.32)
Median (Range)	171.0 (156 - 197)	173.5 (153 - 191)	174.0 (153 - 195)	172.0 (153 - 197)
BMI (kg/m^2)				
Mean (SD)	24.9 (2.61)	25.0 (2.50)	25.4 (3.54)	25.0 (2.71)
Median (Range)	25.1 (19 - 30)	25.2 (20 - 30)	25.3 (19 - 30)	25.2 (19 - 30)
Race, n (%)				
Black or African American	1 (1.4)	0	1 (5.3)	2 (1.5)
White	73 (98.6)	40 (100.0)	18 (94.7)	131 (98.5)
Ethnicity, n (%)				
Hispanic/Latino	1 (1.4)	0	0	1 (0.8)
Not Hispanic/Latino	73 (98.6)	40 (100.0)	19 (100.0)	132 (99.2)
Smoker, n (%)				
No	69 (93.2)	37 (92.5)	17 (89.5)	123 (92.5)
Yes	5 (6.8)	3 (7.5)	2 (10.5)	10 (7.5)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 9.

2.3.2.2.4. Adverse Events

Unless specified otherwise, 1) the AEs presented below are those with onset during the treatment phase, 2) AEs are reported by preferred term, 3) drug relatedness to study medication (DRV, unless otherwise specified) is per assessment of the investigator, and 4) AE summary tables are by SOC and by preferred term, both ordered alphabetically. All AEs were mapped according to MedDRA version 15.

Summary of Adverse Events

There were no deaths or SAEs reported in this study (Table 7). None of the subjects permanently stopped or temporarily interrupted the study medication due to an AE.

Sixty-four subjects (48.1%) experienced 1 or more treatment-emergent AEs. A difference of >10% in AE reporting was observed between Treatment B (40.5%) and D (40.0%) versus Treatment E (26.3%). All AEs were grade 1 (56 subjects, 42.1%) or grade 2 in severity (8 subjects, 6.0%). Grade 2 AEs were observed only in Treatments A (3 subjects, 4.1%), B (3 subjects, 4.1%) and F (2 subjects, 10.5%).

Twenty-seven subjects (20.3%) had one or more AEs that were considered at least possibly related to DRV, and 26 subjects (19.5%) had one or more AEs that were considered at least possibly related to COBI.

Table 7: Summary of Adverse Events – TMC114IFD1003

	PANEL 1		PANEL 2		PANEL 3		
n (%) of Subjects Experiencing	**DRV/COBI 800/150 mg Single Agents Fasted (A) N=73**	**DRV/COBI 800/150 mg FDC Fasted (B) N=74**	**DRV/COBI 800/150 mg Single Agents Fed (Std) (C) N=38**	**DRV/COBI 800/150 mg FDC Fed (Std) (D) N=40**	**DRV/COBI 800/150 mg FDC Fasted (E) N=19**	**DRV/COBI 800/150 mg FDC, Fed (High-fat) (F) N=19**	**All Subjects N=133**
≥1 AE	23 (31.5)	30 (40.5)	13 (34.2)	16 (40.0)	5 (26.3)	6 (31.6)	64 (48.1)
≥1 SAE	0	0	0	0	0	0	0
≥1 Grade 1 AE	20 (27.4)	27 (36.5)	13 (34.2)	16 (40.0)	5 (26.3)	4 (21.1)	56 (42.1)
≥1 Grade 2 AE	3 (4.1)	3 (4.1)	0	0	0	2 (10.5)	8 (6.0)
≥1 Grade 3-4 AE	0	0	0	0	0	0	0
≥1 AE for Which DRV was Permanently Stopped	0	0	0	0	0	0	0
≥1 AE for Which COBI was Permanently Stopped	0	0	0	0	0	0	0
≥1 AE at Least Possibly Related to DRV	11 (15.1)	17 (23.0)	1 (2.6)	3 (7.5)	0	1 (5.3)	27 (20.3)
≥1 AE at Least Possibly Related to COBI	10 (13.7)	15 (20.3)	1 (2.6)	3 (7.5)	0	1 (5.3)	26 (19.5)

N=total number of subjects with data; n=number of subjects with observation; Std=standard
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 24.

Common Adverse Events

The incidence of AEs reported in more than 1 subject in any SOC or preferred term is presented in Table 8. For the complete table of AEs, refer to Module 5.3.1.2/TMC114IFD1003-CSR/Table 25.

The most common treatment-emergent AEs by SOC (reported in at least 10% subjects) were Nervous System Disorders (33.1%), Gastrointestinal Disorders (19.5%), and Musculoskeletal and Connective Tissue Disorders (13.5%).

The most frequently reported AEs by preferred term (in at least 5% of subjects) were headache (30.1%), muscle spasms (9.0%), and diarrhea (8.3%).

For the incidence of AEs with at least grade 2 in severity, per SOC and preferred term, refer to Module 5.3.1.2/TMC114IFD1003-CSR/Table 26. The most common grade 2 AEs by SOC were Nervous System Disorders (5 subjects, 3.8%), with grade 2 headache being the most common preferred term (5 subjects, 3.8%). Grade 2 muscle spasms was reported in 2 subjects (1.5%); all other grade 2 AEs were reported in only 1 subject. There were no grade 3 or 4 AEs in the study.

For the incidence of AEs at least possibly related to the study medication, refer to Module 5.3.1.2/TMC114IFD1003-CSR/Table 27. Most AEs considered at least possibly related to study medication were observed in Treatment B followed by Treatment A. There were no AEs reported to be at least possibly related to DRV or COBI in Treatment E. For most AEs, the relationship to DRV and COBI was considered to be the same (ie, both not or doubtfully related, or both at least possibly related.

At least 1 AE considered at least possibly related to DRV was reported in 20.3% of subjects. By SOC, they concerned mainly (in at least 5% of subjects) Gastrointestinal Disorders (13.5%) and Nervous System Disorders (8.3%). By preferred term, the most frequent AEs considered at least possibly related to DRV (in at least 5% of subjects) were headache (8.3%) and diarrhea (7.5%).

At least 1 AE considered at least possibly related to COBI was reported in 19.5% of subjects. By SOC, they concerned mainly (in at least 5% of subjects) Gastrointestinal Disorders (12.8%) and Nervous System Disorders (8.3%). By preferred term, the most frequent AEs considered at least possibly related to COBI (in at least 5% of subjects) were headache (8.3%) and diarrhea (7.5%).

There was 1 subject with a skin event of interest in the study (Panel 1, Treatment Sequence AB). In Treatment A and treatment B, the subject experienced rash on Day 1 of the treatment session, and the AE resolved on Day 2 of each treatment session. The rash was grade 1 in Treatment A, and grade 2 in Treatment B, possibly related to DRV and COBI in Treatment A and probably related to DRV and COBI in Treatment B. On both occasions, the subject received levocetirizine dihydrochloride therapy for 1 day. No concomitant abnormalities in laboratory results or vital signs were reported for this subject.

Table 8: Incidence of Adverse Events Reported in More Than 1 Subject in any System Organ Class or Preferred Term – TMC114IFD1003

	PANEL 1		PANEL 2		PANEL 3		
System Organ Class Preferred Term, n (%)	**DRV/COBI 800/150 mg Single Agents Fasted (A) N=73**	**DRV/COBI 800/150 mg FDC Fasted (B) N=74**	**DRV/COBI 800/150 mg Single Agents Fed (Std) (C) N=38**	**DRV/COBI 800/150 mg FDC Fed (Std) (D) N=40**	**DRV/COBI 800/150 mg FDC Fasted (E) N=19**	**DRV/COBI 800/150 mg FDC, Fed (High-fat) (F) N=19**	**All Subjects N=133**
Subjects with 1 or more AEs	***23 (31.5)***	***30 (40.5)***	***13 (34.2)***	***16 (40.0)***	***5 (26.3)***	***6 (31.6)***	***64 (48.1)***
Gastrointestinal Disorders	**9 (12.3)**	**11 (14.9)**	**4 (10.5)**	**3 (7.5)**	**4 (21.1)**	**2 (10.5)**	**26 (19.5)**
Abdominal Discomfort	2 (2.7)	1 (1.4)	0	0	0	0	3 (2.3)
Abdominal Pain	2 (2.7)	2 (2.7)	0	0	0	0	4 (3.0)
Diarrhoea	4 (5.5)	5 (6.8)	0	3 (7.5)	1 (5.3)	1 (5.3)	11 (8.3)
Flatulence	1 (1.4)	1 (1.4)	0	2 (5.0)	0	0	4 (3.0)
Nausea	0	4 (5.4)	2 (5.3)	0	0	0	6 (4.5)
Vomiting	2 (2.7)	0	0	0	2 (10.5)	1 (5.3)	4 (3.0)
General Disorders & Administration Site Conditions	**2 (2.7)**	**0**	**0**	**1 (2.5)**	**0**	**0**	**3 (2.3)**
Fatigue	1 (1.4)	0	0	1 (2.5)	0	0	2 (1.5)
Infections and Infestations	**1 (1.4)**	**1 (1.4)**	**0**	**1 (2.5)**	**0**	**0**	**3 (2.3)**
Oral Herpes	1 (1.4)	1 (1.4)	0	0	0	0	2 (1.5)
Musculoskeletal and Connective Tissue Disorders	**4 (5.5)**	**7 (9.5)**	**3 (7.9)**	**4 (10.0)**	**1 (5.3)**	**0**	**18 (13.5)**
Back Pain	1 (1.4)	0	2 (5.3)	1 (2.5)	0	0	4 (3.0)
Muscle Spasms	3 (4.1)	7 (9.5)	0	2 (5.0)	1 (5.3)	0	12 (9.0)
Pain in Extremity	0	0	1 (2.6)	1 (2.5)	0	0	2 (1.5)
Nervous System Disorders	**10 (13.7)**	**17 (23.0)**	**11 (28.9)**	**7 (17.5)**	**4 (21.1)**	**6 (31.6)**	**44 (33.1)**
Dizziness	1 (1.4)	2 (2.7)	2 (5.3)	0	0	0	4 (3.0)
Headache	9 (12.3)	15 (20.3)	9 (23.7)	6 (15.0)	4 (21.1)	6 (31.6)	40 (30.1)
Paresthesia	1 (1.4)	0	0	1 (2.5)	0	0	2 (1.5)
Reproductive System and Breast Disorders	**2 (2.7)**	**0**	**0**	**0**	**0**	**0**	**2 (1.5)**
Respiratory, Thoracic and Mediastinal Disorders	**1 (1.4)**	**1 (1.4)**	**0**	**1 (2.5)**	**0**	**0**	**3 (2.3)**
Oropharyngeal Pain	1 (1.4)	0	0	1 (2.5)	0	0	2 (1.5)
Skin and Subcutaneous Tissue Disorders	**2 (2.7)**	**1 (1.4)**	**1 (2.6)**	**1 (2.5)**	**0**	**0**	**4 (3.0)**

N=total number of subjects with data; n=number of subjects with observation; Std=standard
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 24.

2.3.2.2.5. Clinical Laboratory Evaluations

Only treatment-emergent abnormalities are reported, ie, those abnormalities that first occurred or worsened versus reference during treatment. The laboratory reports had to be interpreted for clinical significance by the investigator. Any clinically relevant change observed from the signing of the ICF onwards had to be reported as an AE.

Laboratory Values Over Time

Descriptive statistics of the actual laboratory values and changes from reference are provided in Module 5.3.1.2/TMC114IFD1003-Anal-Saf-Lab/TSFLAB01 and TSFLAB02, respectively. Laboratory values were inspected for obvious trends in change over time. No consistent or clinically relevant changes in blood chemistry or hematology were observed.

Incidence of Laboratory Abnormalities

The incidence of treatment-emergent graded laboratory abnormalities observed in more than 1 subject in at least 1 treatment phase is presented in Table 9. For the incidence of treatment-emergent nongraded laboratory abnormalities, refer to Module 5.3.1.2/ TMC114IFD1003-CSR/Table 29.

There were generally no relevant or consistent differences between the treatment groups in the incidence of graded or nongraded abnormalities.

The most frequent graded abnormalities were increased cholesterol levels: total cholesterol (41.4%) and LDL cholesterol (26.3%). The majority of these abnormalities were grade 1. The most frequent nongraded abnormalities (observed in more than 15% of subjects) were decreased protein (21.1%), increased monocytes (18.8%), and decreased eosinophils (16.5%).

Three subjects had a grade 3 treatment-emergent laboratory abnormality (increased amylase, increased ALT, and increased pancreatic lipase in 1 subject each). In addition, 3 subjects had a grade 3 abnormality in the follow-up phase (2 subjects with increased LDL and 1 subject with increased triglycerides). For details on these events, please refer to Module 5.3.1.2/ TMC114IFD1003-CSR/Section 6.2.3.

No laboratory abnormalities were reported as AEs.

Table 9: Incidence of Graded Laboratory Abnormalities in More Than 1 Subject in at Least 1 Treatment Session – TMC114IFD1003

Laboratory Parameter Grade [a], n (%)	PANEL 1 DRV/COBI 800/150 mg Single Agents Fasted (A)	PANEL 1 DRV/COBI 800/150 mg FDC Fasted (B)	PANEL 2 DRV/COBI 800/150 mg Single Agents Fed (Std) (C)	PANEL 2 DRV/COBI 800/150 mg FDC Fed (Std) (D)	PANEL 3 DRV/COBI 800/150 mg FDC Fasted (E)	PANEL 3 DRV/COBI 800/150 mg FDC, Fed (High-fat) (F)	All Subjects
Subjects Treated (N)	**73**	**74**	**38**	**40**	**19**	**19**	**133**
Amylase							
Grade 1	0	0	1 (2.6)	2 (5.0)	0	1 (5.3)	3 (2.3)
Grade 3	1 (1.4)	0	0	0	0	0	1 (0.8)
Cholesterol							
Grade 1	16 (21.9)	22 (29.7)	14 (36.8)	7 (17.5)	4 (21.1)	6 (31.6)	44 (33.1)
Grade 2	4 (5.5)	3 (4.1)	2 (5.3)	2 (5.0)	0	2 (10.5)	11 (8.3)
Hypoalbuminaemia							
Grade 1	7 (9.6)	4 (5.4)	0	2 (5.0)	0	0	12 (9.0)
LDL Cholesterol							
Grade 1	9 (12.3)	12 (16.2)	4 (10.5)	5 (12.5)	4 (21.1)	4 (21.1)	28 (21.1)
Grade 2	5 (6.8)	5 (6.8)	0	0	0	0	7 (5.3)
Pancreatic Lipase							
Grade 1	0	2 (2.7)	0	0	1 (5.3)	0	3 (2.3)
Grade 2	1 (1.4)	1 (1.4)	1 (2.6)	1 (2.5)	0	1 (5.3)	4 (3.0)
Grade 3	0	0	0	1 (2.5)	0	0	1 (0.8)

N=total number of subjects with data; n=number of subjects with observation; Std=standard.
[a] DAIDS grades.
Source: Module 5.3.1.2/TMC114IFD1003-CSR/Table 28.

2.3.2.2.6. Vital Signs and Physical Examination

Vital Signs

For descriptive statistics of the actual measurements and the changes from reference, refer to Module 5.3.1.2/TMC114IFD1003-Anal-Saf-VS/TSFVIT01 and TSFVIT02, respectively. Median changes in vital signs parameters were generally small, and none of the changes were considered clinically relevant.

A crosstabulation of the worst vital signs abnormalities versus reference is provided in Module 5.3.1.2/TMC114IFD1003-Anal-Saf-VS/TSFVIT03. No clinically relevant differences in the incidence of vital signs abnormalities between the treatment groups were observed.

The most frequent vital signs abnormalities were increased standing systolic blood pressure and DBP, observed in 6.8% and 6.0% of subjects, respectively. All vital signs abnormalities were grade 1 increased, except for 1 grade 2 increased standing DBP reported in 1 subject.

None of the vital signs abnormalities were reported as an AE.

Physical Examination

Abnormal new findings (ie, not present at screening) in physical examination were noted in 5 subjects (2 in Panel 1 and 3 in Panel 2). Four of these findings were reported as a grade 1 AE (gingival bleeding and gingival discoloration, oral herpes, acne, and dry skin).

2.3.2.2.7. Summary and Conclusions for Safety Data in Study TMC114IFD1003

The safety results of study TMC114IFD1003 demonstrated that a single administration of DRV/COBI 800/150 mg as FDC tablet G006 or coadministered as single agents in healthy adult subjects was generally safe and well tolerated.

Of the 133 randomized and treated subjects, 130 received treatment as planned, ie, 2 single administrations of DRV/COBI 800/150 mg as a FDC tablet (G006), or coadministered as single agents under fed or fasted conditions, with a 7-day washout phase between administrations. Three subjects (2.3%) dropped out before study completion, 1 because of a protocol violation and 2 withdrew consent.

Sixty-four subjects (48.1%) experienced 1 or more treatment-emergent AE. The most common AEs by SOC (reported in at least 10% subjects) were Nervous System Disorders (33.1%), Gastrointestinal Disorders (19.5%), and Musculoskeletal and Connective Tissue Disorders (13.5%). The most frequently reported AEs by preferred term (in at least 5% of subjects) were headache (30.1%), muscle spasms (9.0%), and diarrhea (8.3%). No clinically relevant differences between treatments in incidence of AEs were observed.

No deaths or other SAEs were observed in this study. All AEs were grade 1 (42.1%) or grade 2 (6.0%) in severity. There were no premature study discontinuations due to an AE.

Twenty-seven subjects (20.3%) had 1 or more AEs that were considered at least possibly related to DRV, while 26 subjects (19.5%) had 1 or more AEs that were considered at least possibly related to COBI. There were 2 grade 2 AEs with an at least possible drug relationship: grade 2 vomiting was considered at least possibly related to DRV and to COBI, and grade 2 rash was considered at least possibly related to DRV.

Median changes in laboratory parameters and vital signs parameters were generally small and not considered clinically relevant. No laboratory or vital sign abnormality was reported as an AE.

In conclusion, administration of DRV/COBI 800/150 mg as FDC tablet G006 or coadministered as single agents under fed and fasted conditions was generally safe and well tolerated in healthy adult subjects. No safety signals were detected during treatment with DRV/COBI 800/150 mg in adult healthy subjects.

3. SAFETY DATA IN HIV-1 INFECTED SUBJECTS

In this section of the SCS, the safety data in HIV-1 infected subjects are presented. In Section 3.1, the safety data with DRV/rtv 800/100 mg once daily are briefly summarized. A brief statement on the safety of COBI in HIV-1 infected subjects is given in Section 3.2. In Section 3.3, the safety data with DRV/COBI 800/150 mg once daily are presented, ie, the results of the Week-24 primary analysis of study GS-US-216-0130, including data up to the cut-off date ([redacted]), when the last subject had his/her Week-24 visit or discontinuation visit. In Section 3.4, a summary is presented of available Week-48 safety data of the ongoing study GS-US-216-0130 (including data up to the cut-off date of [redacted]), and of the SAEs considered by the investigator to be related to DRV/COBI reported during ongoing studies with DRV/COBI and received up until the cut-off date of [redacted] for this SCS.

3.1. Safety Data with DRV/rtv 800/100 mg

In HIV-1 infected subjects, the safety of treatment with DRV/rtv 800/100 mg once daily in combination with other ARTs has been demonstrated by the 192-week study TMC114-C211 in 343 ART-naïve HIV-1 infected adult subjects (refer to Module 5.3.5.1/ TMC114-C211-W192-CRR), by the 48-week study TMC114-C229 in 294 ART-experienced HIV-1 infected adult subjects without DRV RAM (refer to Module 5.3.5.1/ TMC114-C229-W48-CRR), and by postmarketing experience.[2,8]

Study TMC114-C211 (ARTEMIS) was a randomized, active-controlled, open-label, 192-week, Phase 3 study to evaluate the efficacy, safety and tolerability, resistance characteristics and pharmacokinetics of DRV with rtv in combination with other antiretroviral drugs (ARVs) for the treatment of HIV-1 infection in treatment-naïve adults. Subjects were treated with DRV/rtv 800/100 mg once daily or a daily dose of lopinavir (LPV)/rtv 800/200 mg in combination with a fixed backgroung regimen consisting of TDF 300 mg once daily and FTC 200 mg once daily. The primary objective was to establish non-inferiority in virologic response of DRV/rtv to LPV/rtv. Secondary objectives included the evaluation of the safety and tolerability over 192 weeks. Identified risks for DRV/rtv prior to this study included hepatotoxicity, hyperglycemia, lipid abnormalities, viral resistance and drug interactions. The patient exposure in study TMC114-C211 was comparable to products of the same class at the same stage. In the Week-48 safety analysis,

no new safety signals were identified in the treatment-naïve population. Overall, the safety and tolerability findings from the Week-48 analysis, combined with the knowledge already gained from studies and experience in treatment-experienced subjects demonstrate a safety profile similar to that seen with other boosted PIs. In the Week-96 safety analysis, no substantial changes in the incidence of AEs were observed compared to the Week-48 data. In the Week-192 safety analysis, no new safety signals were identified and the safety profile was in general comparable to that of Week 48 and Week 96. The Week-192 analysis identified 3 additional DRV/rtv ADRs of at least grade 2 compared to the Week-24 analysis (lipodystrophy, osteonecrosis, and diabetes – see Section 3.3.11 for the Week-24 ADR analysis of TMC114-C211). These ADRs are expected to also occur when DRV is boosted with COBI. The ADRs to DRV/rtv 800/100 mg once daily in ART-naïve HIV-1 infected adult subjects are presented in Table 10.

No apparent relationship was observed between the AUC_{24h} and C_{0h} of DRV and the occurrence of AEs of interest, including rash-, cardiac-, gastrointestinal-, liver-, lipid- and glucose-related AEs, or AEs in the system organ classes of nervous system disorders and psychiatric disorders (refer to Module 5.3.5.1/TMC114-C211-W48-CRR/Section 4.8.2).

Table 10: Adverse Drug Reactions to DRV/rtv 800/100 mg Once Daily at Least Grade 2 - TMC114-C211 Week-192 Analysis

System Organ Class Adverse Drug Reaction[a] n (%)	DRV/rtv 800/100 mg once daily + TDF/FTC N=343	LPV/rtv 800/200 mg daily dose + TDF/FTC N=346
Gastrointestinal Disorders		
Abdominal Pain	20 (5.8)	21 (6.1)
Acute Pancreatitis	2 (0.6)	2 (0.6)
Diarrhoea	30 (8.7)	55 (15.9)
Dyspepsia	1 (0.3)	1 (0.3)
Flatulence	3 (0.9)	3 (0.9)
Nausea	14 (4.1)	13 (3.8)
Vomiting	7 (2.0)	12 (3.5)
General disorders and Administration Site Conditions		
Asthenia	3 (0.9)	0
Fatigue	3 (0.9)	10 (2.9)
Hepatobiliary Disorders		
Acute Hepatitis	1 (0.3)	3 (0.9)
Immune System Disorders		
(Drug) Hypersensitivity[c]	2 (0.6)	5(1.4)
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)
Metabolism and nutrition disorders		
Anorexia	5 (1.5)	3 (0.9)
Diabetes Mellitus	2 (0.6)	3 (0.9)
Musculoskeletal and Connective Tissue Disorders		
Myalgia	2 (0.6)	5 (1.4)
Osteonecrosis[c]	1 (0.3)	0
Nervous System Disorders		
Headache	23 (6.7)	19 (5.5)
Psychiatric Disorders		
Abnormal Dreams	1 (0.3)	1 (0.3)
Skin and Subcutaneous Tissue Disorders		
Angioedema[c]	2 (0.6)	0
Lipodystrophy[b]	3 (0.9)	6 (1.7)
Pruritus	4 (1.2)	3 (0.9)
Rash	10 (2.9)	16 (4.6)
Stevens-Johnson Syndrome	1 (0.3)	0
Urticaria[c]	4 (1.2)	2 (0.6)

N=total number of subjects with data; n=number of subjects with ADR; qd= once daily
[a] Excluding laboratory abnormalities reported as ADRs.
[b] Lipohypertrophy, lipodystrophy, and lipoatrophy.
[c] ADRs identified from postmarketing experience.
Source: Module 5.3.5.1/TMC114-C211-W192-CRR

Grade 2 to 4 DAIDS abnormalities (grade during DRV/rtv treatment worse than baseline grade) in selected laboratory parameters, considered laboratory-related DRV/rtv ADRs, observed in ART-naïve adult subjects are presented in Table 11.

Table 11: Laboratory-related Adverse Drug Reactions (DAIDS Grade 2 to 4) with DRV/rtv 800/100 mg once daily - TMC114-C211 Week 192 Analysis

Laboratory Parameter DAIDS Grade, n (%)	Limit	DRV/rtv 800/100 mg once daily + TDF/FTC N=343	LPV/rtv 800/200 daily dose + TDF/FTC N=346
Alanine Aminotransferase			
Grade 2	>2.5 to ≤5.0 x ULN	30 (8.8)	32 (9.4)
Grade 3	>5.0 to ≤10.0 x ULN	10 (2.9)	12 (3.5)
Grade 4	>10.0 x ULN	3 (0.9)	10 (2.9)
Aspartate Aminotransferase			
Grade 2	>2.5 to ≤5.0 x ULN	25 (7.3)	34 (9.9)
Grade 3	>5.0 to ≤10.0 x ULN	15 (4.4)	8 (2.3)
Grade 4	>10.0 x ULN	4 (1.2)	9 (2.6)
Alkaline Phosphatase			
Grade 2	>2.5 to ≤5.0 x ULN	5 (1.5)	5 (1.5)
Grade 3	>5.0 to ≤10.0 x ULN	0	2 (0.6)
Triglycerides			
Grade 2	500-750 mg/dL	9 (2.6)	34 (9.9)
Grade 3	751-1200 mg/dL	6 (1.8)	17 (5.0)
Grade 4	>1200 mg/dL	5 (1.5)	4 (1.2)
Total Cholesterol[a]			
Grade 2	240-300 mg/dL	78 (22.9)	93 (27.1)
Grade 3	>300 mg/dL	5 (1.5)	19 (5.5)
LDL Cholesterol[a]			
Grade 2	160-190 mg/dL	48 (14.1)	42 (12.3)
Grade 3	≥ 191 mg/dL	30 (8.8)	21 (6.1)
Elevated Glucose Levels			
Grade 2	126-250 mg/dL	37 (10.8)	33 (9.6)
Grade 3	251-500 mg/dL	4 (1.2)	1 (0.3)
Pancreatic Lipase			
Grade 2	>1.5 to ≤3.0 x ULN	9 (2.6)	6 (1.7)
Grade 3	>3.0 to ≤5.0 x ULN	2 (0.6)	4 (1.2)
Grade 4	>5.0 x ULN	0	3 (0.9)
Pancreatic Amylase			
Grade 2	>1.5 to ≤2.0 x ULN	16 (4.7)	8 (2.3)
Grade 3	>2.0 to ≤5.0 x ULN	16 (4.7)	14 (4.1)
Grade 4	>5.0 x ULN	0	3 (0.9)

N=total number of subjects; n=number of subjects with observation.
[a] Grade 4 data not applicable for cholesterol in the DAIDS grading scale.
Source: Module 5.3.5.1/TMC114-C211-W192-CRR

Study TMC114-C229 (ODIN) was a 48-week, randomized (1:1 ratio), open-label, non-inferiority study comparing DRV/rtv 800/100 mg once daily (N=294) with DRV/rtv 600/100 mg twice daily (both in combination with an individually selected optimized background regimen consisting of more than 2 NRTIs) in treatment-experienced HIV-1 infected subjects with screening genotype resistance testing showing no DRV RAMs. In the Week-48 analysis of study TMC114-C229, the safety profile of the DRV/rtv 800/100 mg once daily dosing regimen in ART-experienced adult subjects with 0 DRV RAMs was in line with the known safety profile for DRV. The safety profile of DRV/rtv in study TMC114-C229 is discussed in Sections 3.3.11 (Week 24) and 3.4.1.4 (Week 48).

Within both treatment groups, no apparent relationship was observed between the pharmacokinetic parameters for DRV or rtv and the occurrence of AEs leading to permanent

discontinuation of the study drug; or between DRV or rtv pharmacokinetic parameters and rash-, cardiac-, gastrointestinal-, liver-, lipid- and glucose-related AEs; or AEs in the SOCs of nervous system disorders or psychiatric disorders system; or laboratory lipid abnormalities. In addition, a pooled analysis for DRV and rtv exposure in the 2 treatment groups versus gastrointestinal-related AEs and maximum changes in lipid parameters showed no relevant relationships between DRV or rtv exposure and these safety parameters.

3.2. Safety Data with COBI 150 mg

Gilead has characterized the safety profile of COBI in HIV-1 infected subjects during its COBI development programs.[10,11] The collected safety data do not provide pertinent information for the present application, as they are affected by the ARV COBI is boosting (either EVG or ATV). Therefore, they are not further discussed. Information relevant to the FDC and not affected by the administration of EVG or ATV is discussed in Sections 3.3 and 3.4.2.

3.3. Safety Data with DRV/COBI 800/150 mg

3.3.1. Study Design of GS-US-216-0130

Study GS-US-216-0130 is a Phase 3b open-label, single-arm, multicenter study in HIV-1 infected, ART-naïve or ART-experienced adult subjects with no DRV RAMs. The primary objective of this study was to evaluate the safety and tolerability of DRV/COBI 800/150 mg coadministered as single agents once daily plus 2 NRTIs after 24 weeks of treatment.

A total of 314 subjects were enrolled, and 313 subjects received at least 1 dose of study medication, ie, DRV/COBI 800/150 mg once daily coadministered as single agents. Of these 313 subjects, 295 (94.2%) were ART-naïve and 18 (5.8%) were ART-experienced. Subjects were considered treatment-naïve if they had never received treatment with an approved or investigational ARV drug. Subjects were considered treatment-experienced if they had been on a stable ARV regimen for at least 12 weeks prior to screening. For further details on inclusion and exclusion criteria, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 7.3.

Subjects were scheduled to receive DRV/COBI 800/150 mg once daily coadministered as single agents plus 2 fully active investigator-selected NRTIs selected after resistance testing at screening. All treatments were to be administered orally under fed conditions for a treatment period of 48 weeks. In subjects with the M184V/I reverse transcriptase mutation present at screening, FTC or lamivudine could be included as a third (not-fully active) NRTI for the purpose of maintaining the M184V mutation.

The primary Week-24 analysis (safety, efficacy, and resistance analyses) was performed when all subjects had been treated for 24 weeks or discontinued earlier (cut-off date [redacted]). The subject's medical condition, any AEs, laboratory evaluations for efficacy and safety, and study medication adherence were monitored and documented at screening, at baseline/Day 1, and at all subsequent study visits. For more details on the timing of the treatment and assessments, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 7.5.1 and Module 5.3.5.2/ GS-US-216-0130-W24-SAP.

For more information on the efficacy results of the GS-US-216-0130 study, refer to the Summary of Clinical Efficacy (Module 2.7.3/Section 2). For more information on the pharmacokinetic results of the GS-US-216-0130 study, refer to the Summary of Clinical Pharmacology Studies (Module 2.7.2). Refer to Section 3.3.12 and Section 6 of this document for a summary and the conclusions of the safety results of the GS-US-216-0130 study.

For completeness, the safety data are tabulated in 3 columns: the total subject group and the 2 subgroups by previous ARV treatment experience. In this SCS, the focus is on the total subject group because of the small sample size of treatment-experienced subjects, and because the safety profile of DRV/rtv once daily is similar in treatment-experienced and treatment-naïve subjects.

3.3.2. Subject Disposition

Of the 397 subjects screened, 314 were enrolled in the study at 56 sites in the United States. The ITT population comprised 313 subjects who received at least 1 dose of both study medications DRV and COBI. Of the 313 subjects, 295 were treatment-naïve and 18 were treatment-experienced, and 182 (58.1%) had screening HIV-1 RNA ≤100,000 copies/mL (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 8.1). All the data presented in this document are data on the ITT unless otherwise specified.

Overall, 39 subjects (12.5%) discontinued study medication prior to the Week-24 analysis cut-off date (Table 12). The most common (>1% of subjects) reasons for premature discontinuation of study medication were AE(s) (4.8%), lost to follow-up (3.5%), subject noncompliance (1.9%), and withdrawal of consent (1.6%).

Table 12: Disposition of Subjects – GS-US-216-0130 Week-24 Analysis

Subject Disposition, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Subjects Prematurely Discontinuing Study Medication	36 (12.2)	3 (16.7)	39 (12.5)
Reasons for Discontinuing Study Medication			
Adverse Event	15 (5.1)	0	15 (4.8)
Investigator's Discretion	1 (0.3)	0	1 (0.3)
Withdrew Consent	4 (1.4)	1 (5.6)	5 (1.6)
Lost to Follow-up	9 (3.1)	2 (11.1)	11 (3.5)
Subject Noncompliance	6 (2.0)	0	6 (1.9)
Protocol Violation	1 (0.3)	0	1 (0.3)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-2.

3.3.3. Extent of Exposure

The median (range) duration of exposure to study medication was 31.4 weeks (0.1 to 42.4 weeks), with a median exposure of 31.9 weeks in the treatment-naïve subjects and a median exposure of 26.6 weeks in treatment-experienced subjects. A total of 281 subjects (89.8%) had received the study medication for at least 24 weeks at the time of the cut-off date for this analysis, 89.8% of the treatment-naïve subjects and 88.9% of the treatment-experienced subjects (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.1).

The total of patient-years exposure is 179.9 patient-years (ie, the sum of treatment durations in years, calculated as the mean treatment duration in weeks x N/52).

3.3.4. Treatment Adherence

Adherence to DRV and COBI was measured by pill count, ie, the ratio of the number of pills taken (dispensed minus returned) over the number of prescribed pills for the period the subject was in the study.

Up to Week 24, adherence to the prescribed DRV/COBI study medication was 99.0% in all subjects, 99.2% in treatment-naïve subjects and 97.3% in treatment-experienced subjects (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 3.2.1). An adherence rate of ≥95% up to the Week 24 visit was recorded in 94.6% in the treatment-naïve subjects and in 77.8% of the treatment-experienced subjects.

3.3.5. Demographic and Other Characteristics of Study Population

Demographic data and baseline disease characteristics are summarized in Table 13 and Table 14, respectively.

The majority of subjects were male (89.1%), their median age was 35 years (range 18 to 72 years); most were white (59.7%) or black (34.5%), and their ethnicity was most often not Hispanic or Latino (78.3%). The median baseline BMI was 25.7 kg/m^2 (range 16.5 to 45.3 kg/m^2).

Table 13: Demographic Data – GS-US-216-0130 Week-24 Analysis

Parameter	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Age (years)			
Median (Range)	34 (18 - 72)	48 (22 - 69)	35 (18 - 72)
Sex, n (%)			
Male	266 (90.2)	13 (72.2)	279 (89.1)
Female	29 (9.8)	5 (27.8)	34 (10.9)
Race, n (%)			
White	176 (59.7)	11 (61.1)	187 (59.7)
Black or African Heritage	101 (34.2)	7 (38.9)	108 (34.5)
American Indian or Alaska Native	4 (1.4)	0	4 (1.3)
Asian	4 (1.4)	0	4 (1.3)
Native Hawaiian or Pacific Islander	2 (0.7)	0	2 (0.6)
Other	8 (2.7)	0	8 (2.6)
Ethnicity, n (%)			
Hispanic or Latino	64 (21.7)	4 (22.2)	68 (21.7)
Not Hispanic or Latino	231 (78.3)	14 (77.8)	245 (78.3)
Height (cm)			
Median (Range)	175.3 (149.9 - 210.8)	175.3 (152.4 - 185.4)	175.3 149.9 - 210.8)
BMI (kg/m^2)			
Median (Range)	25.9 (16.5 - 45.3)	24.3 (18.0 - 43.0)	25.7 (16.5 - 45.3)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-4.

The median baseline HIV-1 RNA value was 4.8 $\log_{10}$ copies/mL (range 2.6 to 7.0 $\log_{10}$ copies/mL), median baseline CD4+ cell count was 361.0x10^6 cells/L (range 5 to 1,473 x10^6

cells/L), and median baseline CD4+ cell percentage was 23.2% (range 0.8 to 47.4%). The majority of subjects (80.2%) had asymptomatic HIV-1 infection, 8.9% of subjects had symptomatic HIV-1 infection, and 10.9% were diagnosed with AIDS. Five subjects (1.6%) were HBsAg positive, and 8 (2.6%) were hepatitis C virus seropositive.

Table 14: Disease Characteristics – GS-US-216-0130 Week-24 Analysis

Disease Characteristics	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Baseline HIV-1 RNA, log_{10} Copies/mL			
Mean (SD)	4.8 (0.76)	4.8 (1.04)	4.8 (0.78)
Median (range)	4.8 (2.6 – 7.0)	5.0 (2.7 – 6.8)	4.8 (2.6 – 7.0)
Baseline HIV-1 RNA Category, n (%)			
≤100,000 Copies/mL	173 (58.6)	9 (50.0)	182 (58.1)
>100,000 Copies/mL	122 (41.4)	9 (50.0)	131 (41.9)
Baseline CD4+ Cell Count, $x10^6$ cells/L			
Mean (SD)	378.2 (199.94)	197.8 (214.30)	367.8 (204.79)
Median (range)	370.0 (6 – 1473)	107.0 (5 – 643)	361.0 (5 – 1473)
Baseline CD4+ Cell Count Category, n (%)			
≤$50x10^6$ Cells/L	17 (5.8)	5 (27.8)	22 (7.0)
51 to $200x10^6$ Cells/L	30 (10.2)	7 (38.9)	37 (11.8)
201 to $350x10^6$ Cells/L	85 (28.8)	2 (11.1)	87 (27.8)
351 to $500x10^6$ Cells/L	94 (31.9)	1 (5.6)	95 (30.4)
>$500x10^6$ Cells/L	69 (23.4)	3 (16.7)	72 (23.0)
Baseline CD4+ Cell %			
Mean (SD)	22.6 (9.99)	11.9 (10.25)	21.9 (10.29)
Median (range)	23.8 (0.8 – 47.4)	7.8 (0.8 – 30.6)	23.2 (0.8 – 47.4)
Years Since HIV Diagnosis			
Mean (SD)	NA	10.8 (7.13)	NA
Median (range)	NA	8.5 (2.0 - 24.0)	NA
HIV Disease Status, n (%)			
Asymptomatic	241 (81.7)	10 (55.6)	251 (80.2)
Symptomatic	26 (8.8)	2 (11.1)	28 (8.9)
AIDS	28 (9.5)	6 (33.3)	34 (10.9)
HBsAg Status, n (%)			
Positive	5 (1.7)	0	5 (1.6)
Negative	289 (98.0)	18 (100.0)	307 (98.1)
Undetermined	1 (0.3)	0	1 (0.3)
HCV Antibody Status, n (%)			
Positive	7 (2.4)	1 (5.6)	8 (2.6)
Negative	288 (97.6)	17 (94.4)	305 (97.4)

N=total number of subjects with data; n=number of subjects with observation; NA=not applicable.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 8-5.

3.3.6. Adverse Events

Unless specified otherwise, 1) the AEs presented below are those that were reported during the treatment period, 2) AEs are reported by preferred term, 3) drug relatedness to study medication (DRV, unless otherwise specified) is per assessment of the investigator, and 4) AE summary tables are by SOC and by preferred term, both ordered alphabetically. All AEs were mapped according to MedDRA version 15. Treatment-emergent AEs were defined as events that began or increased in severity on or after the date of the first dose of treatment and on or before the date of the last dose of that treatment plus 30 days.

3.3.6.1. Primary Endpoint: Grade 3 or 4 Adverse Events

The primary safety endpoint of this study was the onset of any grade 3 (severe) or grade 4 (life threatening) AEs that occurred in the Week-24 primary analysis. The grade 3 or 4 AEs reported in more than 1 subject are presented in Table 15. For all grade 3 or 4 AEs, please refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 4.1.1.1.

Overall, 18 subjects (5.8%) experienced at least 1 grade 3 (5.1%) or grade 4 (0.6%) AE. All grade 3 or 4 AEs were reported in 1 subject (0.3%), except for hypersensitivity (3 subjects, 1.0%) and maculo-papular rash (2 subjects, 0.6%). There were 2 grade 4 AEs in 1 subject each, idiopathic thrombocytopenic purpura and hypersensitivity.

Table 15: Grade 3 or 4 Adverse Events Reported in More Than 1 Subject - GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Number of Subjects Experiencing Any Grade 3 or 4 AE	***16 (5.4)***	***2 (11.1)***	***18 (5.8)***
Grade 3	***14 (4.7)***	***2 (11.1)***	***16 (5.1)***
Grade 4	***2 (0.7)***	***0***	***2 (0.6)***
Immune System Disorders	**4 (1.4)**	**0**	**4 (1.3)**
Hypersensitivity, Grade 3 or 4	3 (1.0)	0	3 (1.0)
Grade 3	2 (0.7)	0	2 (0.6)
Grade 4	1 (0.3)	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Rash Maculo-papular, Grade 3	2 (0.7)	0	2 (0.6)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-2.

3.3.6.2. Summary of Adverse Events

Overall, 87.9% of subjects experienced at least 1 AE (Table 16). Fifteen subjects (4.8%) experienced one or more SAEs, including 3 subjects (1.0%) who had a drug-related SAE (see Section 3.3.6.4). Treatment was permanently discontinued because of 1 or more AEs in 15 subjects (4.8%), see Section 3.3.6.4. Five subjects (1.6%) experienced at least 1 study drug-related grade 3 or grade 4 AE.

Table 16: Summary of Adverse Events – GS-US-216-0130 Week-24 Analysis

n (%) of Subjects Experiencing	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
≥1 AE	260 (88.1)	15 (83.3)	275 (87.9)
≥1 Grade 3 or 4 AE	16 (5.4)	2 (11.1)	18 (5.8)
≥1 Grade 2, 3, or 4 AE	133 (45.1)	6 (33.3)	139 (44.4)
≥1 AE related to DRV/COBI	117 (39.7)	6 (33.3)	123 (39.3)
≥1 Grade 3 or 4 AE Related to DRV/COBI	5 (1.7)	0	5 (1.6)
≥1 Grade 2, 3, or 4 AE Related to DRV/COBI	41 (13.9)	1 (5.6)	42 (13.4)
≥1 SAE	13 (4.4)	2 (11.1)	15 (4.8)
≥1 SAE Related to DRV/COBI	3 (1.0)	0	3 (1.0)
≥1 AE Leading to Study Medication Discontinuation	15 (5.1)	0	15 (4.8)
≥1 AE Leading to Study Medication Interruption	9 (3.1)	0	9 (2.9)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-3.

3.3.6.3. Common Adverse Events

The incidence of AEs reported in more than 10% of treatment-naïve or treatment-experienced subjects is presented in Table 17. The incidence of AEs was highest (>15% of all subjects) in the SOCs Gastrointestinal Disorders (52.4%), Infections and Infestations (48.9%), Skin and Subcutaneous Tissue Disorders (28.1%), Nervous System Disorders (19.8%), and General Disorders and Administration Site Conditions (15.3%). By preferred term, the most frequently occurring AEs (in >5% of all subjects) were diarrhea (24.9%), nausea (21.4%), upper respiratory tract infection (9.9%), headache (9.3%), rash (preferred term, 8.6%), vomiting (8.3%), fatigue (6.4%), flatulence (6.1%), nasopharyngitis (5.8%), and sinusitis (5.4%). These observations are consistent with those expected in this subject population and the known safety profile of the study medications.[9,11]

Table 17: Incidence of Adverse Events Reported in More Than 5% of All Subjects – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Any Adverse Event	***260 (88.1)***	***15 (83.3)***	***275 (87.9)***
Gastrointestinal Disorders	**154 (52.2)**	**10 (55.6)**	**164 (52.4)**
Diarrhoea	73 (24.7)	5 (27.8)	78 (24.9)
Flatulence	18 (6.1)	1 (5.6)	19 (6.1)
Nausea	66 (22.4)	1 (5.6)	67 (21.4)
Vomiting	24 (8.1)	2 (11.1)	26 (8.3)
General Disorders and Administration Site Conditions	**46 (15.6)**	**2 (11.1)**	**48 (15.3)**
Fatigue	20 (6.8)	0	20 (6.4)
Infections and Infestations	**144 (48.8)**	**9 (50.0)**	**153 (48.9)**
Upper Respiratory Tract Infection	31 (10.5)	0	31 (9.9)
Nasopharyngitis	16 (5.4)	2 (11.1)	18 (5.8)
Sinusitis	16 (5.4)	1 (5.6)	17 (5.4)
Nervous System Disorders	**59 (20.0)**	**3 (16.7)**	**62 (19.8)**
Headache	27 (9.2)	2 (11.1)	29 (9.3)
Skin and Subcutaneous Tissue Disorders	**84 (28.5)**	**4 (22.2)**	**88 (28.1)**
Rash (preferred term)	27 (9.2)	0	27 (8.6)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-4.

The incidence of AEs considered related to DRV/COBI per assessment of the investigator during the treatment period is provided in Table 18.

Overall, 39.3% of subjects experienced at least 1 AE that was considered related to DRV/COBI (Table 18). Diarrhea (14.7%) and nausea (14.4%) were the only AEs considered to be study drug-related in more than 5% of subjects, most drug-related AEs were recorded in 1 or 2 subjects. Five subjects (1.6%) experienced 1 or more grade 3 study drug-related AEs: hypersensitivity, peripheral neuropathy, immune reconstitution syndrome, allergic dermatitis, maculo-papular rash, and vesicular rash (refer to Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Section 11.2.5). There were no grade 4 drug-related AEs.

Table 18: Incidence of Adverse Events Related to the Study Medication Reported in at Least 2 Subjects – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
At Least 1 AE Related to Study Medication[a]	***117 (39.7)***	***6 (33.3)***	***123 (39.3)***
Blood and Lymphatic System Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Gastrointestinal Disorders	**84 (28.5)**	**6 (33.3)**	**90 (28.8)**
Abdominal Pain	3 (1.0)	0	3 (1.0)
Abdominal Pain Upper	7 (2.4)	1 (5.6)	8 (2.6)
Diarrhoea	42 (14.2)	4 (22.2)	46 (14.7)
Dry Mouth	3 (1.0)	0	3 (1.0)
Dyspepsia	2 (0.7)	0	2 (0.6)
Flatulence	12 (4.1)	0	12 (3.8)
Frequent Bowel Movements	2 (0.7)	0	2 (0.6)
Nausea	44 (14.9)	1 (5.6)	45 (14.4)
Vomiting	5 (1.7)	0	5 (1.6)
General Disorders and Administration Site Conditions	**13 (4.4)**	**0**	**13 (4.2)**
Fatigue	10 (3.4)	0	10 (3.2)
Malaise	2 (0.7)	0	2 (0.6)
Immune System Disorders	**3 (1.0)**	**0**	**3 (1.0)**
Hypersensitivity	2 (0.7)	0	2 (0.6)
Investigations	**2 (0.7)**	**0**	**2 (0.6)**
Metabolism and Nutrition Disorders	**5 (1.7)**	**0**	**5 (1.6)**
Decreased Appetite	3 (1.0)	0	3 (1.0)
Musculoskeletal and Connective Tissue Disorders	**3 (1.0)**	**1 (0.3)**	**4 (1.3)**
Myalgia	2 (0.7)	0	2 (0.6)
Nervous System Disorders	**22 (7.5)**	**1 (5.6)**	**23 (7.3)**
Dizziness	3 (1.0)	0	3 (1.0)
Dysgeusia	2 (0.7)	0	2 (0.6)
Headache	12 (4.1)	1 (5.6)	13 (4.2)
Peripheral Neuropathy	2 (0.7)	0	2 (0.6)
Psychiatric Disorders	**12 (4.1)**	**0**	**12 (3.8)**
Abnormal Dreams	6 (2.0)	0	6 (1.9)
Insomnia	3 (1.0)	0	3 (1.0)
Skin and Subcutaneous Tissue Disorders	**27 (9.2)**	**0**	**27 (8.6)**
Dermatitis	2 (0.7)	0	2 (0.6)
Pruritus	4 (1.4)	0	4 (1.3)
Rash	10 (3.4)	0	10 (3.2)
Rash Maculo-papular	5 (1.7)	0	5 (1.6)
Rash Macular	4 (1.4)	0	4 (1.3)

N=total number of subjects with data; n=number of subjects with observation.
[a] Causality assessment by the investigator.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 5.1.1.5.

3.3.6.4. Deaths, Serious Adverse Events, and Other Significant Adverse Events

There were no deaths in the Week-24 analysis of this study.

Fifteen subjects (4.8%) experienced at least 1 SAE. For a table of all SAEs in the Week-24 analysis of this study, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-7. All SAEs were reported in 1 subject except for pyrexia (n=2). Three SAEs were considered related to DRV/COBI, each occurring in 1 subject: immune reconstitution syndrome (grade 3), rash

(preferred term, grade 1, led to treatment discontinuation), and maculo-papular rash (grade 3, led to treatment discontinuation).

The incidence of AEs leading to permanent discontinuation of study medication is provided in Table 19. Fifteen subjects (4.8%) discontinued the study drugs due to an AE. Most AEs leading to discontinuation were in the SOC of Skin and Subcutaneous Tissue Disorders (7 subjects; 2.2%). The most common AEs that led to discontinuation were rash (preferred term) and maculo-papular rash, both of which were experienced by 3 subjects each (1.0%). Nausea and hypersensitivity each resulted in discontinuation of 2 subjects (0.6%). All AEs that led to discontinuation were considered by the investigators to be study drug-related, except for idiopathic thrombocytopenic purpura and mycobacterium avium complex infection.

Table 19: Incidence of Adverse Events Leading to Permanent Discontinuation – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Any AE Leading to Discontinuation	**15 (5.1)**	**0**	**15 (4.8)**
Blood and Lymphatic System Disorders	**1 (0.3)**	**0**	**1 (0.3)**
Idiopathic Thrombocytopenic Purpura	1 (0.3)	0	1 (0.3)
Gastrointestinal Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Dyspepsia	1 (0.3)	0	1 (0.3)
Nausea	2 (0.7)	0	2 (0.6)
Vomiting	1 (0.3)	0	1 (0.3)
Immune System Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Hypersensitivity	2 (0.7)	0	2 (0.6)
Infections and Infestations	**1 (0.3)**	**0**	**1 (0.3)**
Mycobacterium Avium Complex Infection	1 (0.3)	0	1 (0.3)
Nervous System Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Headache	1 (0.3)	0	1 (0.3)
Dysgeusia	1 (0.3)	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**7 (2.4)**	**0**	**7 (2.2)**
Dermatitis Allergic	1 (0.3)	0	1 (0.3)
Rash	3 (1.0)	0	3 (1.0)
Rash Maculo-papular	3 (1.0)	0	3 (1.0)
Rash Macular	1 (0.3)	0	1 (0.3)
Rash Vesicular	1 (0.3)	0	1 (0.3)

N=number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-8.

3.3.6.5. Adverse Events of Interest to DRV/COBI

Eleven clinical entities of interest, each consisting of grouped preferred terms, were used to further evaluate the safety profile of DRV/COBI. Criteria for generating such clinical entities of interest were AEs that (1) are considered relevant in the HIV population, (2) are considered class effects of ARVs, or (3) were identified as being of potential importance based on earlier clinical data. For the full list of preferred terms included in the AE of interest analysis, refer to Module 5.3.5.2/GS-US-216-0130-SAP-W24-addendum/Section 5.1.1 and Attachment 1. Of the 11 clinical entities of interest, 9 are represented in Table 20, the groupings ‘Cardiac conduction abnormalities’ and ‘Fat redistribution’ are not in the table because none of the AEs in these entities were reported throughout the study.

Overall, 23.6% of subjects experienced at least 1 AE of interest, 24.4% in the treatment-naïve subgroup and 11.1% in the treatment-experienced subgroup (Table 20 and Module 5.3.5.2/ GS-US-216-0130-Anal-W24-SAF-AE/TSFAEOI02). Adverse events of interest were most prevalent in the AE groupings of Rash (grouped term 16.3%), Lipid Abnormalities (2.9%) and Severe Skin Reactions (2.6%); the incidence was <2% in the other AE of interest groupings. One AE of interest was reported by more than 2% of subjects, ie, rash (preferred term, 8.6%).

Most AEs of interest were grade 1, 9.3% of subjects experienced a grade 2 AE of interest, and 1.6% a grade 3 AE of interest. All AEs of interest at least grade 2 were recorded in 1 or 2 subjects only, except for the preferred terms of rash (7 subjects, 2.2%) and maculo-papular rash (4 subjects, 1.3%). A serious AE of interest was reported in 3 subjects (1.0%): rash (preferred term), maculo-papular rash and immune reconstitution syndrome. Seven subjects (2.2%) discontinued because of a rash-related AE of interest (grouped term).

Table 20: Adverse Events of Interest – GS-US-216-0130 Week-24 Analysis

	All Subjects N=313				
Grouped Term of AEs of Interest Preferred Term, n (%)	**Any AEOI**	**AEOI at Least Grade 2**	**AEOI at Least Grade 3**	**Serious AEOI**	**AEOI Leading to Permanent Stop**
At Least 1 AE of Interest	***74 (23.6)***	***29 (9.3)***	***5 (1.6)***	***3 (1.0)***	***7 (2.2)***
Rash	**51 (16.3)**	**19 (6.1)**	**2 (0.6)**	**2 (0.6)**	**7(2.2)**
Rash	27 (8.6)	7 (2.2)	0	1 (0.3)	3 (1.0)
Rash Maculo-papular	6 (1.9)	4 (1.3)	2 (0.6)	1 (0.3)	3 (1.0)
Rash Papular	5 (1.6)	2 (0.6)	0	0	0
Rash Macular	4 (1.3)	2 (0.6)	0	0	1 (0.3)
Rash Pruritic	4 (1.3)	1 (0.3)	0	0	0
Rash Erythematous	2 (0.6)	1 (0.3)	0	0	0
Rash Generalized	2 (0.6)	1 (0.3)	0	0	0
Drug Eruption	1 (0.3)	1 (0.3)	0	0	0
Rash Vesicular	1 (0.3)	1 (0.3)	1 (0.3)	0	1 (0.3)
Lipid Abnormalities	**9 (2.9)**	**3 (1.0)**	**0**	**0**	**0**
Hypercholesterolaemia	4 (1.3)	1 (0.3)	0	0	0
Hypertriglyceridaemia	4 (1.3)	0	0	0	0
Blood Triglycerides Increased	3 (1.0)	2 (0.6)	0	0	0
Severe Skin Reactions	**8 (2.6)**	**3 (1.0)**	**0**	**0**	**0**
Conjunctivitis	3 (1.0)	0	0	0	0
Stomatitis	2 (0.6)	2 (0.6)	0	0	0
Blister	1 (0.3)	0	0	0	0
Drug Eruption	1 (0.3)	1 (0.3)	0	0	0
Mouth Ulceration	1 (0.3)	0	0	0	0
Hepatotoxicity	**5 (1.6)**	**3 (1.0)**	**2 (0.6)**	**0**	**0**
Hepatic Enzyme Increased	3 (1.0)	1 (0.3)	1 (0.3)	0	0
Transaminases Increased	2 (0.6)	2 (0.6)	1 (0.3)	0	0
Renal/Creatinine Effects	**3 (1.0)**	**0**	**0**	**0**	**0**
Blood Creatinine Increased	3 (1.0)	0	0	0	0
Hyperglycaemia	**3 (1.0)**	**1 (0.3)**	**0**	**0**	**0**
Diabetes Mellitus Inadequate Control	2 (0.6)	1 (0.3)	0	0	0
Type 2 Diabetes Mellitus	1 (0.3)	0	0	0	0
Coronary Artery Events	**2 (0.6)**	**1 (0.3)**	**0**	**0**	**0**
Blood Creatine Phosphokinase Abnormal	1 (0.3)	1 (0.3)	0	0	0
Blood Creatine Phosphokinase Increased	1 (0.3)	0	0	0	0
Pancreatitis	**2 (0.6)**	**1 (0.3)**	**0**	**0**	**0**
Hyperlipasaemia	1 (0.3)	1 (0.3)	0	0	0
Pancreatitis	1 (0.3)	0	0	0	0
Immune Reconstitution Syndrome	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**	**0**
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0

N=total number of subjects with data; n=number of subjects with observation; AEOI=AE of interest.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAEOI02, TSFAEOI03, TSFAEOI04, TSFAEOI07, and TSFAEOI08.

3.3.6.6. Narratives

Criteria for the generation of narratives in study GS-US-216-0130 were: AEs with fatal outcome, other SAEs (regardless of causality), AEs leading to discontinuation, grade 3 or 4 AEs of interest, and pregnancy cases. For detailed clinical narratives, refer to Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Section 15.2 and to Appendix 1.

The data presented in the narratives principally reflect those available in the Week-24 analysis. Nevertheless, whenever the pharmacovigilance database (ie, the Council for International Organizations of Medical Sciences [CIOMS] reports) contained additional information that was considered relevant to understand SAEs, this information was added to the narratives. Consequently, the narratives included with this report may contain more information than the data included in the Week-24 analysis.

3.3.7. Clinical Laboratory Evaluations

Samples for laboratory safety testing were taken at screening, baseline, and at Weeks 2, 4, 8, 12, 16, 24, and at the end of follow-up, ie, 30 days after treatment discontinuation. Laboratory abnormalities were graded using the GSI Grading Scale for Severity of Adverse Events and Laboratory Abnormalities (refer to Module 5.3.5.2/GS-US-216-0130-CTP-v2/Appendix 4). Only treatment-emergent abnormalities are reported, ie, those abnormalities that first occurred or worsened after the start of DRV/COBI treatment. For details on the Week-24 laboratory safety of study GS-US-216-0130, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.6.

The laboratory reports had to be interpreted for clinical significance by the investigator. Any clinically relevant change observed after the signing of the ICF had to be reported as an AE (see Section 3.3.7.3).

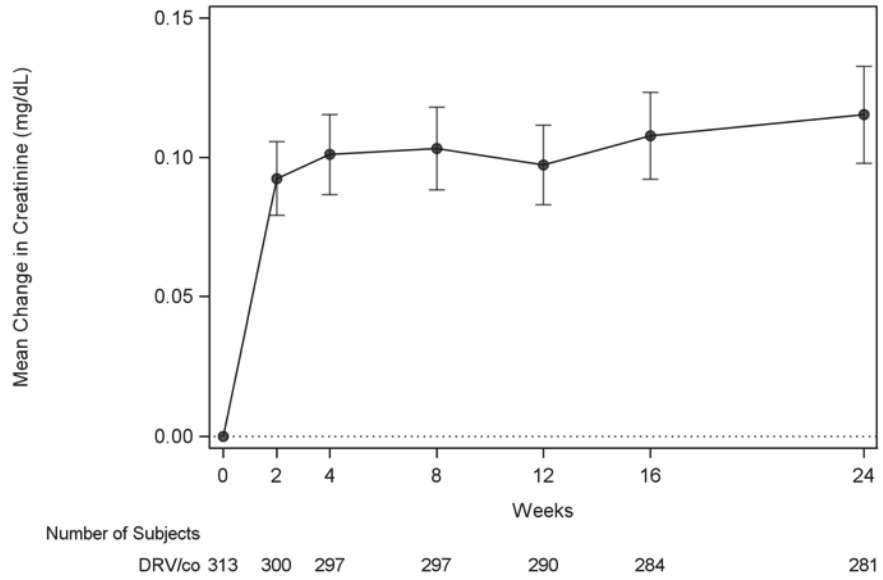
3.3.7.1. Laboratory Values Over Time

There were no clinically relevant changes from baseline through Week 24 in mean values for the hematology parameters or clinical chemistry parameters, for the lipid parameters (fasting HDL cholesterol, fasting LDL cholesterol, fasting total cholesterol to HDL cholesterol ratio, or fasting glucose), or for the liver-related laboratory tests (AST, ALT, bilirubin [direct, indirect and total]).

Renal Laboratory Parameters

An increase from baseline in serum creatinine was observed from Week 2 onwards (mean change 0.09 mg/dL, Figure 1), the increase remained stable till Week 24 (mean change 0.12 mg/dL).

Figure 1: Mean (±95% CI) Change From Baseline Over Time in Serum Creatinine – GS-US-216-0130 Week-24 Analysis



Source: Module 5.3.5.2/GS-US-216-0130-W24-Anal-LAB/GSFLAB01CREAT.

The mean changes from baseline in the eGFR were calculated using the Cockcroft-Gault method ($eGFR_{CG}$), the modification of diet in renal disease method ($eGFR_{MDRD}$), and by cystatin C clearance ($eGFR_{CC}$). When using eGFR based on creatinine clearance ($eGFR_{CG}$ and $eGFR_{MDRD}$), a decrease was noted from Week 2 onwards, the level remained relatively stable from then onwards. The mean (SD) $eGFR_{CG}$ change from baseline was -9.6 (13.7) mL/min at Week 2, and –11.5 (15.5) mL/min at Week 24. However, the eGFR calculated by cystatin C clearance ($eGFR_{CC}$) did not change significantly over time. These results are consistent with the known COBI inhibitory effects on renal tubular creatinine secretion and an absence of effect on the glomerular filtration (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 5.3.14).

The COBI-induced increase in serum creatinine has a notable effect on the urine fractional excretion of phosphate (EF_{PO4}). Mean values for phosphorus were generally within normal ranges throughout the study and did not fluctuate meaningfully across visits. Urine FE_{PO4} was tabulated without and with adjustments for serum creatinine. For a detailed description of the method of analysis and the results, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/ Section 11.6.3.2. The mean increase from baseline in the urine FE_{PO4} at Week 24 when calculated using adjusted serum creatinine values (mean [SD] change 0.7 [5.5]%) were smaller than the increases calculated using unadjusted serum creatinine values (mean [SD] change 2.2 [5.9]%; refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 5.6.3. and Table 5.6.4). This observation suggests that the increase from baseline in the urine FE_{PO4} using unadjusted serum creatinine values is largely caused by the inhibitory effects of COBI on renal tubular creatinine secretion.

In order to assess renal safety in the study, specific laboratory criteria were selected to identify subjects with subclinical kidney disease. Urinalyses were done by dipstick test, except for urine phosphate and creatinine. For a detailed description of the criteria and methods used, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 11.2.6.2. No abnormalities in any of the 3 tubular dysfunction markers (hypophosphatemia, proteinuria, normoglycemic glucosuria) were

reported in the Week-24 analysis. However, 6 subjects (1.9%) had a confirmed creatinine increase from baseline ≥0.4 mg/dL at 1 or more visits. For these 6 subjects, the maximum observed increases from baseline at any visit ranged from 0.41 to 0.67 mg/dL. In all but 1 of these subjects, the observed change from baseline at the last recorded creatinine value before data cut-off was <0.4 mg/dL, meaning that the increased creatinine levels observed during the study did not remain elevated, but rather began to return to the baseline value at or prior to the data cut-off. None of these 6 subjects had concurrent changes of 1 or 2 grades in serum phosphate levels, urine protein levels, or urine glucose levels; none of these subjects experienced AEs of hypophosphatemia, proteinuria, or glycosuria. In this study, no subjects discontinued the study drugs due to a renal AE (see Table 19). A threshold of 0.4 mg/dL was used in the STRIBILD program to identify subjects with potentially meaningful glomerular dysfunction.[10] The underlying assumption is that a serum creatinine increase greater than 0.4 mg/dL is less likely to be solely due to the inhibitory effect of COBI or rtv on renal tubular creatinine secretion and warrants further investigation.

In conclusion, there were no anomalies suggestive of renal tubular dysfunction. The renal laboratory assessments showed changes consistent with the COBI inhibitory effects on renal tubular creatinine secretion. An increase in serum creatinine due to the COBI inhibitory effect generally does not exceed 0.4 mg/dL from baseline.

3.3.7.2. Incidence of Laboratory Abnormalities

An overview of the incidence with treatment-emergent (ie, worsened versus baseline) GSI grade 3 or 4 laboratory abnormalities observed in at least 1% of subjects is presented in Table 21. This tabulation is irrespective of whether or not the abnormality was reported as an AE.

The majority of grade 3 or 4 clinical laboratory abnormalities were associated with changes in creatine kinase (18 subjects or 5.8%) and ALT (7 subjects or 2.3%). All other grade 3 or 4 abnormalities occurred in less than 2% of subjects.

There were no grade 3 or 4 abnormalities in creatinine levels. Creatinine was abnormally high in 23 subjects (7.4%), the increase was grade 1 in 22 subjects (7.1%) and grade 2 in 1 subject (0.3%). All graded creatinine levels were observed in treatment-naïve subjects, except for 1 grade 1 abnormality in a treatment-experienced subject (refer to Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Table 5.5.1).

Table 21: Incidence of Grade 3 or 4 Treatment-emergent Graded Laboratory Abnormalities in at Least 1% of Subjects – GS-US-216-0130 Week-24 Analysis

Laboratory Parameter Grouping **Laboratory Parameter** Grade [a], n (%)	**Treatment-naïve**	**Treatment-experienced**	**All Subjects**
General Hematology			
Neutrophils	**N=292**	**N=18**	**N=310**
Grade 3	2 (0.7)	0	2 (0.6)
Grade 4	2 (0.7)	0	2 (0.6)
Grade 3 or 4	4 (1.4)	0	4 (1.3)
General Clinical Chemistry			
ALT	**N=292**	**N=18**	**N=310**
Grade 3	5 (1.7)	0	5 (1.6)
Grade 4	2 (0.7)	0	2 (0.6)
Grade 3 or 4	7 (2.4)	0	7 (2.3)
Amylase	**N=292**	**N=18**	**N=310**
Grade 3	5 (1.7)	1 (5.6)	6 (1.9)
Grade 4	0	0	0
Grade 3 or 4	5 (1.7)	1 (5.6)	6 (1.9)
AST	**N=292**	**N=18**	**N=310**
Grade 3	3 (1.0)	1 (5.6)	4 (1.3)
Grade 4	2 (0.7)	0	2 (0.6)
Grade 3 or 4	5 (1.7)	1 (5.6)	6 (1.9)
Creatine Kinase	**N=292**	**N=18**	**N=310**
Grade 3	8 (2.7)	0	8 (2.6)
Grade 4	10 (3.4)	0	10 (3.2)
Grade 3 or 4	18 (6.2)	0	18 (5.8)
Gamma Glutamyl Transferase	**N=292**	**N=18**	**N=310**
Grade 3	4 (1.4)	0	4 (1.3)
Grade 4	1 (0.3)	0	1 (0.3)
Grade 3 or 4	5 (1.7)	0	5 (1.6)
Pancreatic Lipase	**N=292**	**N=18**	**N=310**
Grade 3	2 (0.7)	0	2 (0.6)
Grade 4	3 (1.0)	0	3 (1.0)
Grade 3 or 4	5 (1.7)	0	5 (1.6)
Total Cholesterol (Fasting)	**N=273**	**N=17**	**N=290**
Grade 3	3 (1.1)	0	3 (1.0)
Grade 4	0	0	0
Grade 3 or 4	3 (1.1)	0	3 (1.0)
Triglycerides (Fasting)	**N=273**	**N=17**	**N=290**
Grade 3	4 (1.5)	0	4 (1.4)
Grade 4	0	0	0
Grade 3 or 4	4 (1.5)	0	4 (1.4)
Urinalysis			
Urine Red Blood Cells (Hematuria, Quantitative)	**N=291**	**N=18**	**N=309**
Grade 3	3 (1.0)	1 (5.6)	4 (1.3)
Grade 4	0	0	0
Grade 3 or 4	3 (1.0)	1 (5.6)	4 (1.3)

N=total number of subjects with data; n=number of subjects with laboratory toxicity.
[a] GSI Grades.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-10.

3.3.7.3. Laboratory Abnormalities Reported as Adverse Event

Laboratory-related AEs experienced by at least 1% of subjects are presented in Table 22. Clinical laboratory abnormalities were reported as AEs in the SOCs of Investigations (7.7%), Metabolism and Nutrition Disorders (6.7%), and Renal and Urinary Disorders (3.2%).

None of the laboratory-related AEs were reported as serious, and there were no permanent treatment discontinuations due to a laboratory-related AE in the Week-24 analysis of the study. Hypercholesterolemia and hypertriglyceridemia were the most frequent AEs, experienced by 4 subjects (1.3%) each. Increased blood creatinine was reported as an AE in 3 subjects (1.0%). In 1 of these subjects, this AE was considered related to DRV/COBI; the increased creatinine levels resolved with continued treatment. Other laboratory-related AEs considered by the investigator to be related to DRV/COBI were neutropenia, anemia, and hyperlipasemia. The events of neutropenia and anemia resolved; the AE of hyperlipasemia was ongoing at time of report writing, although the laboratory abnormality resolved with continued treatment and there was no report of pancreatitis.

Table 22: Clinical Laboratory Abnormalities Reported as an Adverse Event in at Least 1% of Subjects – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Investigations	**22 (7.5)**	**2 (11.1)**	**24 (7.7)**
Blood Creatinine Increased	3 (1.0)	0	3 (1.0)
Blood Triglycerides Increased	3 (1.0)	0	3 (1.0)
Hepatic Enzyme Increased	3 (1.0)	0	3 (1.0)
Metabolism and Nutrition Disorders	**18 (6.1)**	**3 (16.7)**	**21 (6.7)**
Hypercholesterolaemia	4 (1.4)	0	4 (1.3)
Hypertriglyceridaemia	3 (1.0)	1 (5.6)	4 (1.3)
Renal and Urinary Disorders	**8 (2.7)**	**2 (11.1)**	**10 (3.2)**
Hematuria	3 (1.0)	0	3 (1.0)
Proteinuria	2 (0.7)	1 (5.6	3 (1.0)
Dysuria	1 (0.3)	1 (5.6)	2 (0.6)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-9.

3.3.8. Physical Findings and Other Observations Related to Safety

Based on a review of body weight values, concomitant medication uses, reports of study drug overdoses, pregnancies, and ECG findings, no other clinically relevant safety observations were made (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Sections 11.7, 11.8 and 11.9).

3.3.9. Pharmacokinetic/Pharmacodynamic Relationships

The exposure-response relationships between DRV exposure and safety parameters were assessed. No apparent relationship was observed between DRV AUC_{24h} and the occurrence of the ADRs of rash (preferred term), diarrhea, nausea, or vomiting, or between DRV AUC_{24h} and the worst toxicity grade in alkaline phosphatase, ALT, AST, amylase, pancreatic lipase, glucose, total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides.

3.3.10. Adverse Drug Reactions

The AEs from the primary Week-24 analysis of the GS-US-216-0130 study were reviewed by medical experts for identification of ADRs associated with DRV/COBI, according to the principles described in Appendix 2. The incidences of ADRs are derived from the statistical analysis of AEs, but the exact numbers and percentages may differ due to the grouping of preferred terms. An overview of the DRV/COBI ADRs and the grouping of preferred terms into medical concepts and their resulting SOCs are provided in Appendix 3. For laboratory abnormalities considered as ADRs, the DAIDS grading scale was used (see Section 1.3).

A summary of the ADR profile of DRV/COBI 800/150 mg once daily is presented in Table 23. Overall, 196 subjects (62.6%) experienced at least 1 ADR in the Week-24 analysis of the study. The incidence of ADRs at least grade 2 was 19.8%, and of ADRs grade 3 or 4 was 2.9%. Four subjects (1.3%) experienced a serious ADR, and 12 subjects (3.8%) prematurely discontinued the study medication because of an ADR.

Table 23: Summary of DRV/COBI Adverse Drug Reactions – GS-US-216-0130 Week-24 Analysis

n (%) of Subjects Experiencing	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
At Least 1 ADR	184 (62.4)	12 (66.7)	196 (62.6)
At Least 1 Grade 2, 3 or 4 ADR	61 (20.7)	1 (5.6)	62 (19.8)
At Least 1 Grade 3 or 4 ADR	9 (3.1)	0	9 (2.9)
At Least 1 Serious ADR	4 (1.4)	0	4 (1.3)
At Least 1 ADR Leading to Permanent Discontinuation	12 (4.1)	0	12 (3.8)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAE01, TSFAE02, TSFAE03, TSFAE04, and TSFAE05.

Most ADRs were reported in the SOCs Gastrointestinal Disorders (45.0%), Skin and Subcutaneous Disorders (18.2%), Nervous System Disorders (9.3%), General Disorders and Administration Site Conditions (6.4%), and Metabolism and Nutrition Disorders (5.4%); the incidence of ADRs was <5% in all other SOCs (Table 24). Individual ADRs with an incidence >10% were diarrhea (25.2%), nausea (21.4%), and rash (grouped term, 16.0%).

Adverse drug reactions with severity at least grade 2 were reported in 62 subjects (19.8%); the most frequently reported ADRs with grade 2 or more (incidence >2%) were rash (grouped term, 5.8%), diarrhea (5.1%), and nausea (3.2%). Four subjects (1.3%) experienced 1 serious ADR: hypersensitivity, immune reconstitution syndrome, rash (preferred term) and maculo-papular rash. Twelve subjects permanently discontinued treatment because of one or more ADRs, the ADRs leading to discontinuation were rash (grouped term, 7 subjects, 2.2%), hypersensitivity and nausea (2 subjects each, 0.6%), and headache, vomiting and dyspepsia (1 subject each, 0.3%).

The review did not identify new ADRs associated with DRV/COBI, compared to the well documented ADR safety profile of DRV, and that of COBI in HIV-1 infected subjects (see also Section 3.3.11).

Table 24: DRV/COBI Adverse Drug Reactions – GS-US-216-0130 Week-24 Analysis

System Organ Class (Grouped) [a] Preferred Term n (%)	All Subjects N=313				
	Any ADR	**ADRs at Least Grade 2**	**ADRs at Least Grade 3**	**Serious ADRs**	**ADRs Leading to Permanent Stop**
At Least 1 ADR	***196 (62.6)***	***62 (19.8)***	***9 (2.9)***	***4 (1.3)***	***12 (3.8)***
Gastrointestinal Disorders	**141 (45.0)**	**28 (8.9)**	**2 (0.6)**	**0**	**2 (0.6)**
Abdominal Distension	4 (1.3)	0	0	0	0
Abdominal Pain[a]	23 (7.3)	4 (1.3)	1 (0.3)	0	0
Diarrhoea[a]	79 (25.2)	16 (5.1)	1 (0.3)	0	0
Dyspepsia	6 (1.9)	1 (0.3)	0	0	1 (0.3)
Flatulence	19 (6.1)	3 (1.0)	0	0	0
Nausea	67 (21.4)	10 (3.2)	1 (0.3)	0	2 (0.6)
Pancreatitis Acute	1 (0.3)	0	0	0	0
Vomiting	26 (8.3)	5 (1.6)	1 (0.3)	0	1 (0.3)
General Disorders & Administration Site Conditions	**20 (6.4)**	**2 (0.6)**	**0**	**0**	**0**
Asthenia	1 (0.3)	0	0	0	0
Fatigue	20 (6.4)	2 (0.6)	0	0	0
Hepatobiliary Disorders	**5 (1.6)**	**3 (1.0)**	**2 (0.6)**	**0**	**0**
Hepatic Enzyme Increased[a]	5 (1.6)	3 (1.0)	2 (0.6)	0	0
Immune System Disorders	**7 (2.2)**	**6 (1.9)**	**4 (1.3)**	**2 (0.6)**	**2 (0.6)**
(Drug) Hypersensitivity[a]	6 (1.9)	5 (1.6)	3 (1.0)	1 (0.3)	2 (0.6)
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0
Investigations	**3 (1.0)**	**0**	**0**	**0**	**0**
Increased Blood Creatinine[a]	3 (1.0)	0	0	0	0
Metabolism and Nutrition Disorders	**17 (5.4)**	**4 (1.3)**	**0**	**0**	**0**
Anorexia [a]	6 (1.9)	0	0	0	0
Diabetes Mellitus [a]	2 (0.6)	1 (0.3)	0	0	0
Hypercholesterolaemia [a]	4 (1.3)	1 (0.3)	0	0	0
Hypertriglyceridaemia [a]	7 (2.2)	2 (0.6)	0	0	0
Musculoskeletal and Connective Tissue Disorders	**5 (1.6)**	**2 (0.6)**	**0**	**0**	**0**
Myalgia	5 (1.6)	2 (0.6)	0	0	0
Nervous System Disorders	**29 (9.3)**	**5 (1.6)**	**0**	**0**	**1 (0.3)**
Headache	29 (9.3)	5 (1.6)	0	0	1 (0.3)
Psychiatric Disorders	**8 (2.6)**	**1 (0.3)**	**0**	**0**	**0**
Abnormal Dreams	8 (2.6)	1 (0.3)	0	0	0
Skin and Subcutaneous Tissue Disorders	**57 (18.2)**	**20 (6.4)**	**2 (0.6)**	**2 (0.6)**	**7 (2.2)**
Angioedema[a]	3 (1.0)	0	0	0	0
Pruritus	7 (2.2)	2 (0.6)	0	0	0
Rash[a]	50 (16.0)	18 (5.8)	2 (0.6)	2 (0.6)	7 (2.2)
Rash	27 (8.6)	7 (2.2)	0	1 (0.3)	3 (1.0)
Rash Erythematous	2 (0.6)	1 (0.3)	0	0	0
Rash Generalized	2 (0.6)	1 (0.3)	0	0	0
Rash Macular	4 (1.3)	2 (0.6)	0	0	1 (0.3)
Rash Maculo-papular	6 (1.9)	4 (1.3)	2 (0.6)	1 (0.3)	3 (1.0)
Rash Papular	5 (1.6)	2 (0.6)	0	0	0
Rash Pruritic	4 (1.3)	1 (0.3)	0	0	0
Urticaria	3 (1.0)	0	0	0	0

N=total number of subjects with data; n=number of subjects with ADR.
[a] Grouped term; the grouped preferred terms are described in Appendix 3.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAE01, TSFAE02, TSFAE03, TSFAE04, and TSFAE05.

Graded DAIDS abnormalities in selected laboratory parameters, considered ADRs, are presented in Table 25 (AST, ALT, alkaline phosphatase, total cholesterol, LDL cholesterol, triglycerides, glucose, amylase, lipase, creatinine). The incidence of grade 3 or 4 abnormalities was <2.0% for all parameters, except for the laboratory parameters of LDL cholesterol where 3.4% of subjects had a grade 3 abnormal value, and ALT where 2.3% of subjects had a grade 3 or 4 abnormality.

An increase in serum creatinine was observed in 55 subjects (17.7%), the increase was grade 1 in 45 subjects (14.5%) and grade 2 in 10 subjects (3.2%). These percentages differ from GSI grades described in Section 3.3.7.2 because of different analysis methods (refer to Section 1.3). There were no grade 3 or grade 4 abnormalities in creatinine in either grading system. In both systems, all graded creatinine levels were observed in the treatment-naïve subgroup, except for 1 treatment-experienced subject who had a creatinine level which was categorized grade 1 in the GSI scale (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 5.5.1) and grade 2 in the DAIDS scale (Table 25).

Table 25: Laboratory-related Adverse Drug Reactions – GS-US-216-0130 Week-24 Analysis

Laboratory Parameter Grouping **Laboratory Parameter** Grade [a], n (%)[b]	**Treatment-naïve N=295**	**Treatment-experienced N=18**	**All Subjects N=313**
General Clinical Chemistry			
Amylase (U/L)			
Grade 1	46 (15.8)	2 (11.1)	48 (15.5)
Grade 2	17 (5.8)	0	17 (5.5)
Grade 3	5 (1.7)	1 (5.6)	6 (1.9)
Pancreatic Lipase (U/L)			
Grade 1	14 (4.8)	0	14 (4.5)
Grade 2	7 (2.4)	1 (5.6)	8 (2.6)
Grade 3	2 (0.7)	0	2 (0.6)
Grade 4	3 (1.0)	0	3 (1.0)
Creatinine (mg/dL)			
Grade 1	45 (15.4)	0	45 (14.5)
Grade 2	9 (3.1)	1 (5.6)	10 (3.2)
Lipids and Glucose			
Cholesterol (mg/dL)			
Grade 1	43 (15.6)	4 (23.5)	47 (16.0)
Grade 2	19 (6.9)	2 (11.8)	21 (7.2)
Grade 3	3 (1.1)	0	3 (1.0)
Glucose (mg/dL)			
Grade 1	23 (8.3)	2 (11.8)	25 (8.5)
Grade 2	9 (3.3)	2 (11.8)	11 (3.8)
LDL Cholesterol (mg/dL)			
Grade 1	32 (11.6)	2 (11.8)	34 (11.6)
Grade 2	19 (6.9)	2 (11.8)	21 (7.2)
Grade 3	9 (3.3)	1 (5.9)	10 (3.4)
Triglycerides (mg/dL)			
Grade 2	3 (1.1)	-	3 (1.0)
Grade 3	4 (1.4)	-	4 (1.4)
Liver Function			
ALT (U/L)			
Grade 1	20 (6.8)	0	20 (6.5)
Grade 2	8 (2.7)	1 (5.6)	9 (2.9)
Grade 3	5 (1.7)	0	5 (1.6)
Grade 4	2 (0.7)	0	2 (0.6)
Alkaline Phosphatase (U/L)			
Grade 1	4 (1.4)	-	4 (1.3)
Grade 2	3 (1.0)	-	3 (1.0)
AST (U/L)			
Grade 1	19 (6.5)	1 (5.6)	20 (6.5)
Grade 2	19 (6.5)	0	19 (6.1)
Grade 3	3 (1.0)	1 (5.6)	4 (1.3)
Grade 4	2 (0.7)	0	2 (0.6)

N=total number of subjects with data; n=number of subjects with observation.
[a] DAIDS grades.
[b] The number of subjects with data can vary per laboratory parameter, but the % reflects the true percentage of observed abnormalities.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-LAB/TSFLAB05.

3.3.11. Adverse Drug Reactions in Study GS-US-216-0130 and in Historical Studies With DRV/rtv 800/100 mg Once Daily

In order to put the ADR profile of DRV/COBI 800/150 mg once daily coadministered as single agents into perspective, the results of the Week-24 ADR analysis of study GS-US-216-0130 are

presented side-by-side with the Week-24 ADR analyses of 2 historical controls: the DRV/rtv 800/100 mg once daily treatment arm of study TMC114-C211 (also referred to as ARTEMIS) in 343 ART-naïve HIV-1 infected adult subjects which were on a background regimen of FTC/TDF, and the DRV/rtv 800/100 mg once daily treatment arm of study TMC114-C229 (also referred to as ODIN) in 294 ART-experienced HIV-1 infected adult subjects with no DRV RAMs, and a CD4+ cell count ≥50 x10^6 cells/L at screening which were on an investigator-selected optimized background regimen consisting of at least 2 NRTIs.

Comparisons between studies are to be interpreted with caution given the inherent limitations associated with the use of historical data as control. The small sample size of the treatment-experienced subgroup further limits the interpretation of this historical comparison with this subgroup.

Four tables are presented, an ADR summary (Table 26), a table with ADRs at least grade 2 (Table 27), a table with details on the ADR rash (grouped term, Table 28), and a table with laboratory-related ADRs (Table 29).

Table 26: Summary of Adverse Drug Reactions in GS-US-216-0130, DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229 Week-24 Analyses

Type of ADR n (%) of Subjects Experiencing	GS-US-216-0130 DRV/COBI 800/150 mg qd N=313	TMC114-C211 DRV/rtv 800/100 mg qd N=343	TMC114-C229 DRV/rtv 800/100 mg qd N=294
≥1 ADR	196 (62.6)	207 (60.3)	108 (36.7)
≥1 Grade 2, 3 or 4 ADR	62 (19.8)	79 (23.0)	43 (14.6)
≥1 Grade 3 or 4 ADR	9 (2.9)	27 (7.9)	6 (2.0)
≥1 Serious ADR	4 (1.3)	3 (0.9)	0
≥1 ADR Leading to Permanent Discontinuation	12 (3.8)	7 (2.0)	4 (1.4)

N=total number of subjects with data; n=number of subjects with observation; qd=once daily.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAE01, TSFAE02, TSFAE03, TSFAE04, TSFAE05, TSFAE13, TSFAE14, TSFAE15, TSFAE16, and TSFAE17.

Overall, the incidence of ADRs (any grade) was similar with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130 (62.6%) and in the treatment-naïve subjects treated with DRV/rtv 800/100 mg once daily in study TMC114-C211 (60.3%), but ADRs were less frequent in the treatment-experienced subjects treated with DRV/rtv in study TMC114-C229 (36.7%). However, ADRs of at least grade 2 showed similar incidences in the 3 studies: 19.8% in GS-US-216-0130, 23.0% in TMC114-C211 and 14.6% in TMC114-C229. The incidences in ADRs at least grade 3, serious ADRs and ADRs leading to discontinuation were low in all 3 studies.

ADRs at least Grade 2

Most ADRs at least grade 2 (Table 27) were reported in the SOCs Gastrointestinal Disorders (8.9% with GS-US-216-0130, 11.4% in TMC114-C211, and 9.9% in TMC114-C229), and Skin and Subcutaneous disorders (6.4%, 3.2% and 2.0%, respectively). The incidence of ADRs at least grade 2 was <2% in all other SOCs. Individual ADRs at least grade 2 with an incidence >2% in GS-US-216-0130 were rash (grouped term, 5.8%, 1.5% and 1.7%), diarrhea (5.1%, 4.7% and

4.8%) and nausea (3.2%, 2.3% and 3.7%) in studies GS-US-216-0130, TMC114-C211 and TMC114-C229, respectively.

Table 27: Adverse Drug Reactions at Least Grade 2 in GS-US-216-0130, With Incidences in the DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229 – Week-24 Analyses

System Organ Class (Grouped)[a] Preferred Term[b], n (%)	GS-US-216-0130 DRV/COBI N=313	TMC114-C211 DRV/rtv N=343	TMC114-C229 DRV/rtv N=294
Any ADR at Least Grade 2	***62 (19.8)***	***79 (23.0)***	***43 (14.6)***
Gastrointestinal Disorders	**28 (8.9)**	**39 (11.4)**	**29 (9.9)**
Abdominal Pain[a]	4 (1.3)	9 (2.6)	7 (2.4)
Diarrhoea	16 (5.1)	16 (4.7)	14 (4.8)
Dyspepsia	1 (0.3)	1 (0.3)	1 (0.3)
Flatulence	3 (1.0)	2 (0.6)	2 (0.7)
Nausea	10 (3.2)	8 (2.3)	11 (3.7)
Vomiting	5 (1.6)	5 (1.5)	9 (3.1)
General Disorders and Administration Site Conditions	**2 (0.6)**	**4 (1.2)**	**1 (0.3)**
Fatigue	2 (0.6)	1 (0.3)	0
Hepatobiliary Disorders	**3 (1.0)**	**11 (3.2)**	**0**
Hepatic Enzyme Increased[a]	3 (1.0)	10 (2.9)	0
Immune System Disorders	**6 (1.9)**	**3 (0.9)**	**0**
(Drug) Hypersensitivity[a]	5 (1.6)	2 (0.6)	0
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)	0
Investigations			
Blood Creatinine Increased[a]	0	1 (0.3)	2 (0.7)
Metabolism and Nutrition Disorders	**4 (1.3)**	**12 (3.5)**	**9 (3.1)**
Diabetes Mellitus[a]	1 (0.3)	0	0
Hypertriglyceridaemia[a]	2 (0.6)	2 (0.6)	1 (0.3)
Hypercholesterolaemia[a]	1 (0.3)	4 (1.2)	2 (0.7)
Musculoskeletal and Connective Tissue Disorders	**2 (0.6)**	**1 (0.3)**	**1 (0.3)**
Myalgia	2 (0.6)	1 (0.3)	1 (0.3)
Nervous System Disorders	**5 (1.6)**	**15 (4.4)**	**7 (2.4)**
Headache	5 (1.6)	15 (4.4)	7 (2.4)
Psychiatric Disorders	**1 (0.3)**	**1 (0.3)**	**0**
Abnormal Dreams	1 (0.3)	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	**20 (6.4)**	**11 (3.2)**	**6 (2.0)**
Rash[a]	18 (5.8)	5 (1.5)	5 (1.7)
Rash	7 (2.2)	4 (1.2)	4 (1.4)
Rash Erythematous	1 (0.3)	0	0
Rash Generalized	1 (0.3)	0	0
Rash Macular	2 (0.6)	0	0
Rash Maculo-papular	4 (1.3)	2 (0.6)	1 (0.3)
Rash Papular	2 (0.6)	0	0
Rash Pruritic	1 (0.3)	0	0
Pruritus[a]	2 (0.6)	2 (0.6)	1 (0.3)

N=total number of subjects with data; n=number of subjects with observation.
[a] Grouped term. The grouped preferred terms are described in Appendix 3.
[b] Only events identified as ADRs in study GS-US-216-0130 are presented in this table. ADRs occurring in the historical studies but not in GS-US-216-0130 are not presented here, they can be found in the source table.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAE14.

ADRs any Grade

Overall, the incidences of individual ADRs (any grade) in the Week-24 analyses of study GS-US-216-0130 and of the historical studies were similar. For 4 ADRs, ie, rash, nausea, vomiting and flatulence, the incidences were higher in study GS-US-216-0130 than in the historical studies. The differences did not indicate a clinical concern (Appendix 4).

The incidence of the ADR rash (any grade) was 16.0% in study GS-US-216-0130, 8.2% in study TMC114-C211, and 5.8% in study TMC114-C229. In Table 28, additional information is provided on the rash cases in these 3 studies: severity, relation to study medication, incidence of rash leading to permanent discontinuation, and median time to onset. Overall, the higher incidence of rash, and of rash events leading to discontinuation in study GS-US-216-0130 was due to grade 1 and grade 2 events. Five out of the 48 subjects with a grade 1-2 rash (10.4%) discontinued treatment in GS-US-216-0130, none in TMC114-C211 (0/26) and 1 out of 17 (5.9%) in TMC114-C229. There were no noticeable differences in the incidence of grade 3 rashes (2 cases or 0.6% in studies GS-US-216-0130 and TMC114-C211, and none in TMC114-C229). There were no cases of grade 4 rash. The rash events in study GS-US-216-0130 are therefore considered of limited medical concern. Factors not controlled for while comparing these different studies might have contributed to the noted differences.

The incidence of nausea was 21.4% in GS-US-216-0130, 14.6% in TMC114-C211 and 12.2% in TMC114-C229, the incidence of vomiting was 8.3%, 4.7% and 4.1%, respectively, and the incidence of flatulence 6.1%, 2.0% and 2.0%, respectively. These differences are driven by grade 1 events, since the incidences of these ADRs at least grade 2 is similar in the 3 studies (Table 26); the differences in incidence are therefore of no clinical concern.

The incidences of all other ADRs are similar in study GS-US-216-0130 and in the historical studies.

Table 28: Detailed Analysis of the Adverse Drug Reaction Rash in GS-US-216-0130, and in the DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229 – Week-24 Analyses

Rash[a] Characteristic n (%)	GS-US-216-0130 DRV/COBI N=313	TMC114-C211 DRV/rtv N=343	TMC114-C229 DRV/rtv N=294
Any Rash ADR (Grouped Term)	***50 (16.0)***	***28 (8.2)***	***17 (5.8)***
Grade			
Grade 1	33 (10.5)	26 (7.6)	12 (4.1)
Grade 2	16 (5.1)	4 (1.2)	5 (1.7)
Grade 3	2 (0.6)	2 (0.6)	0
Rash ADR Leading to Discontinuation	7 (2.2)	2 (0.6)	1 (0.3)
Rash ADR Related to Study Medication[b]	23 (7.3)	12 (3.5)	11 (3.7)
Rash ADR Reported as SAE	2 (0.6)	0	0
Median Time to Onset of Rash (Days)	15 (2 – 224)	21 (1 – 165)	10 (1 – 167)

N=total number of subjects with data; n=number of subjects with observation.
[a] Grouped term. The grouped preferred terms are described in Appendix 3.
[b] Causality assessment by the investigator.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAE13, TSFAE 14, TSFAE 15, TSFAE 16, TSFAE 17 and data on file.

Laboratory-related ADRs

Graded DAIDS abnormalities in selected laboratory parameters, considered to be DRV/COBI ADRs, are presented in Table 29 (AST, ALT, alkaline phosphatase, total cholesterol, LDL cholesterol, triglycerides, glucose, amylase, lipase, creatinine).

The incidence and severity of the laboratory-related ADRs in study GS-US-216-0130 are generally in line with those reported in the historical studies. Graded creatinine abnormalities were more frequent in the GS-US-216-0130 study (17.7%) than in the historical studies (3.3% in TMC114-C211, 4.1% in TMC114-C229); this may be attributable to the known inhibitory effects of COBI on renal tubular creatinine secretion. Graded amylase/lipase levels were also recorded more frequently in study GS-US-216-0130 than in the historical studies. None of the subjects had associated treatment-emergent signs or symptoms suggestive of pancreatitis. The laboratory changes during DRV/COBI treatment consisted mainly of a 1-grade change versus baseline, and most were isolated and transient or fluctuating.

Table 29: Laboratory-related Adverse Drug Reactions in GS-US-216-0130, With Incidences in the DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229 – Week-24 Analyses

Laboratory Parameter Grouping **Laboratory Parameter**[a] Grade[b], n (%)[c]	**GS-US-216-0130 DRV/COBI N=313**	**TMC114-C211 DRV/rtv N=334**	**TMC114-C229 DRV/rtv N=294**
General Clinical Chemistry			
Amylase (U/L)			
Grade 1	48 (15.5)	27 (8.1)	17 (6.0)
Grade 2	17 (5.5)	10 (3.0)	5 (1.8)
Grade 3	6 (1.9)	8 (2.4)	4 (1.4)
Pancreatic Lipase (U/L)			
Grade 1	14 (4.5)	5 (1.5)	4 (1.4)
Grade 2	8 (2.6)	3 (0.9)	2 (0.7)
Grade 3	2 (0.6)	0	1 (0.4)
Grade 4	3 (1.0)	0	0
Creatinine (mg/dL)			
Grade 1	45 (14.5)	10 (3.0)	3 (1.1)
Grade 2	10 (3.2)	0	5 (1.8)
Grade 3	0	1 (0.3)	3 (1.1)
Grade 4	0	0	1 (0.4)
Lipids and Glucose			
Total Cholesterol (mg/dL)			
Grade 1	47 (16.0)	61 (18.3)	34 (12.0)
Grade 2	21 (7.2)	33 (9.9)	12 (4.2)
Grade 3	3 (1.0)	3 (0.9)	4 (1.4)
Glucose (mg/dL)			
Grade 1	25 (8.5)	29 (8.7)	23 (8.1)
Grade 2	11 (3.8)	13 (3.9)	15 (5.3)
LDL Cholesterol (mg/dL)			
Grade 1	34 (11.6)	45 (13.5)	39 (13.7)
Grade 2	21 (7.2)	34 (10.2)	17 (6.0)
Grade 3	10 (3.4)	5 (1.5)	4 (1.4)
Triglycerides (mg/dL)			
Grade 2	3 (1.0)	3 (0.9)	5 (1.8)
Grade 3	4 (1.4)	2 (0.6)	5 (1.8)
Liver Function			
ALT (U/L)			
Grade 1	20 (6.5)	23 (6.9)	23 (8.1)
Grade 2	9 (2.9)	10 (3.0)	3 (1.1)
Grade 3	5 (1.6)	10 (3.0)	0
Grade 4	2 (0.6)	2 (0.6)	0
Alkaline Phosphatase (U/L)			
Grade 1	4 (1.3)	15 (4.5)	6 (2.1)
Grade 2	3 (1.0)	4 (1.2)	1 (0.4)
AST (U/L)			
Grade 1	20 (6.5)	21 (6.3)	16 (5.6)
Grade 2	19 (6.1)	15 (4.5)	1 (0.4)
Grade 3	4 (1.3)	10 (3.0)	1 (0.4)
Grade 4	2 (0.6)	2 (0.6)	0

Table footnotes are presented on the next page.

N=total number of subjects with data; n=number of subjects with ADR.
[a] Only graded abnormalities observed in study GS-US-216-0130 are presented, with matching data in the historical studies. For graded abnormalities occurring in the historical studies but not in study GS-US-216-0130, refer to the source tables.
[b] DAIDS grades.
[c] The number of subjects with data varies per parameter, the % reflects the true percentage of observed abnormalities.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-LAB/TSFLAB05, TSFLAB07A and TSFLAB07B, Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 5.5.1.

3.3.12. Summary and Conclusions – Week-24 Safety Analysis GS-US-216-0130

Treatment with DRV/COBI 800/150 mg once daily coadministered as single agents was generally well tolerated during a median exposure of 31.4 weeks in 313 HIV-1 infected subjects.

In the Week-24 analysis, 5.8% of subjects experienced at least 1 grade 3 (4.7%) or grade 4 (0.7%) AE (primary endpoint). All grade 3 or 4 AEs were reported in 1 subject (0.3%), except for hypersensitivity (3 subjects, 1.0%) and maculo-papular rash (2 subjects, 0.6%). Five subjects (1.6%) experienced at least 1 grade 3 AE that was study drug-related: neuropathy peripheral and immune reconstitution syndrome (both reported in the same subject), hypersensitivity, allergic dermatitis, maculo-papular rash, and vesicular rash (reported in 1 subject each). There were 2 grade 4 AEs in 1 subject each, idiopathic thrombocytopenic purpura and hypersensitivity; neither were assessed as drug-related.

Overall, 87.9% of subjects experienced at least 1 AE. The incidence of AEs was highest (>10%) in the SOCs Gastrointestinal Disorders (52.4%), Infections and Infestations (48.9%), Skin and Subcutaneous Tissue Disorders (28.1%), and Psychiatric Disorders (11.5%). By preferred term, the most frequently occurring AEs (in >5% of subjects) were diarrhea (24.9%), nausea (21.4%), upper respiratory tract infection (9.9%), headache (9.3%), rash (preferred term, 8.6%), vomiting (8.3%), fatigue (6.4%), flatulence (6.1%), nasopharyngitis (5.8%), and sinusitis (5.4%). These observations are consistent with those expected in this subject population and the known safety profile of the study medications.

Fifteen subjects (4.8%) experienced one or more SAEs, including 3 subjects (1.0%) who had a SAE considered by the investigator to be related to the study medication (immune reconstitution syndrome, rash, and maculo-papular rash). Treatment was permanently discontinued in 15 subjects (4.8%) because of 1 or more AEs. Most AEs leading to discontinuation were in the SOC of Skin and Subcutaneous Tissue Disorders (7 subjects, 2.2%). The most common AEs that led to discontinuation were rash and maculo-papular rash, both of which were experienced by 3 subjects (1.0%). Nausea and hypersensitivity each resulted in discontinuation of 2 subjects (0.7%). All but 2 AEs that led to discontinuation were considered by the investigators to be study drug-related.

In the analysis of AEs of interest to DRV/COBI, rash (grouped term, 16.3%), lipid abnormalities (2.9%) and severe skin reactions were the AE of interest groups with incidences >2%. Overall, 23.6% of subjects experienced at least 1 AE of interest, 24.4% in the treatment-naïve subgroup and 11.1% in the treatment-experienced subgroup.

In the laboratory safety analysis, the eGFR based on cystatin clearance (GFR_{CC}) was stable over time, whereas an increase in creatinine level and a modest decrease in eGFR based on creatinine clearance (GFR_{CG} and GFR_{MDRD}) were noted from Week 2 onwards: the mean change in creatinine was +0.09 mg/dL and the mean change in $eGFR_{CG}$ was !9.6 mL/min at Week 2. These changes stabilized and remained more or less constant through Week 24: the mean change in creatinine was +0.12 mg/dL and the mean change in $eGFR_{CG}$ was !11.5 mL/min at Week 24. There were no grade 3 or 4 abnormalities in creatinine. There were no laboratory abnormalities suggestive of proximal renal tubular dysfunction. Renal laboratory assessments showed changes consistent with the inhibitory effects of COBI on renal tubular creatinine secretion. There were no clinically relevant changes from baseline in the Week-24 analysis in mean values of the other clinical chemistry parameters, the lipid parameters (fasting HDL cholesterol, fasting LDL cholesterol, fasting total cholesterol to HDL cholesterol ratio, or fasting glucose), or for the liver-related laboratory tests (AST, ALT, bilirubin [direct, indirect and total]). The majority of grade 3 or 4 clinical laboratory abnormalities were associated with changes in creatine kinase (5.8%) and ALT (2.3%). All other grade 3 or 4 abnormalities occurred in less than 2% of subjects. All laboratory-related AEs were grade 1, not serious, and did not lead to treatment discontinuation. The most frequently reported laboratory-related AEs, hypercholesterolemia and hypertriglyceridemia, were recorded in 4 subjects (1.3%) each.

No other clinically relevant safety observations were made in a review of body weight values, concomitant medication uses, reports of study drug overdoses, pregnancies, and ECG findings.

The majority of the ADRs (as defined per company's assessment) to DRV/COBI treatment were mild in severity. The most frequent (≥2%) ADRs of grade 2 or more were rash (5.8%), diarrhea (5.1%), and nausea (3.2%). The most frequent (≥2 subjects, 0.6%) ADRs of grade 3 or 4 were rash and hypersensitivity (0.6% each). All other grade 3 or 4 ADRs were reported in 1 subject (0.3%). Twelve subjects (3.8%) discontinued treatment due to 1 or more ADRs. The ADR profile of DRV/COBI 800/150 mg once daily coadministered as single agents is consistent with the safety profile of the single agents DRV and COBI, though with a higher incidence of mild to moderate rash. Grade 1 or 2 creatinine levels were recorded more frequently in study GS-US-216-0130 (17.7%) than in the historical studies (3.3% in TMC114-C211, 4.1% in TMC114-C229); this is attributable to the known inhibitory effects of COBI on renal tubular creatinine secretion.

In conclusion, DRV/COBI 800/150 mg once daily coadministered as single agents was generally well tolerated in 313 treatment-naïve and treatment-experienced HIV-1 infected adult subjects. The reported AEs and DRV/COBI ADRs were consistent with those expected in the subject population and the known safety profiles of the single agents.

3.4. Safety Data in Ongoing Studies

In this section, a summary is presented of

- the available Week-48 safety data of the ongoing study GS-US-216-0130 (Section 3.4.1).
- safety data from the ongoing study GS-US-236-0118 in HIV-1 infected subjects with mild to moderate renal impairment (eGFR between 50 and 89 mL/min, inclusive) (Section 3.4.2).
- SAEs considered by the investigator to be related to DRV/COBI, both when administered as single agents or as a FDC tablet, reported in studies which were ongoing at the cut-off date for this SCS ([redacted]) (Section 3.4.3).

3.4.1. Week-48 Safety Analysis of Study GS-US-216-0130

An interim safety analysis was done of the ongoing study GS-US-216-0130 at Week 48, when all subjects had been treated for 48 weeks or discontinued earlier (cut-off date [redacted]).

The mean duration of DRV/COBI treatment was 58.4 weeks in the Week-48 analysis, compared to 30.0 weeks in the Week-24 analysis. The number of patient-years of exposure (mean exposure*N/52) was 351.5 patient-years in the Week-48 analysis and 180.6 patient-years in the Week 24 analysis.

The Week-24 data presented for comparison in the tables in this section (Week-48 interim analysis) can differ slightly from the data in Section 3.3 (Week-24 analysis) due to the availability of additional data after the Week-24 database closure.

In the Week-48 analysis, version 15.1 of the Medical Dictionary for Regulatory Activities was used, while version 15.0 was used in the Week-24 analysis. One notable difference is that the preferred term for the reported AE (verbatim) of ‘IRIS (Zoster Ophtalmicus)’ was ‘Immune reconstitution syndrome’ in the Week-24 analysis, and ‘Immune reconstitution inflammatory syndrome’ in the Week-48 analysis.

3.4.1.1. Adverse Events Analysis

The overall safety profile of DRV/COBI 800/150 mg once daily is similar in the Week-48 analysis as in the Week-24 analysis of study GS-US-216-0130, taking into account the increase in exposure duration. No new pattern or safety signal was observed.

Overall, 91.4% of subjects experienced at least 1 AE, compared to 87.9% in the Week-24 analysis (Table 30 and Appendix 5). The incidence of SAEs was 4.8% in the Week-24 analysis and 8.3% in the Week-48 analysis; none of the new SAEs were considered to be related to the study medication. There was 1 new AE leading to treatment discontinuation in the Week-48 analysis: renal tubular disorder (verbatim: proximal tubulopathy, grade 1, not related, not serious). Overall, there were 5 new subjects with AEs reported as possibly related to the study medication (diarrhea, flatulence, influenza, obesity, depression, abnormal dreams, and insomnia), none were serious, of grade 4, or led to treatment discontinuation.

Table 30: Summary of Adverse Events – GS-US-216-0130 Week-24 and Week-48 Analyses

n (%) of Subjects Experiencing	Week 24 All Subjects N=313	Week 48 All Subjects N=313
Total Patient-years Exposure	***180.6***	***351.6***
≥1 AE	275 (87.9)	286 (91.4)
≥1 Grade 3 or 4 AE	18 (5.8)	24 (7.7)
≥1 Grade 2, 3, or 4 AE	139 (44.4)	166 (53.0)
≥1 AE related to DRV/COBI	123 (39.3)	128 (40.9)
≥1 Grade 3 or 4 AE Related to DRV/COBI	5 (1.6)	5 (1.6)
≥1 Grade 2, 3, or 4 AE Related to DRV/COBI	42 (13.4)	43 (13.7)
≥1 SAE	15 (4.8)	26. (8.3)
≥1 SAE Related to DRV/COBI	3 (1.0)	3 (1.0)
≥1 AE Leading to Study Medication Discontinuation	15 (4.8)	16 (5.1)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-3 and Module 5.3.5.2/ GS-US-216-0130-Anal-W48-SAF-AE/Table 5.1.1.2, Table 5.1.1.3, Table 5.1.1.4, Table 5.1.1.6, Table 5.1.1.7, Table 5.1.1.8, Table 5.1.1.9, Table 5.1.1.10, Table 5.1.1.11.

There were no new grade 4 AEs in the Week-48 analysis (Table 31). None of the new grade 3 AEs reported were considered related to the study medication (see Table 30).

Table 31: Grade 3 or 4 Adverse Events Reported in More Than 1 Subject - GS-US-216-0130 Week-24 and Week 48 Analyses

System Organ Class Preferred Term, n (%)	Week 24 All Subjects N=313	Week 48 All Subjects N=313
Total Patient-years Exposure	***180.6***	***351.6***
Number of Subjects Experiencing Any Grade 3 or 4 AE	***18 (5.8)***	***24 (7.7)***
Grade 3	***16 (5.1)***	***22 (7.0)***
Grade 4	***2 (0.6)***	***2 (0.6)***
Gastrointestinal System Disorders	**2 (0.6)**	**3 (1.0)**
Vomiting, Grade 3	1 (0.3)	2 (0.6)
Immune System Disorders	**4 (1.3)**	**4 (1.3)**
Hypersensitivity, Grade 3 or 4	3 (1.0)	3 (1.0)
Grade 3	2 (0.6)	2 (0.6)
Grade 4	1 (0.3)	1 (0.3)
Nervous System Disorders	**1 (0.3)**	**2 (0.6)**
Peripheral Neuropathy, Grade 3	1 (0.3)	2 (0.6)
Skin and Subcutaneous Tissue Disorders	**2 (0.6)**	**2 (0.6)**
Rash Maculo-papular, Grade 3	2 (0.6)	2 (0.6)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-2 and Module 5.3.5.2/ GS-US-216-0130-Anal-W48-SAF-AE/Table 5.1.1.3

The incidences of AEs considered related to DRV/COBI per assessment of the investigator at Week 24 and Week 48 are provided in Table 32. The incidences were similar at Week 24 and at Week 48: 40.9% of subjects experienced at least 1 AE that was considered related to DRV/COBI, compared to 39.3% at Week 24.

Table 32: Incidence of Adverse Events Related to the Study Medication Reported in at Least 2 Subjects (System Organ Class or Preferred Term) – GS-US-216-0130 Week-24 and Week-48 Analyses

System Organ Class Preferred Term, n (%)	Week 24 N=313	Week 48 N=313
Total Patient-years Exposure	***180.6***	***351.6***
At Least 1 AE Related to Study Medication[a]	***123 (39.3)***	***128 (40.9)***
Blood and Lymphatic System Disorders	**2 (0.6)**	**2 (0.6)**
Gastrointestinal Disorders	**90 (28.8)**	**92 (29.4)**
Abdominal Pain	3 (1.0)	3 (1.0)
Abdominal Pain Upper	8 (2.6)	8 (2.6)
Diarrhoea	46 (14.7)	47 (15.0)
Dry Mouth	3 (1.0)	3 (1.0)
Dyspepsia	2 (0.6)	2 (0.6)
Flatulence	12 (3.8)	13 (4.2)
Frequent Bowel Movements	2 (0.6)	2 (0.6)
Nausea	45 (14.4)	45 (14.4)
Vomiting	5 (1.6)	5 (1.6)
General Disorders and Administration Site Conditions	**13 (4.2)**	**13 (4.2)**
Fatigue	10 (3.2)	10 (3.2)
Malaise	2 (0.6)	2 (0.6)
Immune System Disorders	**3 (1.0)**	**3 (1.0)**
Hypersensitivity	2 (0.6)	2 (0.6)
Infections and Infestations	**1 (0.3)**	**2 (0.6)**
Investigations	**2 (0.6)**	**2 (0.6)**
Metabolism and Nutrition Disorders	**5 (1.6)**	**6 (1.9)**
Decreased Appetite	3 (1.0)	3 (1.0)
Musculoskeletal and Connective Tissue Disorders	**4 (1.3)**	**4 (1.3)**
Myalgia	2 (0.6)	2 (0.6)
Nervous System Disorders	**23 (7.3)**	**21 (6.7)**
Dizziness	3 (1.0)	3 (1.0)
Dysgeusia	2 (0.6)	1 (0.3)
Headache	13 (4.2)	13 (4.2)
Peripheral Neuropathy	2 (0.6)	1 (0.3)
Psychiatric Disorders	**12 (3.8)**	**15 (4.8)**
Abnormal Dreams	6 (1.9)	8 (2.6)
Depression	1 (0.3)	2 (0.6)
Insomnia	3 (1.0)	4 (1.3)
Skin and Subcutaneous Tissue Disorders	**27 (8.6)**	**27 (8.6)**
Dermatitis	2 (0.6)	2 (0.6)
Pruritus	4 (1.3)	4 (1.3)
Rash	10 (3.2)	10 (3.2)
Rash Maculo-papular	5 (1.6)	5 (1.6)
Rash Macular	4 (1.3)	4 (1.3)

N=total number of subjects with data; n=number of subjects with observation.
[a] Causality assessment by the investigator.
Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 5.1.1.5 and Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/Table 5.1.1.5.

Overall, there was no increase over time in the occurrence of AEs of interest: 27.2% of subjects experienced at least 1 AE of interest in the Week-48 analysis, compared to 23.6% in the Week-24 analysis (Table 20 and Appendix 6). The newly reported preferred terms under the AEs of interest were hyperlipidemia, ocular icterus, diabetes mellitus, impaired fasting glucose, ECG ST-T segment abnormal, amylase increased, and lipase increased.

3.4.1.2. Clinical Laboratory Evaluation

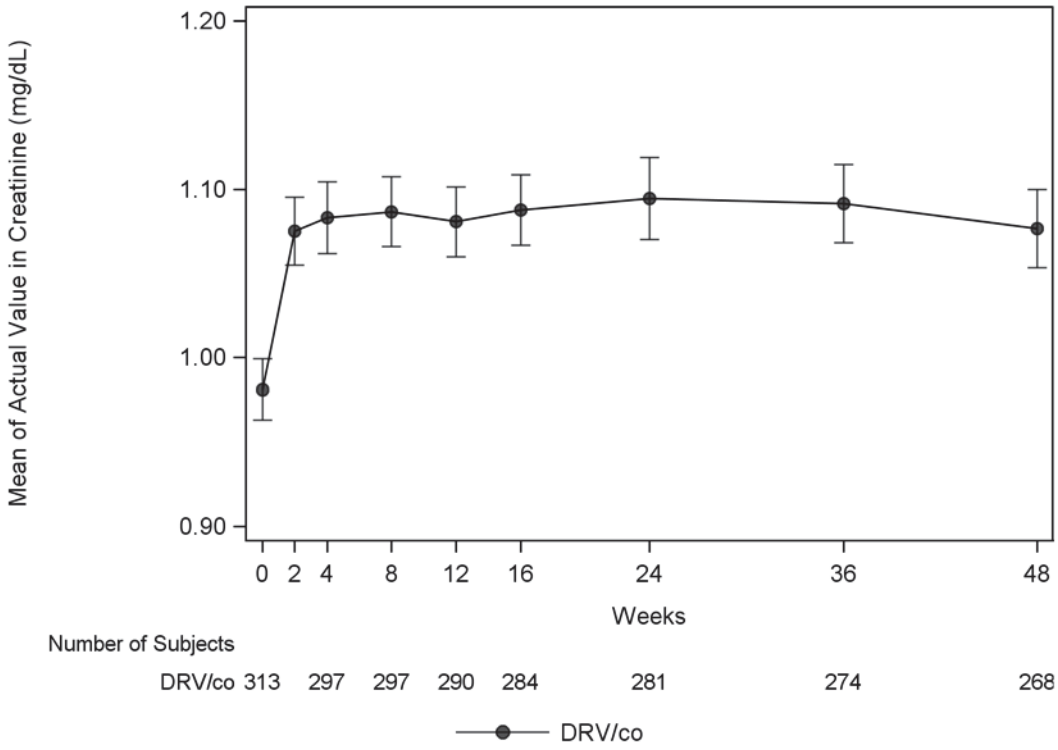
After Week 24, samples for laboratory safety testing were taken at Week 36 and Week 48.

There were no clinically relevant changes from baseline through Week 48 in mean values for the hematology parameters or clinical chemistry parameters, for the lipid parameters (fasting HDL cholesterol, fasting LDL cholesterol, fasting total cholesterol to HDL cholesterol ratio, or fasting glucose), or for the liver-related laboratory tests (AST, ALT, bilirubin [direct, indirect and total]).

The increase from baseline in serum creatinine from Week 2 onwards (mean change 0.09 mg/dL) remained stable during DRV/COBI treatment. The mean change was 0.12 mg/dL at Week 24 (Figure 1) and 0.10 mg/dL at Week 48 (Figure 2).

The mean (SD) $eGFR_{CG}$ change from baseline was -9.6 (13.7) mL/min at Week 2, –11.5 (15.5) mL/min at Week 24, and -9.6 (14.7) mL/min at Week 48. The eGFR calculated by cystatin C clearance ($eGFR_{CC}$) did not change significantly over time.

Figure 2: Mean (±95% CI) Value Over Time in Serum Creatinine – GS-US-216-0130 Week-48 Analysis



Source: Module 5.3.5.2/GS-US-216-0130-W48-Anal-LAB/GSFLAB01CREAT.

None of the subjects had a progressive increase in serum creatinine over the 48 weeks. In the Week-48 analysis, 7 subjects (2.2%, ie, 1 subject more than in the Week-24 analysis) had a confirmed creatinine increase from baseline ≥0.4 mg/dL at 2 or more consecutive visits. In these 7 subjects, the maximum observed increases from baseline at any visit ranged between +0.41 and +0.69 mg/dL. In 4 of these 7 subjects, the observed change from baseline at the last recorded creatinine value before data cut-off was <0.4 mg/dL, meaning that the increased creatinine levels

observed during the study did not remain elevated, but rather began to return to the baseline value at or prior to the data cut-off. None of these 7 subjects had concurrent serum phosphate or urine glucose levels grade 1 or more, or urine protein levels grade 2 or more, or experienced AEs of hypophosphatemia, proteinuria, or glycosuria, except for subject 1236-4051 who presented with glucosuria (see below). Among the 3 subjects with a creatinine increase from baseline by ≥0.4 mg/dL at last available time point (CRF IDs 1236-4051, 1536-4232, and 6046-4024), 2 subjects had no signs of possible subclinical kidney disease or renal AEs. The third subject (CRF ID 1236-4051) discontinued the study medication due to a renal AE: renal tubular disorder (verbatim: proximal tubulopathy, AE started Week 36, grade 1, not serious and assessed by the investigator as not related to the study medication).

3.4.1.3. Adverse Drug Reactions

No new safety signals were identified in the Week-48 analysis. The Week-48 ADR profile of DRV/COBI 800/150 mg once daily in presented in Table 33, using the list of ADRs identified in the Week-24 analysis.

The overall ADR profile of DRV/COBI 800/150 mg once daily at Week 48 is consistent with the Week-24 profile (Table 33). At Week 48, 66.5% of subjects experienced at least 1 ADR, compared to 62.6% of subjects in the Week-24 analysis. Since the Week-24 analysis, 12 additional subjects (3.8%) reported at least 1 ADR, 2 subjects (0.6%) had at least 1 serious ADR and none had an ADR that led to treatment discontinuation. At Week 48, the incidence of ADRs at least grade 2 was 20.4%, and of ADRs grade 3 or 4 was 3.5%. Six subjects (1.9%) experienced a serious ADR, and 12 subjects (3.8%) prematurely discontinued the study medication because of an ADR.

Table 33: Summary of DRV/COBI Adverse Drug Reactions – GS-US-216-0130 Week-24 and Week-48 Analyses

n (%) of Subjects Experiencing	Week 24 All Subjects N=313	Week 48 All Subjects N=313
Total Patient-years Exposure	***180.6***	***351.6***
At Least 1 ADR	196 (62.6)	208 (66.5)
At Least 1 Grade 2, 3 or 4 ADR	62 (19.8)	64 (20.4)
At Least 1 Grade 3 or 4 ADR	9 (2.9)	11 (3.5)
At Least 1 Serious ADR	4 (1.3)	6 (1.9)
At Least 1 ADR Leading to Permanent Discontinuation	12 (3.8)	12 (3.8)

N=total number of subjects with data; n=number of subjects with observation.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFPAE01, TSFPAE02, TSFPAE03, TSFPAE04, and TSFPAE05.

All ADRs reported in the Week-24 and Week-48 analyses are presented in Table 34. The Week-48 ADR review did not identify new ADRs associated with DRV/COBI, compared to the Week-24 ADR profile and the well documented ADR safety profile of DRV/rtv. The findings are in line with those of the Week-24 analysis.

For the ADR tables presenting the incidences at Week 24 and Week 48 of (1) all ADRs at least grade 2, (2) all ADRs at least Grade 3, (3) all serious ADRs and (4) all ADRs leading to treatment

discontinuation, refer to Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFPAE02, TSFPAE03, TSFPAE04, and TSFPAE05, respectively.

Graded DAIDS abnormalities in the selected laboratory parameters, considered to be ADRs, are presented in Table 35 (AST, ALT, alkaline phosphatase, total cholesterol, LDL cholesterol, triglycerides, glucose, amylase, lipase, creatinine). No new trends or safety issues were observed.

Table 34: All DRV/COBI Adverse Drug Reactions – GS-US-216-0130 Week-24 and Week-48 Analyses

System Organ Class (Grouped) [a] Preferred Term, n (%)	Week 24 All Subjects N=313	Week 48 All Subjects N=313
Total Patient-years Exposure	***180.6***	***351.6***
At Least 1 ADR	***196 (62.6)***	***208 (66.5)***
Gastrointestinal Disorders	**141 (45.0)**	**153 (48.9)**
Abdominal Distension	4 (1.3)	6 (1.9)
Abdominal Pain[a]	23 (7.3)	25 (8.0)
Diarrhoea[a]	79 (25.2)	87 (27.8)
Dyspepsia	6 (1.9)	6 (1.9)
Flatulence	19 (6.1)	20 (6.4)
Nausea	67 (21.4)	72 (23.0)
Pancreatic Enzymes Increased	0	1 (0.3)
Pancreatitis Acute	1 (0.3)	1 (0.3)
Vomiting	26 (8.3)	28 (8.9)
General Disorders & Administration Site Conditions	**20 (6.4)**	**23 (7.3)**
Asthenia	1 (0.3)	2 (0.6)
Fatigue	20 (6.4)	22 (7.0)
Hepatobiliary Disorders	**5 (1.6)**	**6 (1.9)**
Hepatic Enzyme Increased[a]	5 (1.6)	6 (1.9)
Immune System Disorders	**7 (2.2)**	**8 (2.6)**
(Drug) Hypersensitivity[a]	6 (1.9)	7 (2.2)
Immune Reconstitution Syndrome[a]	1 (0.3)	1 (0.3)
Investigations	**3 (1.0)**	**3 (1.0)**
Increased Blood Creatinine[a]	3 (1.0)	3 (1.0)
Metabolism and Nutrition Disorders	**17 (5.4)**	**18 (5.8)**
Anorexia [a]	6 (1.9)	6 (1.9)
Diabetes Mellitus [a]	2 (0.6)	3 (1.0)
Hypercholesterolaemia [a]	4 (1.3)	4 (1.3)
Hyperlipidaemia	0	1 (0.3)
Hypertriglyceridaemia [a]	7 (2.2)	7 (2.2)
Musculoskeletal and Connective Tissue Disorders	**5 (1.6)**	**6 (1.9)**
Myalgia	5 (1.6)	6 (1.9)
Nervous System Disorders	**29 (9.3)**	**38 (12.1)**
Headache	29 (9.3)	38 (12.1)
Psychiatric Disorders	**8 (2.6)**	**11 (3.5)**
Abnormal Dreams	8 (2.6)	11 (3.5)
Skin and Subcutaneous Tissue Disorders	**57 (18.2)[b]**	**56 (17.9)[b]**
Angioedema[a]	3 (1.0)	3 (1.0)
Pruritus	7 (2.2)	7 (2.2)
Rash[a]	50 (16.0) [b]	49 (15.7) [b]
Rash	27 (8.6) [b]	25 (8.0) [b]
Rash Erythematous	2 (0.6)	2 (0.6)
Rash Generalized	2 (0.6)	2 (0.6)
Rash Macular	4 (1.3)	4 (1.3)
Rash Maculo-papular	6 (1.9)	6 (1.9)
Rash Papular	5 (1.6)	5 (1.6)
Rash Pruritic	4 (1.3)	5 (1.6)
Urticaria	3 (1.0)	3 (1.0)

N=total number of subjects with data; n=number of subjects with ADR.

[a] Grouped term; the grouped preferred terms are described in Appendix 3.

[b] The verbatim 'Truncal Rash' (coded to preferred term 'Rash' in the Week-24 analysis) was changed to 'Truncal Tenia Versicolor' (coded to 'Tinea Versicolor') in the Week-48 analysis, and verbatim 'Rash Right Axillary Region' (coded to Rash in Week 24 analysis) was changed to 'Acne Rash Right Axillary Region' (coded to 'Dermatitis Acneiform') in the Week-48 analysis.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFPAE01.

Table 35: DRV/COBI Laboratory-related Adverse Drug Reactions – GS-US-216-0130 Week-24 and Week-48 Analyses

Laboratory Parameter Grouping **Laboratory Parameter** Grade [a], n (%)[b]	**Week 24 All Subjects N=313**	**Week 48 All Subjects N=313**
Total Patient-years Exposure	***180.6***	***351.6***
General Clinical Chemistry	***N=310***	***N=310***
Amylase (U/L)		
Grade 1	48 (15.5)	52 (16.8)
Grade 2	17 (5.5)	20 (6.5)
Grade 3	6 (1.9)	8 (2.6)
Pancreatic Lipase (U/L)		
Grade 1	14 (4.5)	18 (5.8)
Grade 2	8 (2.6)	12 (3.9)
Grade 3	2 (0.6)	3 (1.0)
Grade 4	3 (1.0)	4 (1.3)
Creatinine (mg/dL)		
Grade 1	45 (14.5)	47 (15.2)
Grade 2	10 (3.2)	10 (3.2)
Lipids and Glucose	***N=293***	***N=293***
Cholesterol (mg/dL)		
Grade 1	47 (16.0)	65 (22.2)
Grade 2	21 (7.2)	31 (10.6)
Grade 3	3 (1.0)	3 (1.0)
Glucose (mg/dL)		
Grade 1	25 (8.5)	40 (13.7)
Grade 2	11 (3.8)	19 (6.5)
LDL Cholesterol (mg/dL)		
Grade 1	34 (11.6)	49 (16.7)
Grade 2	21 (7.2)	32 (10.9)
Grade 3	10 (3.4)	14 (1.8)
Triglycerides (mg/dL)		
Grade 2	3 (1.0)	4 (1.4)
Grade 3	4 (1.4)	4 (1.4)
Liver Function	***N=310***	***N=310***
ALT (U/L)		
Grade 1	20 (6.5)	29 (9.0)
Grade 2	9 (2.9)	10 (3.2)
Grade 3	5 (1.6)	6 (1.9)
Grade 4	2 (0.6)	3 (1.0)
Alkaline Phosphatase (U/L)		
Grade 1	4 (1.3)	6 (1.9)
Grade 2	3 (1.0)	3 (1.0)
AST (U/L)		
Grade 1	20 (6.5)	23 (7.4)
Grade 2	19 (6.1)	19 (6.1)
Grade 3	4 (1.3)	7 (2.3)
Grade 4	2 (0.6)	2 (0.6)

N=total number of subjects with data; n=number of subjects with observation.
[a] DAIDS grades.
[b] The number of subjects with data can vary per laboratory parameter, but the % reflects the true percentage of observed abnormalities.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-LAB/TSFLAB05 and Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-LAB/TSFLAB05.

3.4.1.4. Historical Comparison of the Week-48 ADR Analysis

As previously shown with the Week-24 data (Section 3.3.11), the results of the Week-48 ADR analysis of study GS-US-216-0130 are presented side-by-side with the DRV/rtv 800/100 mg once daily treatment arm of the Week-48 ADR analyses of 2 historical controls, studies TMC114-C211 and TMC114-C229. These comparisons are to be interpreted with caution given the inherent limitations associated with the use of historical data as control.

Three tables are presented, an ADR summary (Table 36), a table with all ADRs (Table 37) and a table with laboratory-related ADRs (Table 38). For the tables of each the ADR categories in Table 36, refer to Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFAE07, TSFAE08, TSFAE09, TSFAE10, and TSFAE11.

As previously shown for the Week-24 data, overall, the incidence of ADRs (any grade) was similar after 48 weeks of treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130 (66.5%) and after 48 weeks of treatment with DRV/rtv 800/100 mg once daily in the treatment-naïve subjects in study TMC114-C211 (65.9%). Adverse drug reactions were less frequent in the treatment-experienced subjects treated with DRV/rtv in study TMC114-C229 (42.5%). The incidences of rash, nausea, vomiting and flatulence, were higher in study GS-US-216-0130 than in the historical studies (Table 37). These were driven by grade 1 events for the gastrointestinal disorders, and by grade 1 or 2 events for rash. They essentially occurred in the first 24 weeks of treatment as only a very limited number of subjects experienced newly emerging ADRs after the first 24 weeks of treatment. The differences in incidences between study GS-US-216-0130 and the historical controls did not indicate a clinical concern. Adverse drug reactions at least grade 2 showed similar incidences at Week 48 in the 3 studies: 20.4% in GS-US-216-0130, 29.2% in TMC114-C211 and 19.7% in TMC114-C229. Incidences of ADRs at least grade 3, serious ADRs and ADRs leading to discontinuation were low in all 3 studies.

Table 36: Summary of Adverse Drug Reactions in GS-US-216-0130, DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229 Week-48 Analyses

Type of ADR n (%) of Subjects Experiencing	GS-US-216-0130 DRV/COBI 800/150 mg qd N=313	TMC114-C211 DRV/rtv 800/100 mg qd N=343	TMC114-C229 DRV/rtv 800/100 mg qd N=294
Total Patient-years Exposure	***351.6***	***361.5***	***253.5***
≥1 ADR	208 (66.5)	226 (65.9)	125 (42.5)
≥1 Grade 2, 3 or 4 ADR	64 (20.4)	100 (29.2)	58 (19.7)
≥1 Grade 3 or 4 ADR	11 (3.5)	34 (9.9)	9 (3.1)
≥1 Serious ADR	6 (1.9)	3 (0.9)	0
≥1 ADR Leading to Permanent Discontinuation	12 (3.8)	7 (2.0)	5 (1.7)

N=total number of subjects with data; n=number of subjects with observation; qd=once daily.
Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFAE07, TSFAE08, TSFAE09, TSFAE10, and TSFAE11.

Table 37: All DRV/COBI Adverse Drug Reactions – GS-US-216-0130 TMC114-C211 and TMC114-C229 Week-48 Analyses

System Organ Class (Grouped)[a] Preferred Term[b], n (%)	GS-US-216-0130 DRV/COBI Week 48 N=313	TMC114-C211 DRV/rtv Week 48 N=343	TMC114-C229 DRV/rtv Week 48 N=294
Total Patient-years Exposure	***351.6***	***361.5***	***253.5***
At Least 1 ADR	***208 (66.5)***	***226 (65.9)***	***125 (42.5)***
Gastrointestinal Disorders	**153 (48.9)**	**168 (49.0)**	**89 (30.3)**
Abdominal Distension	6 (1.9)	10 (2.9)	4 (1.4)
Abdominal Pain[a]	25 (8.0)	32 (9.3)	14 (4.8)
Diarrhoea[a]	87 (27.8)	116 (33.8)	42 (14.3)
Dyspepsia	6 (1.9)	9 (2.6)	6 (2.0)
Flatulence	20 (6.4)	8 (2.3)	6 (2.0)
Nausea	72 (23.0)	55 (16.0)	38 (12.9)
Pancreatic Enzymes Increased	1 (0.3)	4 (1.2)	2 (0.7)
Pancreatitis Acute	1 (0.3)	2 (0.6)	0
Vomiting	28 (8.9)	21 (6.1)	13 (4.4)
General Disorders & Administration Site Conditions	**23 (7.3)**	**26 (7.6)**	**5 (1.7)**
Asthenia	2 (0.6)	7 (2.0)	2 (0.7)
Fatigue	22 (7.0)	19 (5.5)	3 (1.0)
Hepatobiliary Disorders	**6 (1.9)**	**14 (4.1)**	**1 (0.3)**
Hepatic Enzyme Increased[a]	6 (1.9)	13 (3.8)	1 (0.3)
Immune System Disorders	**7 (2.2)**	**4 (1.2)**	**0**
(Drug) Hypersensitivity[a]	7 (2.2)	3 (0.9)	0
Investigations	**3 (1.0)**	**3 (0.9)**	**3 (1.0)**
Increased Blood Creatinine[a]	3 (1.0)	3 (0.9)	3 (1.0)
Metabolism and Nutrition Disorders	**18 (5.8)**	**33 (9.6)**	**25 (8.5)**
Anorexia[a]	6 (1.9)	11 (3.2)	4 (1.4)
Diabetes Mellitus[a]	3 (1.0)	3 (0.9)	2 (0.7)
Hypercholesterolaemia[a]	4 (1.3)	7 (2.0)	3 (1.0)
Hyperlipidaemia	1 (0.3)	4 (1.2)	3 (1.0)
Hypertriglyceridaemia[a]	7 (2.2)	6 (1.7)	5 (1.7)
Musculoskeletal and Connective Tissue Disorders	**6 (1.9)**	**10 (2.9)**	**4 (1.4)**
Myalgia	6 (1.9)	10 (2.9)	4 (1.4)
Nervous System Disorders	**38 (12.1)**	**60 (17.5)**	**20 (6.8)**
Headache	38 (12.1)	60 (17.5)	20 (6.8)
Psychiatric Disorders	**11 (3.5)**	**3 (0.9)**	**0**
Abnormal Dreams	11 (3.5)	3 (0.9)	0
Skin and Subcutaneous Tissue Disorders	**56 (17.9)**	**57 (16.6)**	**24(8.2)**
Angioedema[a]	3 (1.0)	3 (0.9)	0
Pruritus	7 (2.2)	18 (5.2)	4 (1.4)
Rash[a]	49 (15.7)	35 (10.2)	20 (6.8)
Rash	25 (8.0)	27 (7.9)	15 (5.1)
Rash Erythematous	2 (0.6)	1 (0.3)	0
Rash Generalized	2 (0.6)	0	1 (0.3)
Rash Macular	4 (1.3)	1 (0.3)	0
Rash Maculo-papular	6 (1.9)	2 (0.6)	2 (0.7)
Rash Papular	5 (1.6)	7 (2.0)	2 (0.7)
Rash Pruritic	5 (1.6)	0	0
Urticaria	3 (1.0)	6 (1.7)	0

N=total number of subjects with data; n=number of subjects with ADR

[a] Grouped term; the grouped preferred terms are described in Appendix 3.

[b] Only events identified as ADRs in study GS-US-216-0130 are presented in this table. ADRs occurring in the historical studies but not in GS-US-216-0130 are not presented here, they can be found in the source table.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFAE07

In Table 38, graded DAIDS abnormalities in selected laboratory parameters, considered to be DRV/COBI ADRs, are presented for study GS-US-216-0130 (DRV/COBI ADRs) at Week 48, and for the historical studies TMC114-C211 and TMC114-C229 (DRV/rtv ADRs) at Week 48.

Overall, the incidence and severity of the laboratory-related ADRs observed at Week 48 in study GS-US-216-0130 are in line with those reported at Week 48 in studies TMC114-C211 and TMC114-C229. As was seen at Week 24, graded creatinine abnormalities were more frequent in the GS-US-216-0130 study (18.4%) than in study TMC114-C211 (3.8%, this includes 1 subject with a grade 3 abnormality not shown in Table 38) and TMC114-C229 (4.9%, this includes 3 subjects with grade 3 and 1 subject with grade 4 abnormality not shown in Table 38). The higher incidence of graded creatinine abnormalities in study GS-US-216-0130 may be attributable to the known inhibitory effects of COBI on renal tubular creatinine secretion. Graded amylase/lipase levels were also recorded more frequently in study GS-US-216-0130 than in the historical studies, mainly due a 1-grade change versus baseline during DRV/COBI treatment; most increases were isolated and transient or fluctuating, and the increases were not associated with signs or symptoms suggestive of pancreatitis.

Table 38: Laboratory-related Adverse Drug Reactions – GS-US-216-0130,TMC114-C211 and TMC114-C229 Week-48 Analyses

Laboratory Parameter Grouping **Laboratory Parameter** Grade [a], n (%)[b]	**GS-US-216-0130 DRV/COBI Week 48 N=313**	**TMC114-C211 DRV/rtv Week 48 N=343**	**TMC114-C229 DRV/rtv Week 48 N=286**
Total Patient-years Exposure	***351.6***	***361.5***	***253.5***
General Clinical Chemistry			
Amylase (U/L)			
Grade 1	52 (16.8)	32 (9.4)	21 (7.3)
Grade 2	20 (6.5)	14 (4.1)	9 (3.1)
Grade 3	8 (2.6)	9 (2.6)	7 (2.4)
Pancreatic Lipase (U/L)			
Grade 1	18 (5.8)	5 (1.5)	5 (1.7)
Grade 2	12 (3.9)	5 (1.5)	3 (1.0)
Grade 3	3 (1.0)	1 (0.3)	1 (0.3)
Grade 4	4 (1.3)	0	
Creatinine (mg/dL)			
Grade 1	47 (15.2)	12 (3.5)	3 (1.0)
Grade 2	10 (3.2)	0	7 (2.4)
Lipids and Glucose			
Cholesterol (mg/dL)			
Grade 1	65 (22.2)	69 (20.2)	45 (15.7)
Grade 2	31 (10.6)	40 (11.7)	22 (7.7)
Grade 3	3 (1.0)	4 (1.2)	7 (2.4)
Glucose (mg/dL)			
Grade 1	40 (13.7)	39 (11.4)	37 (12.9)
Grade 2	19 (6.5)	16 (4.7)	18 (6.3)
LDL Cholesterol (mg/dL)			
Grade 1	49 (16.7)	59 (17.3)	48 (16.8)
Grade 2	32 (10.9)	39 (11.4)	20 (7.0)
Grade 3	14 (1.8)	5 (1.5)	8 (2.8)
Triglycerides (mg/dL)			
Grade 2	4 (1.4)	4 (1.2)	10 (3.5)
Grade 3	4 (1.4)	4 (1.2)	4 (1.4)
Liver Function			
ALT (U/L)			
Grade 1	29 (9.0)	32 (9.4)	32 (11.2)
Grade 2	10 (3.2)	17 (5.0)	5 (1.7)
Grade 3	6 (1.9)	10 (2.9)	0
Grade 4	3 (1.0)	2 (0.6)	0
Alkaline Phosphatase (U/L)			
Grade 1	6 (1.9)	19 (5.6)	12 (4.2)
Grade 2	3 (1.0)	4 (1.2)	2 (0.7)
AST (U/L)			
Grade 1	23 (7.4)	31 (9.1)	17 (5.9)
Grade 2	19 (6.1)	19 (5.6)	4 (1.4)
Grade 3	7 (2.3)	10 (2.9)	2 (0.7)
Grade 4	2 (0.6)	3 (0.9)	0

N=total number of subjects with data; n=number of subjects with ADR.

[a] Only graded abnormalities observed in study GS-US-216-0130 are listed, with matching data in the historical studies. For ADRs observed in study TMC114-C211 but not in study GS-US-216-0130, refer to source tables.

[b] DAIDS grades.

[c] The number of subjects with data can vary per laboratory parameter, but the % reflects the true percentage of observed abnormalities.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-LAB/TSFLAB05, and TSFLAB06A and TSFLAB06B.

3.4.1.5. Conclusion of the Week-48 Safety Analysis of GS-US-216-0130

In conclusion, DRV/COBI 800/150 mg once daily coadministered as single agents was generally well tolerated in 313 HIV-1 infected adult subjects over a mean treatment duration of 58.4 weeks. No safety signals were reported from these data. The reported AEs and DRV/COBI ADRs were consistent with those reported in the Week-24 analysis and those expected in the subject population and with the known safety profiles of the single agents.

3.4.2. Safety Data in Study GS-US-236-0118

Study GS-US-236-0118 is an ongoing study in HIV-1 infected subjects with mild to moderate renal impairment (eGFR between 50 and 89 mL/min, inclusive).[3] In Cohort 1 of this study, treatment-naïve HIV-1 infected adults with HIV-1 RNA ≥1,000 copies/mL were enrolled and treated with STR EVG/COBI/FTC/TDF. In Cohort 2, treatment-experienced subjects virologically suppressed at baseline, switched from an ATV/rtv- or DRV/rtv-based treatment regimen with 2 NRTIs to ATV/COBI 300/150 mg or DRV/COBI 800/150 mg once daily treatment with 2 NRTIs (ATV/COBI n=52, DRV/COBI n=21).

Safety data from the Week-24 interim analysis in Cohort 2 showed that there were no clinically meaningful changes in renal parameters in the subjects on a COBI-containing DRV or ATV regimen for a median duration of 39.4 weeks. Small increases from baseline in serum creatinine were noted as early as Week 2, after which they generally stabilized and were nonprogressive with increased treatment duration. Changes from baseline in eGFR were very small and not considered clinically relevant. The observed increases in serum creatinine are expected in subjects initiating a COBI-containing regimen, as a result of the inhibition of tubular creatinine secretion by COBI. These changes do not affect actual glomerular function; therefore, they are not considered clinically relevant. None of the subjects discontinued study medication due to renal AEs. Cobicistat-containing DRV or ATV regimens were generally well tolerated in HIV-1 infected, virologically suppressed subjects with mild to moderate renal impairment.

3.4.3. Serious Adverse Events Related to DRV/COBI Reported After the Cut-off for this Summary

The search for SAEs was performed on the Global Medical Safety database (SCEPTRE) from Johnson & Johnson Pharmaceutical Research & Development cumulatively up until [redacted] (the cut-off date for this SCS). This summary is based on CIOMS reports (refer to Module 2.7.4/FDC-DRV-COBI-20131000-CLS-Saf-att1 and att2).

The search retrieved 9 cases, all from study GS-US-216-0130.

Six reports were follow-up reports which did not contain new information than that provided with the Week-24 analysis. For details, refer to the CIOMS reports #20120311826(4), 20120209481(2), 20120302461(7), 20120311820(1), 20120411981(1), 20120605156(1).

One report (CIOMS report #20120403958[1]) provided significant follow-up information compared to the Week-24 data. The subject (CRF ID 4067) delivered, through caesarian section, a healthy male baby at approximately 36 weeks of gestation. The infant was

described as healthy with a weight of 2,794 grams, length of 18.75 inches, and head circumference of 13 inches. The postpartum course was uncomplicated.

Two reports concerned new cases reported after the cut-off date of the Week-24 analysis ([redacted]) but prior to the cut-off date of the Week-48 analysis ([redacted]). One report was generated for the diagnosis of prostate cancer (SAE, not related) in a 52-year-old black male. The subjects started DRV/COBI treatment on [redacted], he was diagnosed with prostate cancer on [redacted], in Week 35 of DRV/COBI treatment. For further details, refer to the CIOMS report #20121104695(0). The other report concerned 3 SAEs (ectopic pregnancy, exposure during pregnancy and bacterial vaginitis) in a 24-year-old female subject. The subjects started DRV/COBI treatment on [redacted]. She was diagnosed with bacterial vaginitis (grade 2, not drug-related) on [redacted], 2 weeks after treatment start; the AE had resolved 7 days later. She was diagnosed with ectopic pregnancy, exposure during pregnancy and bacterial vaginitis on [redacted], while still on DRV/COBI treatment. She underwent surgery that day to remove the left fallopian tube. The investigator provided no causality for the 3 SAEs; company causality was assessed as doubtful. For further details, please refer to CIOMS report #20130700753(0) in Module 2.7.4/FDC-DRV-COBI-20131000-CLS-Saf-att1 and att2.

4. SAFETY IN SPECIAL GROUPS AND SITUATIONS

4.1. Intrinsic Factors

Five subjects (1.6%) were HBsAg positive, and 8 (2.6%) were hepatitis C virus seropositive in study GS-US-216-0130 (see Table 14). No subgroup analyses were done in the Week-24 safety analysis of the study.

Darunavir or COBI have not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

The safety profile of the combined use of DRV and COBI has not been established in pediatric subjects.

Limited information is available on the use of DRV or COBI in subjects aged 65 or more.

4.2. Extrinsic Factors

No subgroup analyses were done in the safety analysis of study GS-US-216-0130.

4.3. Drug Interactions

For an overview of established and theoretic drug interactions with DRV/rtv and for the dosage recommendations, refer to the CCDS of DRV.[9]

For an overview of established and theoretic drug interactions with COBI and for the dosage recommendations, refer to the COBI product labeling.[11]

For an overview of the theoretic drug interactions and proposed contraindications with DRV/COBI, refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2.

4.4. Use in Pregnancy and Lactation

One treatment-naïve subject became pregnant during study GS-US-216-0130. This 32-year-old white subject started treatment with DRV/COBI on [redacted], but discontinued treatment 11 days later, on [redacted] because of rash. She was confirmed pregnant 15 days later, on [redacted]. She delivered a viable male infant on [redacted], and her postpartum course was uncomplicated. For a complete narrative of this event, refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 15.2.

There are no adequate and well-controlled studies with DRV or COBI in pregnant women. The DRV/COBI FDC should be used during pregnancy only if the potential benefit justifies the potential risk. Studies in animals with DRV and COBI as single agents have not shown evidence of developmental toxicity or effect on reproductive function and fertility.[9,11]

4.5. Overdose

Human experience of acute overdose with DRV is limited. Single doses up to 3,200 mg of the oral solution of DRV and up to 1,600 mg of the tablet formulation of DRV in combination with rtv have been administered to healthy volunteers without untoward symptomatic effects. There is no specific antidote for overdose with DRV.[9]

If overdose of DRV/COBI occurs the subject must be monitored for evidence of toxicity. Treatment of overdose with DRV/COBI consists of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. If indicated, elimination of unabsorbed active substance is to be achieved by emesis. Administration of activated charcoal may also be used to aid in removal of unabsorbed substance.[9] Since DRV and COBI are highly protein bound, dialysis is unlikely to be beneficial in significant removal of the substances.[9,11]

4.6. Drug Abuse

No systematic examination of the abuse potential of DRV/COBI was performed in the preclinical and clinical studies included in this submission and no information regarding the dependence potential of DRV/COBI in animals and humans is yet available.

4.7. Withdrawal and Rebound

Clinical studies or systematic analyses to evaluate the potential withdrawal and rebound effects of DRV alone or coadministered with COBI have not been conducted. Examination of the safety parameters (AE profile and abnormalities for clinical laboratory, vital signs and ECG) during washout periods and during follow-up periods after last intake of study medication showed that the overall safety/tolerability profile of DRV alone or coadministered with COBI was not negatively impacted by interruption or discontinuation of treatment. These findings suggest that serious medical complications are unlikely to result from the interruption or discontinuation of DRV/COBI administration at the recommended dosages.

4.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No studies have been performed on the effects of DRV/COBI on the ability to drive or use machines. However, dizziness has been reported in some subjects during treatment with regimens containing DRV/rtv. This should be borne in mind when considering a patient's ability to drive or operate machinery while taking DRV/COBI.

5. POSTMARKETING DATA

The most recent periodic safety update report for DRV, covering the period between 24 December 2011 and 23 December 2012, concluded that DRV continues to have a favorable benefit-risk profile for the registered indications and that no further changes to the CCDS[9] and the Risk Management Plan are recommended.

The cumulative postmarketing exposure till December 2012, based on the grams of DRV distributed worldwide is estimated to be 6,[redacted] person-months or 5[redacted] person-years.

At the time of finalization of this SCS, no postmarketing data are available for COBI.

6. CONCLUSIONS

The results of the safety analyses of the Phase 1 studies TMC114IFD1001 and TMC114IFD1003 demonstrate that the single or repeated (10 days) administration of DRV/COBI 800/150 mg as FDC in healthy adult subject under fed and fasted conditions was generally safe and well tolerated. There were no new findings compared to the known safety profile of DRV/rtv in adult healthy subjects.

The safety results of study GS-US-216-0130 demonstrate that DRV/COBI 800/150 mg once daily coadministered as single agents was generally well tolerated in 313 treatment-naïve and treatment-experienced HIV-1 infected adult subjects after a median exposure of 31.4 weeks. The AEs and ADRs to DRV/COBI 800/150 mg once daily were consistent with those expected in the subject population and the known safety profiles of the single agents. The ADR profile of DRV/COBI 800/150 mg once daily coadministered as single agents is consistent with the safety profile of the single agents DRV and COBI, though with a higher incidence of mild to moderate rash.

No safety signals were observed in the ongoing studies with DRV/COBI up until the cut-off date for this SCS ([redacted]). The AEs and DRV/COBI ADRs reported in the Week-48 analysis were consistent with those reported in the Week-24 analysis and those expected in the subject population and with the known safety profiles of the single agents.

In conclusion, the safety results presented in the SCS support the use of DRV/COBI 800/150 mg once daily in the intended indication.

REFERENCES

The following reference list is also provided in Module 2.7.5. All literature references are considered supportive but have been included for the convenience of the reviewer.

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10. STRIBILD product information; Gilead Sciences International Ltd. June 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_Product_Information/human/002574/WC500144272.pdf, accessed 25 July 2013.
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APPENDICES

Appendix 1: Narratives of Grade 3 or 4 AEs of Interest in the Week-24 Analysis of GS-US-216-0130

Subject 216-0130-0661-4080

Adverse event of interest: Grade 3 hepatic enzymes increased

This 4[redacted]-year-old white male started treatment with DRV/COBI at the dose of 800/150 mg once daily from 1 December 2011 as part of his ARV therapy including 2 NRTIs (Truvada [tenofovir and emtricitabine]). At Screening, hepatitis B surface antigen and hepatitis C virus antibody were negative. The subject's relevant medical history and concurrent conditions included Gilbert's disease syndrome (2011). The subject's weight was 80.9 kg and BMI was 27.1 kg/m^2.

At screening on 3 November 2011, hepatic enzymes increased (grade 1 AE) was reported; alanine aminotransferase (ALT), alkaline phosphatase (ALP) , aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT) were grade 1 elevated, and direct bilirubin was 0.6 mg/dL (high), indirect bilirubin was 1.1 mg/dL, and total bilirubin was 1.7 mg/dL (grade 1). Details for laboratory values are provided in the following table.

On 1 December 2011, ie, baseline, ALT and GGT had increased to grade 2 elevated, ALP and bilirubin had normalized, and amylase and AST were grade 1 elevated. The grade 1 AE of hepatic enzyme increased resolved on 29 December 2011 (Day 29, Week 4). At that time, enzyme values had decreased but remained elevated, although AST had normalized.

Date/Visit	ALT U/L	ALP U/L	AST U/L	GGT U/L	Direct bili mg/dL	Total bili mg/dL	Amylase U/L
3 Nov 2011 Screening	91 (gr 1),	167 (gr 1)	50 (gr 1),	142 (gr 1),	0.6 (high),	1.7 (gr 1).	82 normal
1 Dec 2011 Baseline	119 (gr 2),	127 normal	85 (gr 1),	177 (gr 2),	0.2 normal	0.6 normal	147 (gr 1),
15 Dec 2011 Day 15 Wk 2	147 (gr 2)	113 normal	101 (gr 2)	221 (gr 2)	0.3 normal	0.7 normal	130 (gr 1)
29 Dec 2011 Day 29 Wk 4	52 (high)	144 (high)	34 normal	115 (g 1)	0.9 (high)	1.7 (gr 1)	64 normal
26 Jan 2012 Day 57 Wk 8	97 (gr 1)	115 normal	69 (gr 1)	121 (gr 1)	0.3 normal	0.8 normal	130 (gr 1)
23 Feb 2012 Day 85 Wk 12	338 (gr 3)	206 (gr 1)	376 (gr 4)	381 (gr 3)	1.6 (high)	2.1 (gr 2)	79 normal
29 Feb 2012 Day 91 Wk 12	131 (gr 2),	148 (high)	67 (gr 1)	256 (gr 2)	0.3 normal	0.6 normal	94 normal
22 Mar 2012 Day 113 Wk 16	127 (gr 2),	90 normal	67 (gr 1)	133 (gr 1)	0.2 normal	0.4 normal	96 normal
18 May 2012 Day 170 Wk 24	135 (gr 2),	83 normal	73 (gr 1)	124 (gr 1)	0.2 normal	0.7 normal	106 (gr 1)
9 Aug 2012 Day 253 Wk 36	96 (gr 1)	89 normal	49 (gr 1)	90 (gr 1)	0.2 normal	0.5 normal	94 normal

On 23 February 2012, ie, 85 days after treatment start, ALT and GGT spiked to grade 3 elevated, and AST was grade 4 elevated, with simultaneous increases in bilirubin and ALP. On that day, hepatic enzyme increased (grade 3 AE) was reported. On 29 February 2012, ie, 91 days after treatment start, the grade 3 elevations had decreased to grade 2, the grade 4 elevation decreased to

grade 1, and bilirubin had normalized. At that time, the grade 3 AE of hepatic enzyme increased improved to a grade 2 AE that was ongoing.

On 18 May 2012, ie, 170 days after treatment start, the subject was reported to have porphyria non-acute (grade 1 AE). The subject began phlebotomy therapy at Week 36 for the porphyria, which was ongoing. The investigator considered the hepatic enzyme increased and porphyria non-acute to be not related to study drug or study procedures.

The subject remained in the study at the time of the Week 24 analysis.

The subject's surrogate markers for HIV-disease during the study were: CD4+ cell count at Screening (3 November 2011) was $124x10^6$ cells/L and 12.1%; at Baseline (1 December 2011) was $239x10^6$ cells/L and 12.3%; at Week 2 (15 December 2011) was $194x10^6$ cells/L and 14.4%, at Week 4 (29 December 2012) was $145\ x10^6$ cells/L and 14.3%, at Week 8 (26 January 2012) was $343x10^6$ cells/L and 16.4%, at Week 12 (23 February 2012) was $179x10^6$ cells/L and 14.8%, at Week 16 (22 March 2012) was $291x10^6$ cells/L and 18.0%, and at Week 24 (18 May 2012) was $308x10^6$ cells/L and 17.8%.

The viral load (copies/mL) at Screening (3 November 2011) was 74,700 copies/mL; at Baseline (1 December 2011) was 160,000 copies/mL; at Week 2 (15 December 2011) was 1,380 copies/mL, at Week 4 (29 December 2012) was 153 copies/mL, and at Week 8 (26 January 2012) through Week 24 (18 May 2012) was <50 copies/mL.

Subject 216-0130-1942-4203

Adverse event of interest: Grade 3 transaminases increased

This 2[redacted]-year-old black female started treatment with DRV/COBI 800/150 mg once daily on 18 January 2012 as part of her ARV therapy including 2 NRTIs (Truvada [tenofovir and emtricitabine]). At Screening, hepatitis B surface antigen and hepatitis C virus antibody were negative. The subject's relevant medical history included cocaine and marijuana abuse, bilateral lumpectomies, *Neisseria gonorrhea*, chronic cough, cholelithiasis, renal lithiasis, enteritis, infectious colitis, anorexia, hypokalemia, and concurrent conditions included bipolar illness, depression, gastroesophageal reflux disease, *Helicobacter pylori*, nausea and vomiting treated with promethazine, abdominal pain, headaches, hypertension, allergic rhinitis, gastroparesis, physical deconditioning, and ovarian cyst. At Screening, hepatic enzymes, lipase, amylase, and bilirubin were normal; creatine kinase was elevated (248 U/L). The subject's weight was 71.7 kg and BMI was 24.8 kg/m^2.

At baseline, on 18 January 2012, alanine aminotransferase was 48 U/L (grade 1), aspartate aminotransferase was 35 U/L (high), and creatine kinase remained elevated at 277 U/L. Other relevant laboratory values remained normal.

On 23 January 2012, ie, 6 days after treatment start, the subject experienced nausea, vomiting, and abdominal pain (grade 3 AEs), for which she was treated on that day with i.v. morphine and i.v. ondansetron. On 25 January 2012, the subject received further treatment with i.v. hydromorphone hydrochloride for abdominal pain and metoclopramide for nausea, and began treatment with oral amoxicillin and clarithromycin for *Helicobacter pylori*. No laboratory data was reported at this time.

On 28 January 2012, ie, 11 days after treatment start, the subject was reported to have biliary dyskinesia (grade 3 SAE) and gastritis (grade 3 SAE), and was hospitalized. On 29 January 2012, the subject received i.v. morphine and oral tramadol for abdominal pain. Intravenous hydromorphone hydrochloride was administered from 30 January 2012 to 9 February 2012. On 1 February 2012, ie, 15 days after treatment start, creatine kinase was within normal range.

On 6 February 2012, ie, 20 days after treatment start, transaminases increased (grade 3 AE) was reported; no laboratory values were provided. The subject underwent a cholecystectomy on that day. The nausea, vomiting, and biliary kinesia resolved on 6 February 2012, the abdominal pain resolved on 9 February 2012, and the gastritis and elevated transaminases were ongoing. The investigator considered all of these events to be not related to study drug and not related to study procedures.

The subject received the last dose of DRV/COBI on 10 February 2012, 24 days after treatment start, and was lost to follow up, as she was arrested on 10 February and did not have her medication with her.

The subject's surrogate markers for HIV-disease during the study were: CD4+ cell count ($x10^6$ cells/L): at Screening (19 December 2011) was $168x10^6$ cells/L and 23.1%; at Baseline

(18 January 2012) was $222x10^6$ cells/L and 19.7%; and at Week 2 (1 February 2012) was $248x10^6$ cells/L and 25.2%.

The viral load (copies/mL) at Screening (19 December 2011) was 115,000 copies/mL; at Baseline (18 January 2012) was 237,000 copies/mL; and at Week 2 (1 February 2012) was 10,400 copies/mL.

Appendix 2: Adverse Drug Reactions Algorithm Used for GS-US-216-0130

ALGORITHM FOR IDENTIFYING ADVERSE DRUG REACTIONS FOR THE GENERATION OF THE ADR SECTION 4.8 OF THE DARUNAVIR/COBICISTAT COMPANY CORE DATA SHEET

Step 1: Creation of Tables and Listings of AEs

1.1 All AEs

A frequency tabulation of all reported treatment-emergent AE preferred terms, and the corresponding numbers (counts) will be created from the to be reviewed dataset. Preferred terms (PT) will be presented per SOC.

1.2 Grouping AEs / PT

Upon medical review, preferred terms will be grouped under the same medical concept where clinically relevant. After grouping, a new frequency tabulation will be generated including the grouping per medical concept.

1.3 Excluding AEs /PT unlikely to represent potential ADRs

From the new Frequency Tabulation, the following preferred terms/medical concepts will be excluded from the review process, as considered unlikely these represented a potential ADR:

1. any preferred terms/medical concepts relating to infections (viral, fungal, bacterial, etc.) or AIDS defining illnesses (CDC Category B and C class), as these relate to conditions associated to the underlying HIV infection itself;
2. any preferred terms/medical concepts relating to malignancies, as such conditions are unlikely to develop as ADRs within the relative short duration of exposure of the subjects in the to be reviewed dataset;
3. any preferred terms/medical concepts relating to Surgical and Medical Procedures, as the procedure as such cannot be an ADR, instead it is the underlying condition leading to the procedure that needs to be reviewed for the potential of being an ADR.

All these preferred terms/medical concepts will be documented in the Frequency Tabulations as **Review Category 'C'** (ie, not to be reviewed).

1.4 Excluding AEs already identified as ADRs

All preferred terms/medical concepts already earlier identified as ADRs to DRV/rtv will be documented in the Frequency Tabulations as Review Category 'D' (ie considered as ADRs to DRV/COBI).

1.5 Selecting the most relevant preferred terms/medical concepts for review

Preferred terms/medical concepts will be selected for review if they fulfilled at least one of the following criteria:

- reached an absolute incidence of 1.0% or higher;
- led – at least in one instance – to permanent study drug discontinuation;
- were– at least in one instance – considered as at least possibly related to DRV/COBI by the investigator;
- were reported – at least in one instance – as a SAE (irrespective of causality);
- corresponded to events of special interest, as listed in the Risk Management Plan of DRV/COBI.

Preferred terms/medical concepts fulfilling these criteria will be documented as Review Category 'A' (ie, to be reviewed).

Those not fulfilling these criteria will be documented as Review Category 'B' (ie, not to be reviewed) in the Frequency Tabulation.

1.6 Selecting Tools (tabulation and list) for helping the review

A frequency tabulation containing the preferred terms/medical concepts of all review categories (A to D) will form the basis of the individual case review. This frequency tabulation will provide:

- the number of subjects per preferred term/medical concept,
- the number of serious cases,
- the number of at least possibly related cases per investigator,
- the number of cases leading to permanent drug discontinuation,
- the review category, as defined above.

For the preferred terms/medical concepts selected for review (Review Category A) an additional list will be created, presenting per preferred term/medical concept:

- the CRF IDs,
- the causality assessment by investigator,
- seriousness,
- if the event led to permanent discontinuation or not,
- the time to onset (ie, time to onset of the 1st event if the subject presented more than 1 identical event).

Pre-filled forms will be generated that contain pre-printed the subject's main details as well as the different assessment criteria upon which the case assessment will be based (see Part 2).

Step 2: The Medical Review Process

2.1 Review of the medical concepts/preferred terms from Review Category A

A medical review will be performed on the preferred terms/medical concepts from Review Category A. These preferred terms/medical concepts will be reviewed until either:

- there is a case where the preferred term/medical concept is considered probably related to DRV/COBI;
- there are 3 well documented cases where the preferred term/medical concept is considered possibly related to DRV/COBI.

When all cases for this preferred term/medical concept are reviewed and the above mentioned stop criteria are not met, this preferred term/medical concept will not be an ADR.

2.2 Documentation of the review

The ADR determination has to follow a documented, structured approach and the reasons for determining the preferred term/medical concept as probably or possibly related to DRV/COBI (or not) will be clearly documented (see Part 2 Criteria For Case Assessment).

Step 3: The Adjudication Process

The assessments provided by the medical review team will be reviewed at individual case and/or at multiple case level, and adjudicated by the Safety Management Team (SMT), including representation from Janssen R&D, ID&V Medical Department, and Global Medical Safety (eg GMS Physician, PV Physician). The ADR designation could include, apart from clinical judgment, multiple case review assessment criteria, as described in table "Multiple Case-review" of Part 2 Criteria For Case Assessment (see below). The medical assessment will also include the accumulated body of evidence with regards to the safety profile of Cobicistat, as provided by Gilead. The preferred term/medical concept retained by the Adjudication Panel as potential ADRs will form the Draft list of potential ADRs.

Step 4: Creation of the Final ADR List

The draft list of potential ADRs will be reviewed and discussed in the SMT medical and safety group. After further review and approval by Gilead, the resulting list will be considered the final ADR list for DRV/COBI, and will form the basis for the generation of the ADR section 4.8 of the Company Core Data Sheet.

- The ADRs (preferred terms/medical concepts) will be presented per SOC.
- The ADRs can be grouped to medical concepts or renamed to other MedDRA preferred terms that cover the same medical concept.
- Preferred terms coding to the SOC Investigations can be relocated to the SOC that cover the medical concept (eg, AST increased to be presented under SOC Hepatobiliary disorders).

PART 2: CRITERIA FOR CASE ASSESSMENT

The medical review to determine an ADR as mentioned above has to use a structured approach and inclusion and exclusion codes (adapted from the CIOMS III and V Working Group) to determine events identified as ADRs and events excluded as ADRs, respectively. The criteria used for the individual case and the multiple case reviews are presented in the table below. The reasons for determining the preferred term as probably or possibly related or downgrading a causality assessment of the investigator are to be clearly documented on the pre-filled form.

Individual Case Review	
Exclusion Codes	**Inclusion Codes**
A. Likely related to the underlying condition (medical history, concomitant medications, concurrent conditions, identified risk factors, etc.)	**Definitive evidence** **D1.** Positive rechallenge
B. Temporal relationship does not support causality – Event occurs prior to study drug administration – Event begins >30 days after last dose of study drug	**D2.** Recognized consequence of overdose
C. After review of the individual event, it appears not to be plausible	**D3.** Event is commonly drug-related (eg, neutropenia, Stevens-Johnson syndrome)
D. Negative rechallenge: time on re-exposure, to the same dose or higher, is longer than the time to onset of the original event	**D4.** Known mechanism
E. Poorly documented event (eg, from compassionate use)	**D5.** Similar findings in animal or *in vitro* models
F. Event does not meet any of the inclusion criteria 1-10	**Supportive evidence** **S1.** Time to onset plausible
	S2. Positive dechallenge, ie, the AE disappears after stopping the drug without a specific treatment being applied known to be effective for the AE
	S3. Lack of confounding risk factors/lack of alternative explanation
	S4. Amount and duration of exposure consistent/plausible with cause and effect
	S5. Comedication unlikely to play a role
	S6. Investigator's causality assessment
	S7. Recognized class effect
	S8. Rarity of event in comparable untreated population
	S9. Pharmacokinetic evidence (eg, interaction)
	S10. Closeness of drug characteristics to those of other drugs known to cause the AE

Multiple Case Review – Criteria supporting an association	
1.	Positive outcome in targeted safety study
2.	Consistently higher incidence vs. active comparator (whether statistically significant or not)
3.	Positive dose response relationship (from Phase 1 or 2 studies)
4.	Higher incidence vs comparator(s) of event specific discontinuations
5.	Earlier onset and/or greater severity vs. active comparator
6.	Consistency in pattern of clinical presentation
7.	Consistency of time to onset
8.	Consistent trend across studies
9.	Consistent pattern of clinical presentation & latency
10.	Class effects

Appendix 3: Grouping of Preferred Terms in Medical Concepts and Resulting System Organ Classes for Identified Adverse Drug Reactions – GS-US-216-0130

For the full list of ADRs, refer to Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAP-Addendum

Grouped Term	Preferred Terms
Abdominal pain	Abdominal pain, Abdominal pain lower, Abdominal pain upper
Acute hepatitis	Cytolytic hepatitis, Hepatitis, Hepatitis acute, Hepatotoxicity
Angioedema	Allergic oedema, Angioedema, Angioneurotic oedema, Circumoral oedema, Conjunctival oedema, Corneal oedema, Epiglottic oedema, Eye oedema, Eye swelling, Eyelid oedema, Face oedema, Gingival oedema, Gingival swelling, Gleich's syndrome, Heredetery angioedema, Laryngeal oedema, Laryngotracheal oedema, Lip oedema, Lip swelling, Oculorespiratory syndrome, Oedema mouth, Oropharyngeal swelling, Palatal oedema, Periorbital oedema, Pharyngeal oedema, Scleral oedema, Small bowel angioedema, Swelling face, Swollen tongue, Tongue oedema, Tracheal oedema
Anorexia	Anorexia, Decreased appetite
Blood creatinine increased	Blood creatinine increased, Blood creatinine abnormal, Creatinine renal clearance abnormal, Creatinine renal clearance decreased, Hypercreatininaemia
Diabetes mellitus	Diabetes mellitus, Diabetes mellitus inadequate control, Diabetes mellitus non-insulin dependent, Glucose tolerance impaired
Diarrhoea	Diarrhoea, Frequent bowel movements
Dyslipidaemia	Dyslipidaemia, Lipid metabolism disorder
Gynecomastia	Gynecomastia, Hypertrophy breast
Hepatic enzyme increased	ALT increased, AST increased, AST abnormal, Blood alkaline phosphatase increased, Gamma-glutamyl transferase increased, Hepatic enzyme increased, Liver function test abnormal, Transaminases increased,
Hypercholesterolaemia	Blood cholesterol increased, Hypercholesterolaemia
Hyperglycaemia	Blood glucose increased, Hyperglycaemia
Hyperlipidaemia	Hyperlipidaemia, Lipids increased
(Drug) Hypersensitivity	Hypersensitivity, Drug hypersensitivity
Hypertriglyceridaemia	Blood triglycerides increased, Hypertriglyceridaemia
Immune reconstitution syndrome[a]	Immune reconstitution syndrome, Immune reconstitution inflammatory syndrome
Lipodystrophy	Facial wasting, Fat atrophy, Fat redistribution, Fat tissue increased, Lipoatrophy, Lipodystrophy acquired, Lipohypertrophy, Partial lipodystrophy
Pancreatic enzymes increased	Blood amylase increased, Lipase increased, Pancreatic enzymes increased, Hyperamylasaemia
Pancreatitis acute	Pancreatitis, pancreatitis acute
Pruritus	Prurigo, Pruritus, Pruritus generalized
Rash	Generalized erythema, Rash, Rash erythematous, Rash generalized, Rash macular, Rash macula-papular, Rash morbilliform, Rash papular, Rash pruritic
Urticaria	Idiopathic urticaria, Urticaria, Urticaria cholinergic, Urticaria chronic, Urticaria papular

[a] This was a grouped term only in the Week-48 analysis. In the Week-24 analysis, the preferred term for Immune reconstitution inflammatory syndrome was Immune reconstitution syndrome (see Section 3.4.1).

Appendix 4: Adverse Drug Reactions (any Grade) in GS-US-216-0130, With Incidences in the DRV/rtv 800/100 mg Once Daily Arm of TMC114-C211 and TMC114-C229 – Week-24 Analyses

System Organ Class (Grouped) Preferred term[a,b], n (%)	GS-US-216-0130 DRV/COBI N=313	TMC114-C211 DRV/rtv N=343	TMC114-C229 DRV/rtv N=294
Any ADR	***196 (62.6)***	***207 (60.3)***	***108 (36.7)***
Gastrointestinal Disorders	**141 (45.0)**	**151 (44.0)**	**83 (28.2)**
Abdominal Distension	4 (1.3)	9 (2.6)	2(0.7)
Abdominal Pain[a]	23 (7.3)	25 (7.3)	12 (4.1)
Diarrhoea[a]	79 (25.2)	101 (29.4)	37 (12.6)
Dyspepsia	6 (1.9)	6 (1.7)	5 (1.7)
Flatulence	19 (6.1)	7 (2.0)	6 (2.0)
Nausea	67 (21.4)	50 (14.6)	36 (12.2)
Pancreatitis Acute	1 (0.3)	1 (0.3)	
Vomiting	26 (8.3)	16 (4.7)	12 (4.1)
General Disorders & Administration Site Conditions	**20 (6.4)**	**22 (6.4)**	**4 (14)**
Asthenia	1 (0.3)	6 (1.7)	2 (0.7)
Fatigue	20 (6.4)	16 (4.7)	2 (0.7)
Hepatobiliary Disorders	**5 (1.6)**	**12 (3.5)**	**1 (0.3)**
Hepatic Enzyme Increased[a]	5 (1.6)	2 (0.6)	1 (0.3)
Immune System Disorders	**7 (2.2)**	**4 (1.2)**	0
(Drug) Hypersensitivity[a]	6 (1.9)	3 (0.9)	0
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)	0
Investigations	**3 (1.0)**	**2 (0.6)**	**3 (1.0)**
Increased Blood Creatinine[a]	3 (1.0)	2 (0.6)	3 (1.0)
Metabolism and Nutrition Disorders	**17 (5.4)**	**22 (6.4)**	**12 (4.1)**
Anorexia[a]	6 (1.9)	9 (2.6)	3 (1.0)
Diabetes Mellitus[a]	2 (0.6)	0	1 (0.3)
Hypercholesterolaemia[a]	4 (1.3)	4 (1.2)	2 (0.7)
Hypertriglyceridaemia[a]	7 (2.2)	3 (0.9)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	**5 (1.6)**	**6 (1.7)**	**3 (1.0)**
Myalgia	5 (1.6)	6 (1.7)	3 (1.0)
Nervous System Disorders	**29 (9.3)**	**47 (13.7)**	**14 (4.8)**
Headache	29 (9.3)	47 (13.7)	14 (4.8)
Psychiatric Disorders	**8 (2.6)**	**3 (0.9)**	**0**
Abnormal Dreams	8 (2.6)	3 (0.9)	0
Skin and Subcutaneous Tissue Disorders	**57 (18.2)**	**48 (14.0)**	**20 (6.8)**
Angioedema[a]	3 (1.0)	3 (0.9)	0
Pruritus	7 (2.2)	13 (3.8)	3 (1.0)
Rash[a]	50 (16.0)	28 (8.2)	17 (5.8)
Rash	27 (8.6)	20 (5.2)	13 (4.4)
Rash Erythematous	2 (0.6)	0	0
Rash Generalized	2 (0.6)	0	1 (0.3)
Rash Macular	4 (1.3)	1 (0.3)	0
Rash Maculo-papular	6 (1.9)	2 (0.6)	2 (0.7)
Rash Papular	5 (1.6)	7 (2.0)	1 (0.3)
Rash Pruritic	4 (1.3)	0	0
Urticaria	3 (1.0)	0	0

N=total number of subjects with data; n=number of subjects with observation.

[a] Grouped term. The grouped preferred terms are described in Appendix 3.

[b] Only events identified as ADRs in study GS-US-216-0130 are presented in this table. ADRs occurring in the historical studies but not in GS-US-216-0130 are not presented here, they can be found in the source table.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W24-SAF-AE/TSFAE13.

Appendix 5: Incidence of Adverse Events Reported in More Than 5% of All Subjects– GS-US-216-0130 Week-24 and Week-48 Analyses

System Organ Class Preferred Term, n (%)	**Week 24** **All Subjects** **N=313**	**Week 48** **All Subjects** **N=313**
Total Patient-years Exposure	***180.6***	***351.6***
Any Adverse Event	***275 (87.9)***	***286 (91.4)***
Gastrointestinal Disorders	**164 (52.4)**	**180 (57.5)**
Diarrhoea	78 (24.9)	86 (27.5)
Flatulence	19 (6.1)	20 (6.4)
Nausea	67 (21.4)	72 (23.0)
Vomiting	26 (8.3)	28 (8.9)
General Disorders and Administration Site Conditions	**153 (48.9)**	**198 (63.3)**
Pyrexia	12 (3.8)	20 (6.4)
Infections and Infestations	**153 (48.9)**	**198 (63.3)**
Upper Respiratory Tract Infection	31 (9.9)	44 (14.1)
Nasopharyngitis	18 (5.8)	39 (9.3)
Sinusitis	17 (5.4)	25 (8.0)
Nervous System Disorders	**62 (19.8)**	**77 (24.6)**
Headache	29 (9.3)	38 (12.1)
Respiratory, Thoracic and Mediastinal Disorders	**62 (19.8)**	**77 (24.6)**
Cough	9 (2.9)	18 (5.8)
Oropharyngeal Pain	10 (3.2)	17 (5.4)
Skin and Subcutaneous Tissue Disorders	**88 (28.1)**	**105 (33.5)**
Rash	27 (8.6)[a]	25 (8.0)[a]

N=total number of subjects with data; n=number of subjects with observation.

[a] The AE term 'Truncal Rash' (coded to Rash in Week 24 analysis) was changed to 'Truncal Tenia Versicolor' (coded to 'Tinea Versicolor') in the Week-48 analysis, and the AE term 'Rash Right Axillary Region' (coded to Rash in Week 24 analysis) was changed to 'Acne Rash Right Axillary Region' (coded to 'Dermatitis Acneiform') in the Week-48 analysis.

Source: Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 11-4 and
Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/Table 5.1.1.2.

Appendix 6: Adverse Events of Interest – GS-US-216-0130 Week-48 Analysis

Grouped Term of AEs of Interest Preferred Term, n (%)	All Subjects (N=313) Any AEOI	AEOI at Least Grade 2	AEOI at Least Grade 3	Serious AEOI	AEOI Leading to Permanent Stop
At Least 1 AE of Interest	***85 (27.2)***	***36 (11.5)***	***7 (2.2)***	***4 (1.3)***	***7 (2.2)***
Rash[a]	**51 (16.3)**	**18 (5.6)**	**2 (0.6)**	**2 (0.6)**	**7 (2.2)**
Rash[a]	25 (8.0)	6 (1.9)	0	1 (0.3)	3 (1.0)
Rash Maculo-papular	6 (1.9)	4 (1.3)	2 (0.6)	1 (0.3)	3 (1.0)
Rash Papular	5 (1.6)	2 (0.6)	0	0	0
Rash Pruritic	5 (1.6)	1 (0.3)	0	0	0
Rash Macular	4 (1.3)	2 (0.6)	0	0	1 (0.3)
Rash Erythematous	2 (0.6)	1 (0.3)	0	0	0
Rash Generalized	2 (0.6)	1 (0.3)	0	0	0
Rash Vesicular	2 (0.6)	1 (0.3)	1 (0.3)	0	1 (0.3)
Drug Eruption	1 (0.3)	1 (0.3)	0	0	0
Lipid Abnormalities	**10 (3.2)**	**4 (1.3)**	**0**	**0**	**0**
Hypercholesterolaemia	4 (1.3)	1 (0.3)	0	0	0
Hypertriglyceridaemia	4 (1.3)	0	0	0	0
Blood Triglycerides Increased	3 (1.0)	2 (0.6)	0	0	0
Hyperlidaemia	1 (0.3)	1 (0.3)	0	0	0
Severe Skin Reactions	**16 (5.1)**	**8 (2.6)**	**0**	**0**	**0**
Conjunctivitis	10 (3.2)	4 (1.3)	0	0	0
Stomatitis	2 (0.6)	2 (0.6)	0	0	0
Blister	2 (0.6)	1 (0.3)	0	0	0
Drug Eruption	1 (0.3)	1 (0.3)	0	0	0
Mouth Ulceration	1 (0.3)	0	0	0	0
Hepatotoxicity	**7 (2.2)**	**3 (1.0)**	**2 (0.6)**	**0**	**0**
Hepatic Enzyme Increased	4 (1.3)	1 (0.3)	1 (0.3)	0	0
Transaminases Increased	2 (0.6)	2 (0.6)	1 (0.3)	0	0
Ocular icterus	1 (0.3)	0	0	0	0
Hyperglycaemia	**5 (1.6)**	**2 (0.6)**	**1 (0.3)**	**1 (0.3)**	**0**
Diabetes Mellitus Inadequate Control	2 (0.6)	1 (0.3)	0	0	0
Diabetes Mellitus	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0
Impaired Fasting Glucose	1 (0.3)	0	0	0	0
Type 2 Diabetes Mellitus	1 (0.3)	0	0	0	0
Coronary Artery Events	**3 (1.0)**	**1 (0.3)**	**0**	**0**	**0**
Blood Creatine Phosphokinase Abnormal	1 (0.3)	1 (0.3)	0	0	0
Blood Creatine Phosphokinase Increased	1 (0.3)	0	0	0	0
ECG St-t Segment Abnormal	1 (0.3)	0	0	0	0
Pancreatitis	**4 (1.3)**	**2 (0.6)**	**1 (0.3)**	**0**	**0**
Amylase Increased	1 (0.3)	1 (0.3)	1 (0.3)	0	0
Hyperlipasaemia	1 (0.3)	1 (0.3)	0	0	0
Lipase Increased	1 (0.3)	0	0	0	0
Pancreatitis	1 (0.3)	0	0	0	0
Renal/Creatinine Effects	**3 (1.0)**	**0**	**0**	**0**	**0**
Blood Creatinine Increased	3 (1.0)	0	0	0	0
Immune Reconstitution Syndrome	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**	**1 (0.3)**	**0**
Immune Reconstitution Inflammatory Syndrome	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)	0

N=total number of subjects with data; n=number of subjects with observation; AEOI=AE of interest.

[a] AE term 'Truncal Rash' (coded to Rash in the Week-24 analysis) was changed to 'Truncal Tenia Versicolor' (coded to 'Tinea Versicolor') in the Week-48 analysis, and AE term 'Rash Right Axillary Region' (coded to Rash in the Week-24 analysis) was changed to 'Acne Rash Right Axillary Region' (coded to 'Dermatitis Acneiform') in the Week-48 analysis.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TSFAEOI02, TSFAEOI03, TSFAEOI04, TSFAEOI07, and TSFAEOI08.

CIOMS Report for SDE00016486 Search #2 Final

Run Information

User Name: [redacted] ([redacted])

Run Date: [redacted]

Parameters

Results: 9 cases selected from 9 matching the following criteria

Status: NOT = Deleted

J&J Cases Only: = (J&J Drug, J&J Device, Gene Therapy)

Query Report: = SDE00016486 Search #2 (Drug Name DARUNAVIR, Case Types J&J Device, J&J Drug, Gene Therapy, Drug Character Suspect or Suspect Interacting, Partner Cases Excluded, Start Date [redacted], End Date [redacted], Date Type Version Initially Received, Version Highest In Date Range, Invalid Cases Included, Workflow Cases Excluded, Deleted Cases Excluded, Case Seriousness Serious)

Query Report Case included in report: = Yes

Last Distributed: = Yes

Reported Drug Name: = COBICISTAT

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	US	04	JUL	19[redacted]	2[redacted] Year	M	16	DEC	2011

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

RASH GENERALISED(10037858)

This report was received, via Gilead, from clinical trial GS-US-216-0130: A Phase 3b, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naive and Experienced Adults with No Darunavir Resistance-associated Mutations. EudraCT #: 2011-003501-22. The report concerns a 2[redacted] year old male subject 4111, from the United States: 2011-0048604.

The subject's height was not reported and weight was 75.28

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

800 mg, 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

08-DEC-2011 - 22-DEC-2011

19. THERAPY DURATION

15 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION ??-???-2011 - Ongoing

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 2154
Patient no : 4111

24b. MFR. CONTROL NO.

US-JNJFOC-20120209481(2)

24c. DATE RECEIVED BY MFR.

08-FEB-2012

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.: US-JNJFOC-20120209481**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

kilograms. The subject's concurrent conditions included HIV infection.

The subject was treated with darunavir (unspecified, oral) 800 mg once a day, initiated on 08-DEC-2011 to 22-DEC-2011 for HIV infection. Non-company suspect drugs included cobicistat (tablet, oral) 150mg once a day, initiated on 08-DEC-2011 to 22-DEC-2011 and emtricitabine tenofovir for HIV infection. Concomitant medications were not reported.

On 16-DEC-2011, the subject experienced body rash. He was treated with a total of 8 tablets of Benadryl (diphenhydramine) on 17-DEC-2011 and 18-DEC-2011. He did not need any additional treatment and no hospitalisation was required. On 22-DEC-2011, the subject was seen for a study visit and he was instructed to discontinue all study drugs. On 23-DEC-2011, the subject was seen for a re-check. His body rash was improving and there was less itchiness. On 05-JAN-2012, the event of body rash was considered resolved. Emtricitabine/tenofovir DF was re-started on this date. On 09-JAN-2012, the subject was seen at the study site and did not report any adverse reactions to emtricitabine/tenofovir DF. Kaletra (lopinavir/ritonavir) was started to complete the therapy.

The Investigator considered the causality between body rash and darunavir as most likely and body rash and cobicistat as possibly related.

This report is serious (medically significant).

Additional information was received on 17-FEB-2012.

The Investigator reported that the subject had no history of drug allergies. The event of body rash was not related to emtricitabine/tenofovir disoproxil fumarate or to the study procedure.

Additional information was received from a health professional on 08-FEB-2012.

The patient's height was 72 inches. The patient's concurrent HIV infection began in 2011.

The rash was described as macular papular erythematous, numerous and distributed, covering the entire the body (sparing the face, hands, feet and mouth). It was non-tender and dry. The rash was photographed on 22-DEC-2011. The patient denied any shortness of breath, swelling of throat, difficulty swallowing, joint pain or pain in general.

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR (DARUNAVIR) Tablets

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120209481**

Causality

1. RASH GENERALISED [10037858]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Very Likely / Certain
Causality as per Mfr.	Very Likely / Certain

Seq. No.	2
Drug	COBICISTAT (INVESTIGATIONAL DRUG) Tablet
Daily Dose	1) 150 mg, 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 08-DEC-2011 - Stopped

Causality

1. RASH GENERALISED [10037858]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Seq. No.	3
Drug	EMTRICITABINE W/TENOFOVIR DISOPROXIL FUMARATE (TRUVADA /01778501/)
Daily Dose	2) 1 Dose(s), 1 in 1 Day 1) 1 Dose(s), 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 08-DEC-2011 - Stopped 2) 05-JAN-2012 - Ongoing

Causality

1. RASH GENERALISED [10037858]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Other relevant history (Cont...)

Other History: The patient has no history of drug allergies.
Race: Caucasian

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	US	14	JAN	19[redacted]	5[redacted] Year	M	14	FEB	2012

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

IDIOPATHIC THROMBOCYTOPENIC PURPURA(10021245)

This report was received from a clinical trial GS-US-216-0130 via Gilead Sciences Inc: A phase 3b, open-label single arm study to evaluate the safety and efficacy of Cobicistat-boosted darunavir plus two-fully active nucleoside reverse transcriptase inhibitors in HIV-infected antiretroviral treatment naive and experienced adults with no darunavir resistance associated mutations, EudraCT #: 2011-003501-22, concerns a 5[redacted] year old male patient 4223, from the United States: 1-1440295358.

The subject's weight was 79.18 kilograms and height was not

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

15. DAILY DOSE

800 mg, in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

31-JAN-2012 - 14-FEB-2012

19. THERAPY DURATION

16 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

SYNTHROID (LEVOTHYROXINE SODIUM) Unknown Unknown 10-JAN-2012 - Ongoing

23. OTHER RELEVANT HISTORY

Other History: no known drug allergies

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 6046
Patient no : 4223

24b. MFR. CONTROL NO.
US-JNJFOC-20120302461(7)

24c. DATE RECEIVED BY MFR.
17-MAY-2012

24d. REPORT SOURCE
[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE
[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Describe Reaction(s) (include relevant test/lab data) (Cont...)

reported.

The subject's concurrent conditions and medical history included human immunodeficiency virus (HIV) infection and hypothyroidism.

The subject was treated with darunavir (tablets, oral) 800 mg a day, and Cobicistat (GS-9350, tablets, oral) 150 mg a day, both initiated on 31-JAN-2012 to 14-FEB-2012 for HIV infection. Non-company suspect drugs included emtricitabine/tenofovir disoproxil (unspecified, oral), 500mg a day, initiated on 31-JAN-2012 to 14-FEB-2012 for HIV infection.

Concomitant medications included Synthroid (levothyroxine sodium).

On 12-FEB-2012, the subject experienced intermittent nose bleeds and a lip blister further described as a ' black bruise'' on the left side of his mouth. On 13-FEB-2012, the subject experienced oral bleeding when brushing his teeth and a diffuse red spotted rash over his entire body.

On 14-FEB-2012, the subject was hospitalised due to thrombocytopenia. On 14-FEB-2012, at the study site examination of the subject, non-bleeding petechiae was noted on unspecified sites and purpura of his mouth was noted. Laboratory tests revealed platelet count was 20x10^3 per microlitre (normal range 145-415), remained blood values were normal. On 14-FEB-2012 - skin biopsy of lip revealed subacute spongiotic dermatitis and skin biopsy - right axilla revealed superficial perivascular dermatitis, both probable drug eruptions. The subject was sent to emergency room and admitted to the hospital for idiopathic thrombocytopenic pupura. A repeat platelet count in the hospital revealed <5000 (units and normal range not provided).

Treatment included intravenous immunoglobulin once and Solu-Medrol (Methylprednisolone sodium succinate), intravenous three times a day.

Treatment with darunavir, GS-9350 and emtricitabine/tenofovir disoproxil was withdrawn.

On 17-FEB-2012, the subject's platelet count was 56,000 (units and normal range not provided). The subject had no intracranial bleeding. The subject was discharged on the same day with diffuse petechiae but no new or additional bleeding. Discharge medications included a prednisolone taper (80mg daily). On 23-FEB-2012, the subject was seen for his study early termination visit and his platelet count was 13x10^3 per ul (normal range 145-415) and he was sent to the emergency room and re-admitted for thrombocytopenia.

At the time of reporting, the subject had not recovered from thrombocytopenia.

The Investigator considered the causality between thrombocytopenia and study medications (darunavir, GS-9350 and emtricitabine/tenofovir disoproxil) as possibly related.

The Investigator also assessed the event as not related to the trial procedures.

This report was serious (hospitalisation, medically significant).

This case version was created on 16-MAR-2012 for the purposes of quality improvement. Upon review the following corrections were made: the dose of levothyroxine sodium was not reported (previously entered as 800 mg).

Version 2 created in error.

Additional information was received from the investigator on 16-MAR-2012.

The subject had no known drug allergies.

On 22-FEB-2012, the site received hospital records and the subject was seen for his study early termination visit (previously reported as seen on 23-FEB-2012). Repeat labs were drawn which demonstrated a platelet count of 13,000*10^3/UL (normal range 145-415) [platelet count results were previously reported as for 23-FEB-2012]. The subject was sent to the emergency room and re-admitted for thrombocytopenia on 23-FEB-2012.

The subject was discharged from hospital on 25-FEB-2012. On 07-MAR-2012, the subject was re-admitted to the hospital for low platelet count. The event was ongoing and the subject remained in hospital at the time of this report.

Additional information was received from the investigator on 20-MAR-2012.

The event term was updated to idiopathic thrombocytopenic pupura (previously reported as thrombocytopenia).

The subject was readmitted to hospital on 22-FEB-2012, not 23-FEB-2012 as previously reported. The subject reported that he was compliant with his prednisone regimen and denied any gum bleeding, melena or hematochezia, though he did experience easy bruising. Physical examination noted bruising, ecchymosis, scattered petechiae, and rash. A hematology-oncology consultant diagnosed idiopathic thrombocytopenic pupura secondary to HIV disease, since symptoms were recurring about 10 days since the last study drug exposure. As it had been less than 2 weeks since starting steroids, this event was not considered to be steroid failure. Infectious disease physicians assessed the possibility that antiretroviral medications had contributed to the subject's thrombocytopenia, however based on the initial response to immuno-suppression therapy believed it was likely the subject had idiopathic thrombocytopenic pupura. Treatment included 3 day pulse of methylprednisolone and 2 days of 'IVIG' (Intravenous Immune Globulin).

The subject's platelet count on 23-FEB-2012 and 25-FEB-2012 was <5000 and 69000 (units and reference range not provided) respectively. The subject was discharged from hospital on 25-FEB-2012 prednisone treatment (80mg a day). On 28-FEB-2012 the subject's platelet count was 100,000 (units and reference range not provided) and prednisone therapy was tapered to 60mg a day.

The subject was seen for follow up on 01-MAR-2012. His platelet count was 106,000 (units and reference range not provided) and a new antiretroviral regimen of Epzicom (abacavir/lamivudine) and Sustiva (efavirenz) was initiated.

On 05-MAR-2012 the subject was again admitted to hospital for thrombocytopenia, with a platelet count of <5000 and oral thrush. The subject had been asymptomatic since the initial hospitalisation (without bleeding, epistaxis). Physical examination of the patient noted no rash, slight erythema on the nasal bridge, and multiple bruises on his right arm (from blood draws suring prior hospitalisation). Treatment included Solu-medrol (methylprednisolone) for 3 days, and Epzicom and Sustiva were withheld.

The subject resumed treatment with Epzicom and Sustiva on 08-MAR-2012. His platelet count increased to 23000 and the subject was discharged from hospital with a diagnosis of idiopathic thrombocytopenic pupura. Based on the timing of the event both the infectious disease and hematology services decided that idiopathic thrombocytopenic pupura was most likely secondary to HIV, rather than the antiretroviral therapy. Discharge medications included fluconazole, prednisone, and pantoprazole. The subject was instucted to continue Epzicom, Sustiva and levothyroxine.

On 15-MAR-2012, the subject was reviewed at the investigators clinic. His platelet count was found to be 4000, and he was instructed to return to the emergency room, where he was admitted.

The subject had not recovered from idiopathic thrombocytopenic purpura. He remained hospitalised at the time of this report.

The investigator considered the causality between idiopathic thrombocytopenic pupura and the study medications as not related, and not related to the trial procedure.

This case version was created on 05-APR-2012 for the purpose of quality improvement. Upon

review the following corrections were made: The dates for Version Initially Received, ICH Expedited Start and Latest Information Received were changed to 23-MAR-2012 (previously entered as 09-MAR-2012 in version 3).

Additional information was received on 30-MAR-2012.

An additional reference number was added to the case.

Additional information was received from the Investigator on 17-MAY-2012.

The subject's demographics were updated: The subject's weight was 174.6 pounds and height was 67.5 inches. The subject's was of Hispanic race.

During the subject's hospitalisation on the 15-MAR-2012 as treatment the subject was started on an IV of solumedrol (Methylprednisolone sodium succinate) 1 g every 24 hours for 3 days. On the 18-MAR-2012 the subject's platelets had increased to 54000 (units not provided) and the subject was discharged from hospital on the same day with a discharge medication of 80 mg of prednisone per day. On the 21-MAR-2012 the subject was seen in the study clinic where Labs showed a platelet level of 85000 (units not provided). However on the 26-MAR-2012the subject was again seen in the study clinic where Labs showed a platelet level of 2000(units not provided. Therefore the subject was readmitted to hospital, further information not available regarding this hospitalisation. On the 12-APR-2012 the subject informed the investigator that 2 weeks previously he had started Nplate (romiplostim) injections and that his platelet count was up to 220000 (units not provided) at his last check. Laboratory data was added to the case.

The subject had recovered with sequelae from idiopathic thrombocytopenic purpura on 12-APR-2012.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
CD4 LYMPHOCYTES	31-JAN-2012	304 (25.9%)		
	14-FEB-2012	312		
	20-MAR-2012	552 (36.2%)		
HIV VIRAL LOAD	31-JAN-2012	93600		
	14-FEB-2012	509		
	20-MAR-2012	359		
PLATELET COUNT	14-FEB-2012	<5000 units and range not provided /mcl (per mcl)	140	415
		20x10^3 /mcl (per mcl)		
	17-FEB-2012	56,000 units and range not provided /mcl (per mcl)		
	22-FEB-2012	13x10^3 /mcl (per mcl)		
	23-FEB-2012	<5000 units and range not provided /mcl (per mcl)		
PLATELET COUNT	23-FEB-2012	<5000 g/L (grams/liter)	174	404
	25-FEB-2012	43000 g/L (grams/liter)		
		69000 g/L (grams/liter)		
	28-FEB-2012	100,000 units and range not provided g/L (grams/liter)		
	??-MAR-2012	23000 (prior to discharge on 08-MAR-2012) g/L (grams/liter)		
	01-MAR-2012	106000 units and range not provided g/L (grams/liter)		
	05-MAR-2012	<5000 g/L (grams/liter)		
	08-MAR-2012	43000 g/L (grams/liter)		

Continuation Sheet for CIOMS report **Mfr. Control No.: US-JNJFOC-20120302461**

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
PLATELET COUNT	15-MAR-2012	4000 units and range not provided g/L (grams/liter)	174	404
	18-MAR-2012	54 units and range not provided g/L (grams/liter)		
	21-MAR-2012	85000 units and range not provided g/L (grams/liter)		
	26-MAR-2012	2000 units and range not provided g/L (grams/liter)		
	12-APR-2012	220000 units and range not provided g/L (grams/liter)		
PLATELET COUNT	31-JAN-2012	216 x10^3/ul	140 x10^3/ul	400 x10^3/ul
URINALYSIS	??-???-????	moderate blood		

14-FEB-2012 - skin biopsy lip subacute spongiotic dermatitis (probably drug eruption)

14-FEB-2012 - skin biopsy right axilla: superficial perivascular drmatitis, (probably drug eruption)

14-FEB-2012 - hepatitis B antigen and Hepatitis c antibody negative.

14-FEB-2012 - in house urinalysis revelaed moderate blood pressure

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR (DARUNAVIR) Tablets

Causality

1. IDIOPATHIC THROMBOCYTOPENIC PURPURA [10021245]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No. 2
Drug COBICISTAT (DARUNAVIR NON-COMPANY IMP) Tablet

Daily Dose 1) 150 mg, in 1 Day
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) 31-JAN-2012 - Stopped

Causality

1. IDIOPATHIC THROMBOCYTOPENIC PURPURA [10021245]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120302461**

Causality

Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	3
Drug	EMTRICITABINE/TENOFOVIR DISOPROXIL (TRUVADA /01778501/) Tablets
Daily Dose	1) 500 mg, in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 31-JAN-2012 - Stopped

Causality

1. IDIOPATHIC THROMBOCYTOPENIC PURPURA [10021245]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Other relevant history (Cont...)

Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: HYPOTHYROIDISM ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	US	09	SEP	19[redacted]	3[redacted] Year	M	22	JAN	2012

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

RASH MACULO-PAPULAR(10037868)

This report was received from clinical trial GS-US-216-0130 via Gilead Sciences Inc: A phase 3b, open-label single arm study to evaluate the safety and efficacy of Cobicistat-boosted darunavir plus two-fully active nucleoside reverse transcriptase inhibitors in HIV-infected antiretroviral treatment naive and experienced adults with no darunavir resistance associated mutations, EudraCT #: 2011-003501-22. It concerns a 3[redacted] year old male subject 4190, from the United States: 1-1463117230.

The subject's weight was 79.36 kilograms and height was not

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

800 mg, in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

12-JAN-2012 - 21-JAN-2012

19. THERAPY DURATION

10 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION ??-??-???? - Ongoing

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 2843
Patient no : 4190

24b. MFR. CONTROL NO.

US-JNJFOC-20120311820(1)

24c. DATE RECEIVED BY MFR.

28-FEB-2012

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.: US-JNJFOC-20120311820**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

reported. The subject's concurrent conditions included HIV infection.

The subject was treated with darunavir (tablets, oral) 800 mg a day, initiated on 12-JAN-2012 to 21-JAN-2012 for HIV infection and Cobicistat (GS-9350, tablets, oral) 150 mg a day, initiated on 12-JAN-2012 to 21-JAN-2012 for HIV infection. Non-company suspect drugs included: Truvada (emtricitabine/tenofovir, tablets, oral) 1 dose daily initiated 12-JAN-2012 to 21-JAN-2012 for HIV infection. Concomitant medications were not reported.

On 22-JAN-2012, the subject developed macular-papular rash on his thorax, arms, and legs. He reported the rash to his primary care physician who intructed to hold the study drugs and to start diphenhydramine 50 mg orally every 8 hours as needed. The last dose of the study drug wa staken on 21-JAN-2012. The subject was later seen by the subinvestigator on 24-JAN-2012 and he was instructed to remain off the study drugs and to continue diphenhydramine. The subinvestigator discontinued the subject from the clinical study due to the nature and severity of the rash. On 26-JAN-2012, the subject was examined by the primary investigator. On physical examination, it was noted that the subject's rash was fading but still evident. He was instructed to continue diphenhydramine on an as-needed basis. He remained off all antiretroviral medications. On 01-FEB-2012, the subject reported total resolution of the rash. Diphenhydramine was discontinued, and the event was considered resolved on this date by the Investigator. On 23-FEB-2012, the subject was seen at the site for the 30-day visit. Physical examination was normal. He remained off all antiretroviral medications and this clinical study. He was instructed to follow up with his primary care physician for a new antiretroviral regimen.

Treatment with darunavir, GS-9350 and emtricitabine/tenofovir was withdrawn.

The subject was recovered from macular-papular rash on 01-FEB-2012.

The Investigator considered the causality between macular-papular rash and study drugs (darunavir, GS-9350 and emtricitabine/tenofovir) as possible, and as most likely related to darunavir or possibly emtricitabine. The event was considered not related to trial procedures.

This report was serious (medically significant).

Additional information was received from the investigator on 28-FEB-2012.

The patient's height was 66 inches.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR (DARUNAVIR) Tablets

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120311820**

Causality

1. RASH MACULO-PAPULAR [10037868]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Possible
Causality as per Mfr.	Possible

Seq. No.	2
Drug	COBICISTAT (DARUNAVIR NON-COMPANY IMP) Tablet
Daily Dose	1) 150 mg, in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 12-JAN-2012 - Stopped

Causality

1. RASH MACULO-PAPULAR [10037868]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Possible
Causality as per Mfr.	Possible

Seq. No.	3
Drug	EMTRICITABINE/TENOFOVIR DISOPROXIL (TRUVADA /01778501/) Tablet
Daily Dose	1) 1 Dose(s), in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 12-JAN-2012 - Stopped

Causality

1. RASH MACULO-PAPULAR [10037868]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
PRIVACY	US	19	OCT	19[redacted]	4[redacted] Year	M	29	FEB	2012

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME(10065042)

This report was received from clinical trial GS-US-216-0130: A phase 3b, open-label single arm study to evaluate the safety and efficacy of Cobicistat-boosted darunavir plus two-fully active nucleoside reverse transcriptase inhibitors in HIV-infected antiretroviral treatment naive and experienced adults with no darunavir resistance associated mutations, via Gilead Sciences Inc (2012-0051675), EudraCT #: 2011-003501-22. This report concerns a 4[redacted] year old Caucasian male, subject 4147, from the United States: 1-1462807339.

The subject's weight was 71.65 kilograms and his height was

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

800 mg, in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

21-DEC-2011 - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

BACTRIM (BACTRIM /00086101/) 17-OCT-2011 - Ongoing

(Cont.)

23. OTHER RELEVANT HISTORY

Medical History: ACQUIRED IMMUNODEFICIENCY SYNDROME ??-SEP-2011 - Ongoing

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 1541
Patient no : 4147

24b. MFR. CONTROL NO.

US-JNJFOC-20120311826(4)

24c. DATE RECEIVED BY MFR.

18-SEP-2012

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

not reported. The subject's concurrent conditions included human immunodeficiency virus infection (HIV) beginning in SEP-2011, perianal herpes simplex (virus-2), acquired immunodeficiency syndrome (AIDS) beginning in SEP-2011, and vitamin D deficiency. The subject had no known drug allergies.

The subject was treated with darunavir (tablets, oral) 800 mg a day and Cobicistat (GS-9350, tablet, oral) 150 mg, both initiated on 21-DEC-2011 for HIV infection. Non-company suspect drugs included emtricitabine/tenofovir disoproxil (Truvada), 1 dose a day, initiated on 21-DEC-2011, for HIV infection. Concomitant medications included vitis vinifera extract, bactrim, ergocalciferol, selenium, prasterone, multivitamins and lysine.

On 13-FEB-2012, at the 8-week study visit, the subject was doing well. On approximately 18-FEB-2012, the subject started experiencing intermittent left eye pain. On 29-FEB-2012, the subject was seen for an unscheduled study visit for the eye pain. He was examined and referred to the emergency room. While in the emergency room, his eye lesions worsened and he was admitted to hospital with immune reconstitution inflammatory syndrome (IRIS), manifested as left eye zoster ophthalmicus. Treatment included intravenous Acyclovir, hydrocodone/paracetamol (Vicodin), Erythromycin ointment and Florastor (probiotic: Saccharomyces boulardii lyo). On 02-MAR-2012, the subject received one dose of Valacyclovir, intravenous Acyclovir was discontinued, and the subject was discharged from hospital. Discharge medications included valacyclovir (Valtrex).

The dose of darunavir, Cobicistat and emtricitabine/tenofovir disoproxil was not changed.

At the time of reporting, the subject had not recovered from immune reconstitution inflammatory syndrome.

The Investigator considered the causality between immune reconstitution inflammatory syndrome and the study medications (darunavir, Cobicistat and emtricitabine/tenofovir disoproxil) as possible. The event was considered as not related to trial procedures.

This report is serious (hospitalisation).

Additional information received from the investigator on 01-MAR-2012 was processed with additional information received on 05-MAR-2012 and 06-MAR-2012.

The indication for use of the subject's concomitant medications were updated, and now included vitis vinifera extract for nutritional supplement, bactrim for pneumocystis carinii prophylaxis, ergocalciferol for vitamin d deficiency, selenium for nutritional supplement, prasterone for nutritional supplement, multivitamins for nutritional supplement, and lysine for nutritional supplement.

The subject improved over the course of hospitalisation. He received treatment with intravenous acyclovir from 29-FEB-2012 to 02-MAR-2012, and with vicodin (for pain

associated with zoster), erythromycin ointment (for ophthalmicus) and florestor (for supplement) from 02-MAR-2012. Additionally treatment with valtrex was initiated on 02-MAR-2012 and continued for 11 days.

Additional information received from an investigator on 30-AUG-2012.

The subject had recovered from immune reconstitution inflammatory syndrome on 01-JUN-2012.

Additional information recieved from Gilead on 30-AUG-2012 contained no new medically relevant information and no update was made to this case version 3.

Additional information was received on 18-SEP-2012.

An Other Identification Number was added.

The subject was treated with Cobicistat (GS-9350, tablet, oral) 150 mg, once daily initiated on 21-DEC-2011 for HIV infection. Non-company suspect drugs included Truvada (emtricitabine/tenofovir disoproxil, tablet, oral), 1 dose a day, initiated on 21-DEC-2011, for HIV infection.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
CD4 LYMPHOCYTES	??-SEP-2011	Acquired immunodeficiency syndrome (AIDS)		
HEMATOCRIT	29-FEB-2012	43 (units not provided)		
PLATELET COUNT	29-FEB-2012	204 (units not provided)		
WHITE BLOOD CELL COUNT	29-FEB-2012	3.9 (units not provided)		

29-FEB-2012: Chemistry 7 blood panel: all normal

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR (DARUNAVIR) Tablets

Causality

1. IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME [10065042]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Possible
Causality as per Mfr.	Possible

Seq. No. 2
Drug COBICISTAT (DARUNAVIR NON-COMPANY IMP) Tablet

Daily Dose 1) 150 mg, 1 in 1 Day
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) 21-DEC-2011 - Ongoing

Causality

1. IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME [10065042]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120311826**

Causality

Causality as per reporter	Possible
Causality as per Mfr.	Possible

Seq. No.	3
Drug	EMTRICITABINE/TENOFOVIR DISOPROXIL (TRUVADA /01778501/) Tablet
Daily Dose	1) 1 Dose(s), in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 21-DEC-2011 - Ongoing

Causality

1. IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME [10065042]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Concomitant Drugs (Cont...)

Seq. No.	2
Drug	VITAMIN D (ERGOCALCIFEROL)
Daily Dose	1)
Indication	1) VITAMIN D DEFICIENCY
Therapy Dates/Duration	1) 31-OCT-2011 - Ongoing

Seq. No.	3
Drug	SELENIUM (SELENIUM)
Daily Dose	1)
Indication	1) MEDICAL DIET
Therapy Dates/Duration	1) 31-OCT-2011 - Ongoing

Seq. No.	4
Drug	DHEA (PRASTERONE)
Daily Dose	1)
Indication	1) MEDICAL DIET
Therapy Dates/Duration	1) 31-OCT-2011 - Ongoing

Seq. No.	5
Drug	MULTIVITAMINS (MULTIVITAMINS)
Daily Dose	1)
Indication	1) MEDICAL DIET
Therapy Dates/Duration	1) 31-OCT-2011 - Ongoing

Seq. No.	6
Drug	LYSINE (LYSINE)
Daily Dose	1)
Indication	1) MEDICAL DIET
Therapy Dates/Duration	1) 31-OCT-2011 - Ongoing

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120311826**

Seq. No.	7
Drug	GRAPE SEED EXTRACT (VITIS VINIFERA EXTRACT)
Daily Dose	1)
Indication	1) MEDICAL DIET
Therapy Dates/Duration	1) 31-OCT-2011 - Ongoing

Other relevant history (Cont...)

Medical History: HIV INFECTION ??-SEP-2011 - Ongoing
Other History: Race: Caucasian. no known drug allergies.

Medical History: GENITAL HERPES ??-??-???? - Ongoing : Comments: virus-2
Medical History: VITAMIN D DEFICIENCY ??-??-???? - Ongoing

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
NLC	US	10	JUL	19[redacted]	3[redacted] Year	F	??	???	2011

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

EXPOSURE DURING PREGNANCY(10073513)

This pregnancy report was received from clinical trial GS-US-216-0130: A phase 3b, open-label single arm study to evaluate the safety and efficacy of Cobicistat-boosted darunavir plus two-fully active nucleoside reverse transcriptase inhibitors in HIV-infected antiretroviral treatment naive and experienced adults with no darunavir resistance associated mutations, via Gilead Sciences Inc EudraCT #: 2011-003501-22. This report concerns a 3[redacted] year old Caucasian female subject 4067, from the United States:2011-0048317.

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[X] YES [ ] NO [ ] NA

15. DAILY DOSE

400 mg

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

21-NOV-2011 - 01-DEC-2011

19. THERAPY DURATION

11 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

LEXAPRO (ESCITALOPRAM OXALATE) ??-AUG-2011 - ??-??-????20 mg

(Cont.)

23. OTHER RELEVANT HISTORY

Other History: Subject denies use of alcohol, tobacco and recreational drugs.

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 0991
Patient no : 4067

24b. MFR. CONTROL NO.

US-JNJFOC-20120403958(7)

24c. DATE RECEIVED BY MFR.

23-MAY-2013

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The patient's concurrent conditions included human immunodeficiency virus (HIV) infection. The patient's weight was 169.5 pounds and height was 64 inches. The subject denied use of alcohol, tobacco and recreational drugs.

The patient was treated with darunavir (tablets, oral, batch BEZ0500) 400 mg initiated on 21-NOV-2011 to 01-DEC-2011 for HIV infection and Cobicistat (darunavir non-company imp, tablet, oral, batch BB10068) 150 mg initiated on 21-NOV-2011 to 01-DEC-2011 for HIV infection. Non-company suspect drugs included truvada (emtricitabine/tenofovir, tablets, oral, batch 02008799) 500mg initiated on 21-NOV-2011 for HIV infection. Concomitant medications icluded excitalopram oxalate for depression, trazodone for insomnia and ibuprofen for pain.

On an unspecified date, the patient became pregnant. The patient's last menstrual period was on 19-NOV-2011, with an expected delivery date of 28-AUG-2012. The pregnancy was continuing. The patient had been pregnant before, gravidity 2, parity 1, 0 abnormal outcomes.

Treatment with darunavir and cobicistat was withdrawn and the dose of truvada was not changed.

At the time of reporting the patient had not recovered from drug exposure during pregnancy.

The Investigator did not provide causality between drug exposure during pregnancy and study medications (darunavir, cobicistat and emtricitabine/tenofovir). Company causality was assessed as possible.

This report was not serious.

Additional information, in response to a query, was received on 17-MAY-2012.

The pregnancy register reference number was confirmed as 075474.

Additional information received on 22-AUG-2012 contained no new medically relevant information and no update was made to the case.

Additional information received 21-SEP-2012.

The report contained no new information and no changes were made to the report in this non-regulatory relevant case version.

Case reassessed as serious based on additional information from an investigator on 27-SEP-2012.

The subject's medical history and concurrent conditions included anemia, Trichomonas

infection, urinary tract infection abating 22-NOV-2011, and yeast infection.

The subject's expected date of delivery was 10-AUG-2012 (previously reported as 28-AUG-2012).

On 30-NOV-2012, the subject experienced non-itchy "red dots" on her arms and chest. She indicated that she had recently eaten steak and shrimp. The subject was informed she should not stop the medication because if the "dots" were not itching, it's usually not related to the drug. On 16-DEC-2011, the subject reported she was pregnant. The subject had her first pregnancy appointment on 16-JAN-2012, at which time she was diagnosed with Trichomonas. On 25-JUL-2012, the subject had a spontaneous rupture of membranes and irregular contractions every 6-7 minutes. Fetal heart tones were in the 140's and reactive. An ultrasound was vertex with an estimated fetal weight of 3034 grams. Her pregnancy was complicated by HIV, gestational diabetes mellitus, insulin controlled, type I (GMDA-1), elevated liver function tests (LFT's) (reported as possibly secondary to HIV meds), RH-negative status, tetrahydrocannabinol (THC) (positive on urine drug screen 16-JAN-2012) and benzo abuse (positive urine drug screen 14-JUN-2012; taking Xanax received from a friend), history of Trichomonas (status post treatment with metronidazole), yeast and anemia. The subject was started on pitocin and was noted to have protracted labor. On 26-JUL-2012, the subject had an emergency low transverse Cesarean section. She delivered a viable male with Apgar scores of 8/9. Her postpartum course was uncomplicated. She was discharged on the third postoperative day. She received one dose of Depo-Provera (medroxyprogesterone) prior to her discharge. Her discharge instructions included: follow up in 1 week for a wound check and 6 week postpartum check. She was discharged on the following medications: MOTRIN (ibuprofen), Percocet (acetaminophen and oxycodone), Colace (docusate), and iron. She is to continue Combivir (lamivudine and zidovudine) and Kaletra (emtricitabine and tenofovir disoproxil fumarate).

The subject had recovered from drug exposure during pregnancy on 26-JUL-2012.

This report was also serious (hospitalization).

Additional information was received from the investigator on 16-OCT-2012.

It was reported that the subject experienced a Lactobacillus urinary tract infection during the 1st trimester and anemia during the 3rd trimester.

Other medications included ampicillin (indication group b streptococcal), iron (indication anemia), and Colace (constipation prophylaxis) all during the 3rd trimester

Study medication was discontinued when it was found out the subject was pregnant. She was then placed on a combination of Kaletra (lopinavir/ritonavir) and Combivir (lamivudine/zidovudine) tablets twice daily until she reached the third trimester at which point she was increased to three 200/50 tablets twice daily. The subject was very compliant with taking HIV medications and had an undetectable viral load with an excellent CD4 count response. She went through AZT (azidothymidine) as per protocol and at that time the Combivir was changed to lamivudine. Kaletra was continued until she delivered.

Cefazolin was administered on 27-JUL-2012 during labor as infection prophylaxis.

Delivery of a term male infant was on 27-JUL-2012 (previously reported as 26-JUL-2012). The infant was described as healthy with a weight 2794 grams, length 18.75 inches, and head circumference 13 inches. A follow-up of the infant on 01-AUG-2012 revealed mild jaundice of the nose area only. The infant's hospitalization was not prolonged and he did not receive any special treatment. There was no relationship between the pregnancy outcome and exposure to study drug or concomitant medications. It was determined that the baby did not need nevirapine. He was to receive a 6-week course of zidovudine per protocol. The infant would be seen in follow-up 22-AUG-2012 at the pediatric HIV clinic where a HIV PCR qualitative with hemoglobin and hematocrit would be obtained and repeated in 4-6 weeks. The results of the blood tests would determine if the infant was able to forego PCP prophylaxis with trimethoprim sulfa. A well baby clinic visit on 10-AUG-2012 was within normal limits for development and health of the infant.

The resolution date for drug exposure during pregnancy was amended to 27-JUL-2012 based on updated information.

Additional information was received from an investigator on 20-NOV-2012.

The pregnancy reference number for the baby 0754741 was added to the case.

The subject's current weight was reported as 170 pounds.

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120403958**

Follow up information was received from the nurse on 23-MAY-2013.

The reporter screen and the partner number were updated.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
ULTRASOUND SCAN	25-JUL-2012	vertex with estimated fetal weight of 3034 grams		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR (DARUNAVIR) Tablets

Causality

1. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Recovered
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Provided
Causality as per Mfr.	Possible

Seq. No. 2
Drug COBICISTAT (DARUNAVIR NON-COMPANY IMP) Tablet

Daily Dose 1) 150 mg
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) 21-NOV-2011 - Stopped

Causality

1. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Drug Withdrawn/Discontinued
Outcome after Change in dose	Recovered
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Provided
Causality as per Mfr.	Possible

Seq. No. 3
Drug EMTRICITABINE/TENOFOVIR DISOPROXIL (TRUVADA /01778501/)

Daily Dose 1) 500 mg
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 1) 21-NOV-2011 - Ongoing

Causality

1. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120403958**

Concomitant Drugs (Cont...)

Seq. No.	2
Drug	TRAZODONE (TRAZODONE)
Daily Dose	1) 50 mg
Indication	1) INSOMNIA
Therapy Dates/Duration	1) ??-OCT-2011 - ??-??-????
Seq. No.	3
Drug	ADVIL (IBUPROFEN)
Daily Dose	1)
Indication	1) PAIN
Therapy Dates/Duration	1) ??-OCT-2011 - ??-??-????

Other relevant history (Cont...)

Pregnant Expected Date of Delivery: 10-AUG-2012 LMP Date: 19-NOV-2011
Medical History: ANAEMIA ??-??-???? - ??-??-????
Medical History: FUNGAL INFECTION ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing : Comments: diagnosed May-2011
Medical History: TRICHOMONIASIS ??-??-???? - ??-??-????
Medical History: URINARY TRACT INFECTION ??-??-???? - 22-NOV-2011

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
ARF	US	30	MAR	19[redacted]	4[redacted] Year	M	11	MAR	2012

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PYREXIA(10037660)

CASTLEMAN'S DISEASE(10050251)

KAPOSI'S SARCOMA(10023284)

This report was received, via Gilead Sciences, from clinical trial GS-US-216-0130: A Phase 3b, Open-Label, single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naive and Experienced Adults with No Darunavir Resistance-associated Mutations. EudraCT #: 2011-003501-22 and concerns a 4[redacted] year old Asian male subject 4063, from the United States: 2012-0052517.

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

800 mg, 1 in 1 Day

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

17-NOV-2011 - 11-MAR-2012

19. THERAPY DURATION

116 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

TRUVADA (TRUVADA /01778501/) Oral Oral 17-NOV-2011 - Stopped300 mg,1 in 1 Day

(Cont.)

23. OTHER RELEVANT HISTORY

Drug History: DILAUDID ??-??-??????-??-???? Indication: Reaction: DRUG HYPERSENSITIVITY

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 1978
Patient no : 4063

24b. MFR. CONTROL NO.

US-JNJFOC-20120411981(1)

24c. DATE RECEIVED BY MFR.

04-JUN-2012

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The subject's weight was 178 pounds and height was 71 inches. The subject's concurrent conditions included HIV infection. The subject had previously experienced drug allergy when taking penicillin, dilaudid, and morphine.

The subject was treated with darunavir (tablets, oral) 800 mg once a day, initiated on 17-NOV-2011 to 11-MAR-2012 and 800 mg once a day, initiated on 23-MAR-2012 for HIV infection and darunavir non-company investigational medicinal product Cobicistat (GS-9350, tablet, oral) 150 mg once a day, initiated on 17-NOV-2011 to 11-MAR-2012 and 150 mg once a day, initiated on 23-MAR-2012 for HIV infection. Concomitant medications included Truvada (tenofovir + emtricitabine) for HIV infection, cyclobenzaprine hydrochloride for neck spasm, alprazolam for anxiety, sildenafil for erectile dysfunction, and baclofen for neck spasm.

On 11-MAR-2012, the subject presented to the emergency department with fever and night sweats. The subject was found to be tachycardic with lymphodenopathy. The subject was hospitalised on the same day. Cervial lymph node biopsy on 19-MAR-2012 shhowed Castleman's disease and Kaposi's sarcoma, believed to be related to complications of long standing HIV infection. It has been reported that the subject had run out of the study medications on 11-MAR-2012 and restarted on 23-MAR-2012. The subject started Taxol (paclitaxel) chemotherapy on 04-APR-2012. The subject was seen for an unscheduled visit on 19-APR-2012 in good condition. Unspecified laboratory tests were carried out (results pending) and he was continued on chemotherapy at the time of reporting.

The subject had not recovered from Castleman's disease and Kaposi's sarcoma and had recovered from fever on 13-MAR-2012.

The Investigator considered the causality between the events (fever, Kaposi's sarcoma and) and darunavir as not related and not related to trials procedures.

This report was serious (hospitalisation, medically significant).

Additional information was received from the investigator on 04-JUN-2012.

The subject was reported to be HAART (highly active antiretroviral therapy) naive at the time of study enrollment. His medical history and concurrent conditions included anxiety, erectile dysfunction, and neck spasm. On 07-FEB-2012 (week 12), the subject's CD4 lymphocytes count was 351 (21.1 %) and HIV viral load was 113. On 23-MAR-2012, the dose of Truvada (tenofovir + emtricitabine) was reduced from 300 mg to 200 mg. On 23-MAR-2012 during hospitalization, the subject's CD4 lymphocytes count was 298 (22%) and HIV viral load was 3,562,642. On 14-APR-2012, the subject was discharged from the hospital. During an unscheduled visit on 19-APR-2012, the subject's CD4 lymphocytes count was 433 (21.0 %) and HIV viral load was 430. He came in on 02-MAY-2012, for his week 24 visit. During this visit on 02-MAY-2012, the subject's CD4 lymphocytes count was 387 (21.0%) and HIV viral load was 128. The subject reported some mild fevers in MAY-2012, ending 30-MAY-2012,

possibly attributed to Castleman's disease. The subject was in the care of his oncologist and was continuing to receive Taxol (paclitaxel) chemotherapy from 12-APR-2012 to 06-JUN-2012. The oncologist declared Kaposi's sarcoma resolved as of 06-JUN-2012. Castleman's disease was considered in remission and the subject was to follow up with the oncologist regularly. The subject recovered from fever on 30-MAY-2012 (previously reported as 13-MAR-2012).

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
CD4 LYMPHOCYTES	07-FEB-2012	351 (21.1 %)		
	23-MAR-2012	298 (22%)		
	19-APR-2012	433 (21.0 %)		
	02-MAY-2012	387 (21.0%)		
HIV VIRAL LOAD	07-FEB-2012	113		
	23-MAR-2012	3,562,642		
	19-APR-2012	430		
	02-MAY-2012	128		

19-MAR-2012: cervical node biopsy: Castleman's disease and Kaposi's syndrome

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR (DARUNAVIR) Tablets

Daily Dose 2) 800 mg, 1 in 1 Day
Therapy Dates/Duration 2) 23-MAR-2012 - Ongoing

Causality

1. PYREXIA [10037660]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. CASTLEMAN'S DISEASE [10050251]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

3. KAPOSI'S SARCOMA [10023284]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No. 2
Drug COBICISTAT (DARUNAVIR NON-COMPANY IMP) Tablet

Daily Dose 1) 150 mg, 1 in 1 Day
2) 150 mg, 1 in 1 Day
Indication 1) HIV INFECTION
Route of Admin. 1) Oral
Therapy Dates/Duration 2) 23-MAR-2012 - Ongoing

Therapy Dates/Duration 1) 17-NOV-2011 - Stopped

Causality

1. PYREXIA [10037660]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

2. CASTLEMAN'S DISEASE [10050251]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

3. KAPOSI'S SARCOMA [10023284]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Concomitant Drugs (Cont...)

Seq. No.	1
Drug	TRUVADA (TRUVADA /01778501/)
Daily Dose	2) 200 mg, 1 in 1 Day
Therapy Dates/Duration	2) 23-MAR-2012 - Ongoing
Seq. No.	2
Drug	FLEXERIL (CYCLOBENZAPRINE HYDROCHLORIDE)
Daily Dose	1)
Indication	1) MUSCLE SPASMS
Therapy Dates/Duration	1) 27-JAN-2012 - Stopped
Seq. No.	3
Drug	XANAX (ALPRAZOLAM)
Daily Dose	1)
Indication	1) ANXIETY
Therapy Dates/Duration	1) 02-SEP-2011 - Ongoing
Seq. No.	4
Drug	VIAGRA (SILDENAFIL)
Daily Dose	1)
Indication	1) ERECTILE DYSFUNCTION
Therapy Dates/Duration	1) 13-APR-2011 - Ongoing
Seq. No.	5
Drug	BACLOFEN (BACLOFEN)
Daily Dose	1)
Indication	1) MUSCLE SPASMS

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120411981**

Therapy Dates/Duration 1) 12-MAR-2012 - Ongoing

Other relevant history (Cont...)

Drug History: MORPHINE ??-??-??????-??-???? Indication: Reaction: DRUG HYPERSENSITIVITY
Drug History: PENICILLIN ??-??-??????-??-???? Indication: Reaction: DRUG HYPERSENSITIVITY
Medical History: ANXIETY ??-??-???? - ??-??-????
Medical History: ERECTILE DYSFUNCTION ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: MUSCLE SPASMS ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
UNKNOWN	US	??	???	????	UNK	N	??	???	????

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

HYPERSENSITIVITY(10020751)

This report was received from clinical trial GS-US-216-0130: A Phase 3b, Open-Label, Single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir Plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naïve and -Experienced Adults with No Darunavir Resistance. EudraCT #: 2011-003501-22. This report concerns a subject of unknown age or sex (#4118), from United States: 2012-0056074.

The subject's height and weight were not reported. Medical history included HIV infection

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [ ] NA UNK

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [ ] NA UNK

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

??-??-???? - ??-??-????

19. THERAPY DURATION

UNK

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: HIV INFECTION ??-??-???? - Ongoing

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 0302
Patient no : 4118

24b. MFR. CONTROL NO.

US-JNJFOC-20120605156(1)

24c. DATE RECEIVED BY MFR.

10-JUL-2012

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE

[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20120605156**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

The subject was treated with darunavir (tablets, oral) initiated on an unknown date for HIV infection. Non-company suspect drugs included: cobicistat for HIV infection. Concomitant medications were not reported.

On an unknown date, the subject experienced allergic reaction. Action taken with darunavir and cobicistat and the event outcome were not reported. The reporter provided no causality assessment. The information currently reported in this case does not meet the ICH E2A standard of reasonable causal relationship. In the absence of additional information, the company causality is doubtful.

This report is serious (hospitalisation).

Additional information was received from an investigator on 10-JUL-2012.

This report contains no new information, and no changes were made to this report.
No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	DARUNAVIR (DARUNAVIR) Tablets

Causality

1. HYPERSENSITIVITY [10020751]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Provided
Causality as per Mfr.	Doubtful

Seq. No.	2
Drug	COBICISTAT (INVESTIGATIONAL DRUG)
Daily Dose	1)
Indication	1) HIV INFECTION
Therapy Dates/Duration	1) ??-??-???? - ??-??-????

Causality

1. HYPERSENSITIVITY [10020751]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
DC	US	17	MAR	19[redacted]	5[redacted] Year	M	16	OCT	2012

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PROSTATE CANCER(10060862)

This report was received, via Gilead Sciences, for clinical trial GS-US-216-0130: A Phase 3b, Open-Label, single Arm Study to Evaluate the Safety and Efficacy of Cobicistat-boosted Darunavir plus Two Fully Active Nucleoside Reverse Transcriptase Inhibitors in HIV-1 Infected, Antiretroviral Treatment-Naive and Experienced Adults with No Darunavir Resistance-associated Mutations, EudraCT #: 2011-003501-22, and concerned a 5[redacted]-year-old male of African descent (subject 4259), from the United States: 2012-0063834.

The subject's height was 68 inches and his weight was 161.4

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [ ] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG? [ ] YES [ ] NO [X] NA

15. DAILY DOSE: 800 mg, 1 in 1 Day

16. ROUTE OF ADMINISTRATION: Oral

21. DID EVENT REAPPEAR AFTER REINTRODUCTION? [ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE: HIV INFECTION

18. THERAPY DATES (from/to): 15-FEB-2012 - Ongoing

19. THERAPY DURATION: Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

HYDROCHLOROTHIAZIDE (HYDROCHLOROTHIAZIDE) 14-JAN-2012 - Ongoing

23. OTHER RELEVANT HISTORY

Other History: Race: of African descent
Uncle with prostate cancer. No genetic factors for prostate cancer and no history of vasectomy

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no : 1236
Patient no : 4259

24b. MFR. CONTROL NO.: US-JNJFOC-20121104695(0)

24c. DATE RECEIVED BY MFR.: 25-OCT-2012

24d. REPORT SOURCE [X] STUDY [ ] LITERATURE [X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE [ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.: US-JNJFOC-20121104695**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

pounds. The subject's medical history and concurrent conditions included: former smoker (quit 1-5 years ago), hypertension and HIV infection with an uncle with prostate cancer, no genetic factors for prostate cancer and no history of vasectomy or sexually transmitted diseases (ST's). The subject was enrolled in the study and given darunavir (tablets, oral) 800 mg once a day, initiated on 15-FEB-2012 for HIV infection and cobicistat (GS-9350, tablet, oral) 150 mg once a day, initiated on 15-FEB-2012 for HIV infection. Non-company suspect drugs included: Truvada (emtricitabine and tenofovir disoproxil fumarate, oral) 200-300mg a day initiated on 15-FRB-2012 for HIV infection. Concomitant medications included hydrochlorothiazide for hypertension.

On 16-OCT-2012, the subject experienced malignant neoplasm of prostate. It was reported that the subject was seen at the office on 01-AUG-2012 outside of the study. A physical exam found an enlarged prostate. The subject had a PSA result of 5.84. He was sent to an urologist. He had a biopsy that showed cancer. The subject stated he was diagnosed on 16-OCT-2012. He reported it at his week 36 visit on 24-OCT-12. The subject had no symptoms and unknown cellularity. Treatment was unknown at that time. The subject was under the care of a urologist. The subjects risk factors for prostate cancer included no history of obesity current BMI 24.54, former smoker, subject reported his uncle having prostate cancer no other family member.

The doses of darunavir, cobicistat and emtricitabine and tenofovir disoproxil fumarate were not changed.

The subject had not recovered from malignant neoplasm of prostate.

The investigator considered the causality between malignant neoplasm of prostate and darunavir and cobicistat as not related. The investigator also assessed the event as not related to trial procedures.

This report is serious (medically significant).

This case, involving the same subject is linked to 20120712638.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BODY MASS INDEX	??-???-????	24.54		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR (DARUNAVIR) Tablets

Causality

1. PROSTATE CANCER [10060862]

Change in dose Dose Not changed

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20121104695**

Causality

Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	2
Drug	COBICISTAT (DARUNAVIR NON-COMPANY IMP) Tablet
Daily Dose	1) 150 mg, 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 15-FEB-2012 - Ongoing

Causality

1. PROSTATE CANCER [10060862]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

Seq. No.	3
Drug	TRUVADA (TRUVADA /01778501/)
Daily Dose	1) , 1 in 1 Day
Indication	1) HIV INFECTION
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 15-FEB-2012 - Ongoing

Causality

1. PROSTATE CANCER [10060862]

Change in dose	Dose Not changed
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Other relevant history (Cont...)

Medical History: EX-TOBACCO USER ??-??-???? - ??-??-???? : Comments: quit 1-5 years ago
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: HYPERTENSION ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
VMW	US	02	JUL	19[redacted]	2[redacted] Year	F	10	APR	2013

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- ☐ INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- ☐ LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

ECTOPIC PREGNANCY(10014166)

VAGINITIS BACTERIAL(10062167)

EXPOSURE DURING PREGNANCY(10073513)

This pregnancy report was received from clinical trial GS-US-216-0130: A phase 3b, open-label single arm study to evaluate the safety and efficacy of Cobici, EudraCT #: 2011-003501-22, and concerns a 2[redacted] year old African Descent female patient from the United States; local case ID: 2013-0078359.

The patient's weight was 163.4 pounds and height was 69 inches. The patient's medical history and concurrent

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

DARUNAVIR (DARUNAVIR) Tablets

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

☐ YES ☐ NO ☐ NA UNK

15. DAILY DOSE

16. ROUTE OF ADMINISTRATION

Unknown

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

☐ YES ☐ NO ☐ NA UNK

17. INDICATIONS FOR USE

HIV INFECTION

18. THERAPY DATES (from/to)

??-??-???? - ??-??-????

19. THERAPY DURATION

UNK

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Other History: Race: African Descent
The patient had no history of recreational drugs use.
The patient had no family history of

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : GS-US-216-0130
Center no :
Patient no : 4245

24b. MFR. CONTROL NO.

US-JNJFOC-20130700753(0)

24c. DATE RECEIVED BY MFR.

26-JUN-2013

24d. REPORT SOURCE

☒ STUDY ☐ LITERATURE

☒ HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

☐ INITIAL ☐ FOLLOWUP ☐ FINAL

(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.: US-JNJFOC-20130700753**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

conditions included: no alcohol use, no smoking, and human immunodeficiency virus (HIV). The patient had no history of recreational drugs use. The patient had no family history of malformation, significant obstetrical outcome or heredity disorders. The patient's partner used condom as contraception. The patient had not been pregnant before. On 04-APR-2013, plasma HIV RNA showed 250 Log 10 copies/ ml and CD4+Tcell count was 652 Log 10 copies/ ml. The patient was treated with darunavir (tablets, unknown) dose and frequency unspecified, along with non-company suspect drugs: Truvada, emtricitabine and tenofovir disoproxil fumarate (unspecified, unknown) dose and frequency unspecified, cobicistat (unspecified, unknown) dose and frequency unspecified, all initiated on an unspecified date for HIV. Concomitant medications were not reported. On an unspecified date, the patient became pregnant (drug exposure during pregnancy). The date of the patient's last menstrual period and expected delivery date were both not reported. On 10-APR-2013, during the first trimester, the patient was diagnosed with ectopic pregnancy (with surgery to remove left fallopian tube/ terminate the pregnancy) and the pregnancy was interrupted on the same day. On an unspecified date, the patient experienced bacterial vaginosis. Action taken with darunavir, emtricitabine and tenofovir disoproxil fumarate and investigational drug cobicistat was not reported. The patient had recovered from ectopic pregnancy and drug exposure during pregnancy on 10-APR-2013 and outcome was not reported for bacterial vaginosis. The other factor that may have contributed to ectopic pregnancy was considered as bacterial vaginosis. The investigator provided no causality assessment between ectopic pregnancy, bacterial vaginosis, drug exposure during pregnancy and darunavir. Company causality was assessed as doubtful.

This report was serious (medically significant).

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
BLOOD HIV RNA	04-APR-2013	250 Log 10 copies/ ml		
T-LYMPHOCYTE COUNT	04-APR-2013	CD4 positive; 652 Log 10 copies/ ml		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No. 1
Drug DARUNAVIR (DARUNAVIR) Tablets

Causality

1. ECTOPIC PREGNANCY [10014166]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Provided
Causality as per Mfr.	Doubtful

2. VAGINITIS BACTERIAL [10062167]

Change in dose	Unknown

Causality

Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Provided
Causality as per Mfr.	Doubtful

3. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Provided
Causality as per Mfr.	Doubtful

Seq. No.	2
Drug	TRUVADA (TRUVADA /01778501/) Unspecified
Daily Dose	1)
Indication	1) HIV INFECTION
Route of Admin.	1) Unknown
Therapy Dates/Duration	1) ??-??-???? - ??-??-????

Causality

1. ECTOPIC PREGNANCY [10014166]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

2. VAGINITIS BACTERIAL [10062167]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

3. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Seq. No.	3
Drug	COBICISTAT (INVESTIGATIONAL DRUG) Unspecified
Daily Dose	1)
Indication	1) HIV INFECTION
Route of Admin.	1) Unknown
Therapy Dates/Duration	1) ??-??-???? - ??-??-????

Causality

Continuation Sheet for CIOMS report **Mfr. Control No.:** **US-JNJFOC-20130700753**

Causality

1. ECTOPIC PREGNANCY [10014166]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

2. VAGINITIS BACTERIAL [10062167]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

3. EXPOSURE DURING PREGNANCY [10073513]

Change in dose	Unknown
Outcome after Change in dose	
Outcome after Reintro. of dose	
Causality as per reporter	
Causality as per Mfr.	

Other relevant history (Cont...)

Drug History: CONTRACEPTIVE MEDICATION NOS ??-??-??????-??-???? Indication: Reaction: TREATMENT NONCOMPLIANCE
Medical History: ABSTAINS FROM ALCOHOL ??-??-???? - ??-??-????
Medical History: HIV INFECTION ??-??-???? - Ongoing
Medical History: NON-TOBACCO USER ??-??-???? - ??-??-????

CIOMS II Report

Run Information

User Name: [redacted] ([redacted])

Run Date: [redacted]

Parameters

Query Report Name: SDE00016486 Search #2 Final

Results: 9 cases selected from 9 matching the following criteria

Status: NOT = Deleted

J&J Cases Only: = (J&J Drug, J&J Device, Gene Therapy)

Query Report: = SDE00016486 Search #2 (Drug Name DARUNAVIR, Case Types J&J Device, J&J Drug, Gene Therapy, Drug Character Suspect or Suspect Interacting, Partner Cases Excluded, Start Date [redacted], End Date [redacted], Date Type Version Initially Received, Version Highest In Date Range, Invalid Cases Included, Workflow Cases Excluded, Deleted Cases Excluded, Case Seriousness Serious)

Query Report Case included in report: = Yes

Last Distributed: = Yes

Reported Drug Name: = COBICISTAT

CIOMS II Report

SDE00016486 Search #2 Final

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20120209481(2)	UNITED STATES	Study	2 Year	M	800 mg,1 in 1 Day Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
RASH GENERALISED	Recovered/Resolved	Yes	Very Likely / Certain	LABELED	LABELED

Comments:

Protocol #: GS-US-216-0130, Investigator #: 2154, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION
Suspect Drugs: INVESTIGATIONAL DRUG (150mg-15Day)
TRUVADA /01778501/ (1Dose(s)-15Day,1Dose(s))

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20120302461(7)	UNITED STATES	Study	5 Year	M	800 mg, in 1 Day Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
IDIOPATHIC THROMBOCYTOPENIC PURPURA	Recovered/Resolved With Sequelae	Yes	Not Related	UNLABELED	UNLABELED

Comments:

Protocol #: GS-US-216-0130, Investigator #: 6046, Indication for use: HIV INFECTION
Disease Type: HYPOTHYROIDISM, HIV INFECTION
Suspect Drugs: DARUNAVIR NON-COMPANY IMP (150mg-16Day)
TRUVADA /01778501/ (500mg-16Day)
Concomitant Drugs: LEVOTHYROXINE SODIUM

MedDRA 16.0

CIOMS II Report

SDE00016486 Search #2 Final

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20120311820(1)	UNITED STATES	Study	3 Year	M	800 mg, in 1 Day Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
RASH MACULO-PAPULAR	Recovered/Resolved	Yes	Possible	LABELED	LABELED

Comments: Protocol #: GS-US-216-0130, Investigator #: 2843, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION
Suspect Drugs: DARUNAVIR NON-COMPANY IMP (150mg-10Day)
TRUVADA /01778501/ (1Dose(s)-10Day)

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20120311826(4)	UNITED STATES	Study	4 Year	M	800 mg, in 1 Day Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME	Recovered/Resolved	Yes	Possible	LABELED	LABELED

Comments: Protocol #: GS-US-216-0130, Investigator #: 1541, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, ACQUIRED IMMUNODEFICIENCY SYNDROME, GENITAL HERPES, VITAMIN D DEFICIENCY
Suspect Drugs: DARUNAVIR NON-COMPANY IMP (150mg)
TRUVADA /01778501/ (1Dose(s))
Concomitant Drugs: BACTRIM /00086101/

MedDRA 16.0

CIOMS II Report

SDE00016486 Search #2 Final

Reference #	Country	Source	Age	Sex	Dose		Treat. dur. till onset
		ERGOCALCIFEROL					
		SELENIUM					
		PRASTERONE					
		MULTIVITAMINS					
		LYSINE					
		VITIS VINIFERA EXTRACT					
US-JNJFOC-20120403958(7)	UNITED STATES	Pregnancy Registry Study	3 Year	F	400 mg, in	Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
EXPOSURE DURING PREGNANCY	Recovered/Resolved	Yes	Possible	UNLABELED	UNLABELED

Comments:

Protocol #: GS-US-216-0130, Investigator #: 0991, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, ANAEMIA, URINARY TRACT INFECTION, FUNGAL INFECTION, TRICHOMONIASIS
Suspect Drugs: DARUNAVIR NON-COMPANY IMP (150mg-11Day)
TRUVADA /01778501/ (500mg)
Concomitant Drugs: ESCITALOPRAM OXALATE (20mg)
TRAZODONE (50mg)
IBUPROFEN

MedDRA 16.0

CIOMS II Report

SDE00016486 Search #2 Final

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20120411981(1)	UNITED STATES	Study	4 [redacted] Year	M	800 mg,1 in 1 Day Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PYREXIA	Recovered/Resolved	Yes	Not Related	UNLABELED	UNLABELED
CASTLEMAN'S DISEASE	Not Recovered/Not Resolved	Yes	Not Related	UNLABELED	UNLABELED
KAPOSI'S SARCOMA	Recovered/Resolved	Yes	Not Related	LABELED	LABELED

Comments:

Protocol #: GS-US-216-0130, Investigator #: 1978, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, ANXIETY, ERECTILE DYSFUNCTION, MUSCLE SPASMS
Suspect Drugs: DARUNAVIR NON-COMPANY IMP (150mg-116Day,150mg)
Concomitant Drugs: TRUVADA /01778501/ (300mg)
CYCLOBENZAPRINE HYDROCHLORIDE
ALPRAZOLAM
SILDENAFIL
BACLOFEN

US-JNJFOC-20120605156(1)	UNITED STATES	Study	Unknown	N	, in Tablets Oral	UNK

MedDRA 16.0

CIOMS II Report

SDE00016486 Search #2 Final

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
HYPERSENSITIVITY	Unknown	Yes	Doubtful	LABELED	LABELED

Comments: Protocol #: GS-US-216-0130, Investigator #: 0302, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION
Suspect Drugs: INVESTIGATIONAL DRUG

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20121104695(0)	UNITED STATES	Study	5 Year	M	800 mg,1 in 1 Day Tablets Oral	UNK

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
PROSTATE CANCER	Not Recovered/Not Resolved	Yes	Not Related	UNLABELED	UNLABELED

Comments: Protocol #: GS-US-216-0130, Investigator #: 1236, Indication for use: HIV INFECTION
Disease Type: HIV INFECTION, EX-TOBACCO USER, HYPERTENSION
Suspect Drugs: DARUNAVIR NON-COMPANY IMP (150mg)
TRUVADA /01778501/
Concomitant Drugs: HYDROCHLOROTHIAZIDE

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset
US-JNJFOC-20130700753(0)	UNITED STATES	Study	2 Year	F	, in Tablets Unknown	UNK

MedDRA 16.0

CIOMS II Report

SDE00016486 Search #2 Final

Reference #	Country	Source	Age	Sex	Dose	Treat. dur. till onset

Reaction description	Outcome	Serious	Causality	Core Label	IB Label
ECTOPIC PREGNANCY	Recovered/Resolved	Yes	Doubtful	UNLABELED	UNLABELED
VAGINITIS BACTERIAL	Unknown	Yes	Doubtful	UNLABELED	UNLABELED
EXPOSURE DURING PREGNANCY	Recovered/Resolved	Yes	Doubtful	UNLABELED	UNLABELED

Comments:

Protocol #: GS-US-216-0130, Investigator #: 1780, Indication for use: HIV INFECTION
Disease Type: NON-TOBACCO USER, HIV INFECTION, ABSTAINS FROM ALCOHOL
Suspect Drugs: TRUVADA /01778501/

INVESTIGATIONAL DRUG

MedDRA 16.0

Janssen Research & Development

Summary of Clinical Safety Addendum

Cobicistat-containing Highly Active Antiretroviral Regimens in HIV-1 Infected Patients with Mild to Moderate Renal Impairment

DRV/COBI (darunavir/cobicistat)

Status:	Approved
Date:	25 September 2015
Prepared by:	Janssen Infectious Diseases - Diagnostics BVBA
EDMS number:	Report Body: EDMS-ERI-111366615, 1.0

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ABBREVIATIONS

abbreviation	description of abbreviated term
AE	adverse event
aGFR	actual glomerular filtration rate
ALT	alanine aminotransferase
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
BMI	body mass index
CI	confidence interval
COBI	cobicistat
CSR	clinical study report
DRV	darunavir
ECG	electrocardiogram
$eGFR_{CG}$	estimated glomerular filtration rate using the Cockcroft-Gault method
$eGFR_{CKD-EPI}$	estimated glomerular filtration rate using the chronic kidney disease, epidemiology collaboration method
$eGFR_{MDRD}$	estimated glomerular filtration rate using the Modification of Diet in Renal Disease method
EVG	elvitegravir
FDC	fixed dose combination
FEPO4	urine fractional excretion of phosphate
FTC	emtricitabine
GFR	glomerular filtration rate
GGT	gamma glutamyltransferase
HIV-1	human immunodeficiency virus (type 1)
HLT	high-level term
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
NRTI	nucleoside reverse transcriptase inhibitor
PAM	post-authorization measure
PI	protease inhibitor
PRT	proximal renal tubulopathy
PT	preferred term
Q1, Q3	first quartile, third quartile
RMP	risk management plan
RNA	ribonucleic acid
rtv	low-dose ritonavir
SAE	serious adverse event
SD	standard deviation
SOC	system organ class
STB	Stribild®, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate, coformulated
TDF	tenofovir disoproxil fumarate
ULN	upper limit of the normal range

1. EXPOSURE TO DRUG

This submission supports the provision of final efficacy and safety data (Week 96) from Phase 3 Study GS-US-236-0118 in fulfillment of a post-authorization measure (PAM) for REZOLSTA® (darunavir [DRV]/cobicistat [COBI] fixed dose combination [FDC]). The provision of the final clinical study report (CSR) is an additional pharmacovigilance activity (category 3) in the REZOLSTA risk management plan (RMP).

This summary presents safety data through Week 96 using the final dataset for Study GS-US-236-0118. This Phase 3 study evaluated the effect of COBI-containing regimens on renal parameters and the safety and tolerability of those regimens in human immunodeficiency virus type 1 (HIV-1) infected antiretroviral (ARV) treatment-naïve and ARV treatment-experienced subjects with mild-to-moderate renal impairment (estimated glomerular filtration rate [GFR] using the Cockcroft-Gault method [$eGFR_{CG}$] 50 to <90 mL/min).

1.1. Overall Safety Evaluation Plan and Narratives of Safety Studies

This submission includes final safety data from an open-label, multicenter, multiple-cohort Phase 3 study in HIV-1 infected adult subjects with stable, mild to moderate renal function ($eGFR_{CG}$ of 50 to <90 mL/min), Study GS-US-236-0118. This study was conducted to evaluate the effect of COBI-containing regimens on parameters of renal function in HIV-1 infected subjects with mild to moderate renal impairment and to assess the safety and tolerability of those regimens.

The safety analysis set included all subjects who were enrolled into the study and received at least 1 dose of study drug. Subjects were analyzed according to treatment received. The safety analysis set was used for the safety analyses. Adverse events (AEs) were classified using the Medical Dictionary for Regulatory Activities (MedDRA). Clinical AEs and laboratory abnormalities were graded according to Gilead's Grading Scale for Severity of Adverse Events and Laboratory Abnormalities unless otherwise noted.

A study narrative of Study GS-US-236-0118 is presented below; a tabular summary of the study is provided in Appendix 1.

This was an open-label, multicenter, multiple-cohort study in approximately 100 HIV-1 infected adult subjects with stable, mild to moderate renal function ($eGFR_{CG}$ 50 to <90 mL/min). Subjects were enrolled in 1 of the following 2 cohorts (at least 33 subjects per cohort) to receive 96 weeks of treatment with study drug:

Cohort 1: (ARV treatment-naïve subjects with HIV-1 ribonucleid acid [RNA] ≥1000 copies/mL at screening): Stribild (STB; 150 mg of elvitegravir [EVG], 150 mg of COBI, 200 mg of emtricitabine [FTC], and 300 mg of tenofovir disoproxil fumarate [TDF]; described as the STB cohort)

Cohort 2: (pharmacokinetic enhancer switch in ARV treatment-experienced subjects with stable virologic suppression): COBI 150 mg boosted atazanavir (ATV) 300 mg or COBI 150 mg

boosted DRV 800 mg + 2 nucleoside reverse transcriptase inhibitors (NRTIs) (described as the protease inhibitor [PI]/COBI cohort)

Across both cohorts, there were to be at least 10 subjects with screening $eGFR_{CG}$ 50 to 60 mL/min, and no more than 50 subjects with screening $eGFR_{CG}$ 80 to <90 mL/min.

Subjects returned for study visits at Weeks 2, 4, 8, 12, 16, 24, 32, 40, and 48, and then every 12 weeks thereafter through Week 96. After the Week 96 visit, if STB or COBI were not available in the country in which the study was being conducted, subjects had the option to participate in an extension phase of the study, and/or to rollover into another Gilead sponsored study. During the extension phase of this study, subjects continued receiving their study regimen and attended visits every 12 weeks until all subjects had discontinued from the study or commercial approval of STB or COBI was received in the applicable country.

Further details on the design and results of this study are available in the CSR (Module 5.3.5.2/ GS-US-236-0118 Final CSR).

1.2. Overall Extent of Exposure

In the STB cohort, the median duration of exposure to study drug was 98.0 weeks (first quartile, third quartile [Q1, Q3]: 95.1, 119.0 weeks; Table 1). The majority of the subjects received study drug for !96 weeks (72.7%, 24 subjects). The Kaplan-Meier (KM) estimate for the percentage of subjects with premature discontinuation of study drug at Week 96 was 18% (95% confidence interval [CI]: 5.1 to 31.5).

In the PI/COBI cohort, the median duration of exposure to study drug was 120.1 weeks (Q1, Q3: 64.4, 132.3 weeks Table 1). The majority of the subjects received study drug for !96 weeks (67.1%, 49 subjects). The KM estimate for the percentage of subjects with premature discontinuation of study drug at Week 96 was 24% (95% CI: 13.9 to 33.7).

Table 1: GS-US-236-0118: Duration of Exposure to Study Drug (Safety Analysis Set)

	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Total Exposure to Study Drug (Weeks)[a, b]		
N	33	73
Mean (SD)	93.7 (38.87)	101.2 (45.48)
Median	98.0	120.1
Q1, Q3	95.1, 119.0	64.4, 132.3
Min, Max	1.1, 147.1	0.9, 166.1
Total Exposure to Study Drug, n (%)		
>= 4 Weeks (28 days)	32 (97.0)	72 (98.6)
>= 8 Weeks (56 days)	32 (97.0)	69 (94.5)
>= 12 Weeks (84 days)	31 (93.9)	67 (91.8)
>= 16 Weeks (112 days)	30 (90.9)	67 (91.8)
>= 24 Weeks (168 days)	29 (87.9)	67 (91.8)
>= 32 Weeks (224 days)	29 (87.9)	64 (87.7)
>= 40 Weeks (280 days)	28 (84.8)	64 (87.7)
>= 48 Weeks (336 days)	28 (84.8)	62 (84.9)
>= 60 Weeks (420 days)	26 (78.8)	57 (78.1)
>= 72 Weeks (504 days)	26 (78.8)	53 (72.6)
>= 84 Weeks (588 days)	26 (78.8)	51 (69.9)
>= 96 Weeks (672 days)	24 (72.7)	49 (67.1)
>= 108 Weeks (756 days)	15 (45.5)	46 (63.0)
>= 120 Weeks (840 days)	7 (21.2)	37 (50.7)
>= 132 Weeks (924 days)	3 (9.1)	24 (32.9)
>= 144 Weeks (1008 days)	2 (6.1)	8 (11.0)
>= 156 Weeks (1092 days)	0	3 (4.1)

[a] Denominator for percentages is the number of subjects in the safety analysis set.
[b] Duration of exposure in weeks = (Last Dose Date - First Dose Date + 1)/7.
Programming Details: .../version1/prog/t-trdur.sas v9.2 12MAY2015:10:46
Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 5

1.3. Demographic and Other Characteristics of Study Population

In the STB cohort, 81.8% of subjects in the safety analysis set were male, with a mean age of 50 years (range, 22 to 72 years) (Table 2). Subjects were predominantly white (42.4%) or black (39.4%). The mean (standard deviation [SD]) baseline body mass index (BMI) was 23.7 (3.43) kg/m^2. The mean (SD) baseline HIV-1 RNA level was 4.76 (0.652) $\log_{10}$ copies/mL, and the mean (SD) CD4+ cell count was 356 (174.2) cells/μL (Table 3). Overall, 27.3% of subjects had baseline HIV-1 RNA >100,000 copies/mL. The mean (SD) $eGFR_{CG}$ was 72.6 (14.56) mL/min; 4 subjects (12.1%) had abnormal (graded) serum creatinine. Thirteen subjects (39.4%) had hypertension, 3 subjects (9.1%) had diabetes, and 1 subject (3.0%) had HIV-associated nephropathy. Proteinuria ≥trace was present in 18 subjects (54.5%).

In the PI/COBI cohort, 82.2% of subjects in the safety analysis set were male, with a mean age of 54 years (range, 29 to 73 years) (Table 2). Subjects were predominantly white (76.7%) or black (19.2%). The mean (SD) baseline BMI was 25.6 (3.64) kg/m^2. All subjects had HIV-1 RNA <50 copies/mL at baseline (Table 3). The mean (SD) CD4+ cell count was 627 (263.2) cells/μL. The mean (SD) $eGFR_{CG}$ was 71.4 (12.55) mL/min; 10 subjects (13.7%) had abnormal (graded) serum creatinine. Twenty-eight subjects (38.4%) had hypertension, 14 subjects (19.2%) had diabetes, and 2 subjects (2.7%) had HIV-associated nephropathy.

One subject (1480-2069) had proximal renal tubulopathy (PRT) at baseline. Proteinuria !trace was present in 37 subjects (50.7%).

The protocol required that across both cohorts there were at least 10 subjects with screening $eGFR_{CG}$ 50 to 60 mL/min, and no more than 50 subjects with screening $eGFR_{CG}$ 80 to <90 mL/min. There were 19 subjects with screening $eGFR_{CG}$ 50 to 60 mL/min (STB n=5; PI/COBI n=14) and 27 subjects with screening $eGFR_{CG}$ 80 to <90 mL/min (STB n=10; PI/COBI n=17) (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 4.2).

Table 2: GS-US-236-0118: Demographics and Baseline Characteristics (Safety Analysis Set)

Characteristic[a]	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Age (Years)		
N	33	73
Mean (SD)	50 (12.1)	54 (9.5)
Median	53	56
Q1, Q3	45, 57	47, 60
Min, Max	22, 72	29, 73
Sex, n (%)		
Male	27 (81.8)	60 (82.2)
Female	6 (18.2)	13 (17.8)
Race, n (%)		
American Indian or Alaska Native	1 (3.0)	0
Asian	0	1 (1.4)
Black or African Heritage	13 (39.4)	14 (19.2)
Native Hawaiian or Pacific Islander	0	0
White	14 (42.4)	56 (76.7)
Other	5 (15.2)	2 (2.7)
Ethnicity, n (%)		
Hispanic/Latino	9 (27.3)	19 (26.0)
Non-Hispanic/Latino	24 (72.7)	54 (74.0)
Baseline Weight (kg)		
N	33	73
Mean (SD)	69.7 (11.63)	75.6 (12.32)
Median	68.0	74.4
Q1, Q3	62.1, 77.2	68.2, 81.2
Min, Max	50.8, 100.5	48.1, 107.0
Baseline Height (cm)		
N	33	73
Mean (SD)	171.6 (10.48)	171.8 (8.53)
Median	174.0	172.5
Q1, Q3	165.1, 177.8	167.6, 177.8
Min, Max	147.5, 188.0	147.3, 186.0
Baseline Body Mass Index (kg/m^2)		
N	33	73
Mean (SD)	23.7 (3.43)	25.6 (3.64)
Median	23.8	24.8
Q1, Q3	20.9, 25.2	23.0, 27.8
Min, Max	16.8, 31.8	17.4, 38.1

[a] Denominator for percentages is the number of subjects in the safety analysis set.
Programming Details: .../version1/prog/t-demog.sas v9.2 12MAY2015:10:40
Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 3

Table 3: GS-US-236-0118: Baseline Disease Characteristics (Safety Analysis Set)

Characteristic[a]	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
HIV-1 RNA (log_{10} copies/mL)		
N	33	73
Mean (SD)	4.76 (0.652)	1.69 (0.000)
Median	4.73	1.69
Q1, Q3	4.45, 5.17	1.69, 1.69
Min, Max	3.41, 6.21	1.69, 1.69
HIV-1 RNA Category (copies/mL), n (%)		
< 50	0	73 (100.0)
>= 50 to < 1,000	0	0
>= 1,000 to <= 100,000	24 (72.7)	0
> 100,000	9 (27.3)	0
CD4+ Cell Count (/uL), n (%)		
N	33	73
Mean (SD)	356 (174.2)	627 (263.2)
Median	331	602
Q1, Q3	238, 468	441, 799
Min, Max	5, 839	138, 1486
CD4+ Cell Count Category (/uL), n (%)		
<= 50	1 (3.0)	0
51 to <= 200	3 (9.1)	3 (4.1)
201 to <= 350	13 (39.4)	5 (6.8)
351 to <= 500	10 (30.3)	16 (21.9)
> 500	6 (18.2)	49 (67.1)
CD4+ (%), n (%)		
N	33	73
Mean (SD)	21.2 (9.67)	30.3 (9.56)
Median	20.8	29.7
Q1, Q3	15.7, 25.6	23.3, 35.5
Min, Max	1.4, 41.5	5.6, 52.0
HIV Risk Factors[b], n (%)		
Heterosexual Sex	15 (45.5)	18 (24.7)
Homosexual Sex	18 (54.5)	50 (68.5)
IV Drug Use	0	1 (1.4)
Transfusion	0	2 (2.7)
Vertical Transmission	0	0
Other	0	3 (4.1)
Unknown	0	2 (2.7)
HIV Disease Status, n (%)		
Asymptomatic	28 (84.8)	37 (50.7)
Symptomatic HIV Infection	3 (9.1)	18 (24.7)
AIDS	2 (6.1)	18 (24.7)
HBV Surface Antigen Status, n (%)		
Positive	1 (3.0)	4 (5.5)
Negative	32 (97.0)	69 (94.5)
Indeterminate	0	0
HCV Antibody Status, n (%)		
Positive	2 (6.1)	10 (13.7)
Negative	30 (90.9)	63 (86.3)
Indeterminate	1 (3.0)	0

Characteristic[a]	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Estimated Glomerular Filtration Rate by Cockcroft-Gault (CG) Formula (mL/min)		
N	33	73
Mean (SD)	72.6 (14.56)	71.4 (12.55)
Median	72.9	71.4
Q1, Q3	64.7, 81.1	61.9, 80.7
Min, Max	36.6, 103.6	42.4, 98.3
Estimated Glomerular Filtration Rate by Cockcroft-Gault (CG) Formula Category (mL/min), n (%)		
< 50	1 (3.0)	4 (5.5)
>= 50 to < 60	5 (15.2)	11 (15.1)
>= 60 to < 70	6 (18.2)	20 (27.4)
>= 70 to < 80	11 (33.3)	18 (24.7)
>= 80 to < 90	6 (18.2)	16 (21.9)
>= 90	4 (12.1)	4 (5.5)
Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease (MDRD) Formula (mL/min/1.73m^2)		
N	33	73
Mean (SD)	74.7 (16.80)	66.5 (14.59)
Median	77.1	65.8
Q1, Q3	64.3, 87.2	56.2, 75.2
Min, Max	39.9, 100.6	32.3, 103.2
Estimated Glomerular Filtration Rate by CKD-EPI Based on Serum Cystatin C (mL/min/1.73m^2), Unadjusted		
N	33	73
Mean (SD)	76.6 (23.48)	81.0 (19.00)
Median	77.6	78.6
Q1, Q3	61.7, 90.5	67.0, 94.4
Min, Max	21.1, 121.4	40.8, 135.5
Estimated Glomerular Filtration Rate by CKD-EPI Based on Serum Cystatin C (mL/min/1.73m^2), Adjusted for Age, Sex, and Race[c]		
N	33	73
Mean (SD)	77.4 (24.04)	79.9 (18.69)
Median	76.9	78.2
Q1, Q3	61.7, 90.1	67.1, 92.4
Min, Max	22.9, 130.8	40.1, 128.0
Estimated Glomerular Filtration Rate by CKD-EPI Based on Serum Creatinine (mL/min/1.73m^2)		
N	33	73
Mean (SD)	75.2 (17.13)	67.0 (15.68)
Median	79.2	67.3
Q1, Q3	65.0, 88.1	55.3, 77.3
Min, Max	38.0, 100.2	32.9, 104.0
Urine Fractional Excretion of Phosphate Based on Unadjusted Serum Creatinine (%)		
N	33	71
Mean (SD)	12.0 (5.71)	16.8 (6.98)
Median	12.2	15.9
Q1, Q3	7.6, 14.8	11.2, 22.6
Min, Max	4.5, 30.7	3.0, 37.9

Characteristic[a]	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Baseline Serum Creatinine by Toxicity Grade, n (%)		
No Grade	29 (87.9)	63 (86.3)
Grade 1	1 (3.0)	9 (12.3)
Grade 2	3 (9.1)	1 (1.4)
Grade 3	0	0
Grade 4	0	0
Hypertension	13 (39.4)	28 (38.4)
Diabetes[d]	3 (9.1)	14 (19.2)
HIV-associated Nephropathy	1 (3.0)	2 (2.7)
Urine Protein		
Negative	15 (45.5)	36 (49.3)
Trace	11 (33.3)	14 (19.2)
+1	4 (12.1)	20 (27.4)
+2	1 (3.0)	3 (4.1)
+3	1 (3.0)	0
+4	1 (3.0)	0

[a] Denominator for percentages is the number of subjects in the safety analysis set.
[b] A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.
[c] Adjusted eGFR by CKD-EPI (mL/min/1.73m^2) = 127.7 x cystatin C ^ -1.17 (mg/L) x age ^ -0.13 (yrs) x 0.91 (if female) x 1.06 (if Black).
[d] Database was updated after the Week 48 analyses to include a history of diabetes in Subject 1407-2035 and a history of hypertension in Subject 0112-1018.

Programming Details: .../version1/prog/t-basechr.sas v9.2 12MAY2015:10:39
Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 4

2. ADVERSE EVENTS

This section provides an overall summary of AEs in Study GS-US-236-0118.

2.1. Analysis of Adverse Events

STB Cohort

No treatment-emergent death was reported during Study GS-US-236-0118 (Table 4). In the STB cohort, any serious adverse event (SAE) was reported for 18.2% of subjects (6 subjects); 2 subjects had an SAE that was considered related to study drug by the investigator (increased blood creatine phosphokinase, anemia). Any AE was reported for all subjects (33 subjects); AEs considered related to study drug by the investigator were reported for 48.5% of subjects (16 subjects). Any grade 3 or 4 AE was reported for 21.2% of subjects (7 subjects); grade 3 or 4 AEs considered related to study drug were reported for 12.1% of subjects (4 subjects). Four subjects (12.1%) discontinued study drug due to an AE, including 3 subjects who discontinued due to renal AEs (1 each due to decreased creatinine renal clearance, blood creatinine increased, and abnormal glomerular filtration rate). No subject who discontinued study drug had treatment-emergent laboratory findings consistent with PRT.

PI/COBI Cohort

No treatment-emergent death was reported during Study GS-US-236-0118 (Table 4). In the PI/COBI cohort, any SAE was reported for 15.1% of subjects (11 subjects); 1 subject had an

SAE that was considered related to study drug by the investigator (nephrolithiasis). Any AE was reported for 93.2% of subjects (68 subjects); AEs considered related to study drug by the investigator were reported for 27.4% of subjects (20 subjects). Any grade 3 or 4 AE was reported for 28.8% of subjects (21 subjects); no grade 3 or 4 AE was considered related to study drug by the investigator. Eight subjects (11.0%) discontinued study drug due to an AE, including 3 subjects who discontinued due to renal AEs (abnormal glomerular filtration rate, decreased glomerular filtration rate, and proteinuria and hematuria). None of the subjects who discontinued study drug had treatment-emergent laboratory findings consistent with PRT (Module 5.3.5.2/ GS-US-236-0118 Final CSR/Section 7.3).

Table 4: GS-US-236-0118: Overall Summary of Adverse Events (Safety Analysis Set)

Subjects who had any Treatment-Emergent Event, n (%)	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Any Treatment-Emergent Adverse Event	33 (100.0)	68 (93.2)
Any Grade 2, 3, or 4 Treatment-Emergent Adverse Event	24 (72.7)	58 (79.5)
Any Grade 3 or 4 Treatment-Emergent Adverse Event	7 (21.2)	21 (28.8)
Any Treatment-Emergent Study-Drug-Related Adverse Event	16 (48.5)	20 (27.4)
Any Grade 2, 3, or 4 Treatment-Emergent Study-Drug-Related Adverse Event	8 (24.2)	9 (12.3)
Any Grade 3 or 4 Treatment-Emergent Study-Drug-Related Adverse Event	4 (12.1)	0
Any Treatment-Emergent Serious Adverse Event	6 (18.2)	11 (15.1)
Any Treatment-Emergent Study-Drug-Related Serious Adverse Event	2 (6.1)	1 (1.4)
Any Treatment-Emergent Adverse Event Leading to Premature Study Drug Discontinuation	4 (12.1)	8 (11.0)
Treatment-Emergent Death	0	0

Programming Details: .../version1/prog/t-aebrief.sas v9.2 12MAY2015:10:39
Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 23

2.1.1. Common Adverse Events

2.1.1.1. Frequently Reported Adverse Events

In the STB cohort in Study GS-US-236-0118, any AE was reported for all subjects (33 subjects). The most frequently reported AEs were diarrhea (36.4%, 12 subjects); insomnia (21.2%, 7 subjects); and nausea, nasopharyngitis, and headache (each 18.2%, 6 subjects) (Table 5).

In the PI/COBI cohort, any AE was reported for 93.2% of subjects (68 subjects). The most frequently reported AEs were upper respiratory tract infection (20.5%, 15 subjects); nasopharyngitis (19.2%, 14 subjects), and bronchitis, diarrhea, and headache (each 13.7%, 10 subjects) (Table 5).

Table 5: GS-US-236-0118: Adverse Events Reported for at Least 10% of Subjects in Either Cohort (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a, b, c] n (%)	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Number of Subjects Experiencing Any Treatment-Emergent Adverse Event	*33 (100.0)*	*68 (93.2)*
Gastrointestinal Disorders	20 (60.6)	35 (47.9)
Diarrhoea	12 (36.4)	10 (13.7)
Nausea	6 (18.2)	9 (12.3)
Vomiting	5 (15.2)	4 (5.5)
Hepatobiliary Disorders	2 (6.1)	12 (16.4)
Hyperbilirubinaemia	0	8 (11.0)
Infections and Infestations	24 (72.7)	50 (68.5)
Nasopharyngitis	6 (18.2)	14 (19.2)
Urinary Tract Infection	5 (15.2)	3 (4.1)
Influenza	4 (12.1)	8 (11.0)
Sinusitis	4 (12.1)	7 (9.6)
Syphilis	4 (12.1)	1 (1.4)
Bronchitis	3 (9.1)	10 (13.7)
Upper Respiratory Tract Infection	1 (3.0)	15 (20.5)
Musculoskeletal and Connective Tissue Disorders	11 (33.3)	33 (45.2)
Back Pain	5 (15.2)	5 (6.8)
Pain in Extremity	4 (12.1)	4 (5.5)
Arthralgia	2 (6.1)	9 (12.3)
Nervous System Disorders	9 (27.3)	29 (39.7)
Headache	6 (18.2)	10 (13.7)
Psychiatric Disorders	12 (36.4)	16 (21.9)
Insomnia	7 (21.2)	6 (8.2)
Respiratory, Thoracic and Mediastinal Disorders	7 (21.2)	17 (23.3)
Cough	2 (6.1)	8 (11.0)
Skin and Subcutaneous Tissue Disorders	10 (30.3)	22 (30.1)
Rash	2 (6.1)	8 (11.0)

[a] Adverse events were mapped according to MedDRA 17.1.
[b] System organ class was presented alphabetically and preferred terms were presented by decreasing order based on the frequencies in Cohort 1.
[c] Multiple adverse events were counted only once per subject for each system organ class and preferred term, respectively.

Programming Details: .../version1/prog/t-ae.sas v9.2 12MAY2015:10:39
Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 24

2.1.1.2. Adverse Events by Severity

The majority of the AEs reported in this study were grade 1 or grade 2 in severity (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.3.2).

In the STB cohort, any grade 3 or 4 AE was reported for 21.2% of subjects (7 subjects). All grade 3 or 4 AEs were reported with single subject incidence. Grade 3 or 4 AEs considered related to study drug by the investigator were reported for 12.1% of subjects (4 subjects); the events were anemia, decreased creatinine renal clearance, increased gamma-glutamyl transferase (GGT), and wrist fracture.

In the PI/COBI cohort, any grade 3 or 4 AE was reported for 28.8% of subjects (21 subjects). Grade 3 AEs of hyperbilirubinemia were reported for 6 subjects (8.2%), and grade 3 AEs of

increased blood creatine phosphokinase and increased lipase were each reported for 2 subjects (2.7%); other grade 3 or 4 AEs were reported with single subject incidence. No grade 3 or 4 AEs were considered related to study drug by the investigator.

2.1.1.3. Adverse Events Considered Related to Study Drug

In the STB cohort, AEs considered related to study drug by the investigator were reported for 48.5% of subjects (16 subjects, Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.3.3). The most frequently reported AEs considered related to study drug by the investigator were nausea (4 subjects), vomiting (3 subjects), and blurred vision, diarrhea, upper abdominal pain, decreased glomerular filtration rate, increased blood creatine phosphokinase, hyperglycemia, osteopenia, osteoporosis, headache, and insomnia (each reported for 2 subjects).

In the PI/COBI cohort, AEs considered related to study drug by the investigator were reported for 27.4% of subjects (20 subjects). The most frequently reported AEs considered related to study drug by the investigator were nausea and headache (each reported for 4 subjects); diarrhea and abnormal dreams (each reported for 3 subjects).

2.1.2. Deaths

No treatment-emergent deaths were reported in Study GS-US-236-0118 (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.4).

2.1.3. Other Serious Adverse Events

In the STB cohort, any SAE was reported for 18.2% of subjects (6 subjects; Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.5). No SAEs were reported for >1 subject. Two SAEs were considered related to study drug by the investigator: anemia and increased blood creatine phosphokinase.

In the PI/COBI cohort, any SAE was reported for 15.1% of subjects (11 subjects). No SAEs were reported for >1 subject. One SAE was considered related to study drug by the investigator: nephrolithiasis.

2.1.4. Other Significant Adverse Events

Adverse events that led to discontinuation of study drug are described in this section.

In the STB cohort, 12.1% of subjects (4 subjects) discontinued study drug due to an AE (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.6). No AEs that led to study drug discontinuation were reported for >1 subject. Two AEs that led to study drug discontinuation were also reported as SAEs: Hepatitis C and Hodgkin disease, considered unrelated to study drug by the investigator. Other events that led to study drug discontinuation were nonserious but were considered to be related to study drug by the investigator.

In the PI/COBI cohort, 11.0% of subjects (8 subjects) discontinued study drug due to an AE. Two subjects (2.7%) discontinued study drug due to nausea and headache. No other AEs that led to study drug discontinuation were reported for >1 subject. All events that led to study drug

discontinuation were nonserious, and all except an event of abnormal glomerular filtration rate were considered related to study drug by the investigator.

2.1.5. Analysis of Adverse Events by Organ System or Syndrome

2.1.5.1. Adverse Events of Interest

Renal events were evaluated as prespecified AEs of interest for STB because renal toxicity has been associated with TDF administration, and because COBI, a component of STB, has been shown to inhibit tubular secretion of creatinine, thereby leading to an increase in serum creatinine and decrease in eGFR without an effect on actual GFR (aGFR). Tenofovir DF therapy may cause renal adverse reactions such as renal failure and PRT. These adverse reactions may warrant treatment discontinuation in a small number of patients (~1%); however, their occurrence appears to be well understood by HIV healthcare providers and is readily assessed using simple laboratory tests.

Selected bone fracture events were evaluated as prespecified AEs of interest because bone toxicity has been associated with TDF.

Renal and bone events are not considered AEs of interest for EVG or FTC.

2.1.5.1.1. Renal Events

2.1.5.1.1.1. Analysis Methodology

In order to ensure a comprehensive assessment of renal safety, a review was performed of all relevant data for subjects with clinically significant AEs (SAEs and AEs leading to study drug discontinuation) in the Renal and Urinary Disorders system organ class (SOC) and Renal Function Analyses high-level term (HLT) under Investigations SOCs. Individual cases were then grouped according to the sponsor's assessment of association with PRT. In addition, in order to identify subjects with subclinical kidney disease (ie, those with renal laboratory findings that are suggestive of PRT, as defined below, but without renal AEs), renal laboratory test results were thoroughly assessed. The laboratory definition used for subclinical kidney disease took into account the known effect of COBI on serum creatinine and the clinical relevance of changes in other analytes that are associated with PRT (urine protein, urine glucose, and serum phosphorus).

Renal Adverse Events and Association with Proximal Renal Tubulopathy

All clinically significant AEs (SAEs and AEs leading to study drug discontinuation) in the Renal and Urinary Disorders SOC and Renal Function Analyses HLT under Investigations SOCs, were included for initial assessment. If the AE verbatim terms and preferred terms (PTs) clearly indicated that the AEs were due to structural abnormalities, congenital abnormalities, neoplasm, infection (non-HIV), obstruction, inflammation, vascular disorder, kidney stone, or anatomically related to the ureter, bladder, or urethra, they were not considered to be renal AEs for the purpose of this analysis.

While the most important identified risk of TDF therapy is its association with PRT, there is no clearly established clinical definition of Fanconi syndrome or generalized PRT. Diagnosis is

generally made after careful clinical evaluation of a constellation of symptoms and laboratory assessments. Usually, PRT involves proteinuria (tubular), normoglycemic glycosuria, and hypophosphatemia due to inadequate renal tubular reabsorption, which can lead to changes in glomerular function.

For the data summary, subjects with clinically significant renal AEs (SAEs and AEs leading to study drug discontinuation) were subdivided according to whether the events were associated with PRT. The presence of PRT was determined from clinical and laboratory characteristics using the following criteria:

1) If the specific AE PT was renal tubular disorder or Fanconi syndrome acquired, the subject was considered to have PRT, regardless of laboratory findings.

2) For other subjects, renal safety-related laboratory parameters (serum creatinine, serum phosphate, urine protein, and urine glucose) were reviewed for magnitude of change relative to baseline and concurrence with other laboratory abnormalities. The following criteria for increases for each of the renal laboratory tests were applied:

   — Serum creatinine increase ≥0.4 mg/dL

   — 1-grade-level increase in hypophosphatemia

   — 2-grade-level increase in urine protein

   — 1-grade-level increase in urine glucose concurrent with serum glucose ≤100 mg/dL (normoglycemic glycosuria)

3) For subjects meeting any of these criteria, the clinical circumstances at the time of the laboratory abnormalities (eg, temporal association with study drug administration/discontinuation, medical history, alternative etiologies [eg, concurrent severe sepsis as the underlying reason for the renal event], and concomitant medications) were evaluated to determine whether the subject had PRT.

As a small reversible increase in serum creatinine (~0.1 mg/dL) that is not clinically significant is expected due to the inhibitory effect of COBI on renal tubular creatinine secretion, a threshold of 0.4 mg/dL was used to identify subjects with potentially meaningful glomerular dysfunction in the STB and PI/COBI cohorts. This threshold was derived from pooled data (n=701) from Studies GS-US-236-0102 and GS-US-236-0103 (Week 48 analyses) where the mean +2 SDs change in serum creatinine in the STB group was 0.4 mg/dL. The underlying assumption is that a serum creatinine increase ≥0.4 mg/dL is less likely to be solely due to the inhibitory effect of COBI on renal tubular creatinine secretion and warrants further investigation. The thresholds for other renal laboratory parameters were set considering the frequency in the HIV-1 infected population in general and in the study populations in studies of the COBI tablet and STB. For example, a 2-grade-level increase was set as a threshold for urine protein, as proteinuria is a common finding in the HIV-1 infected population in general.[1,2] However, none of these

thresholds should be used as an absolute criterion without clinical context (as outlined below) to determine the presence of kidney disease.

Subclinical Kidney Disease

In addition to assessment of subjects with renal AEs, all subjects were assessed for potential subclinical PRT that may not have been reported as AEs. A systematic analysis was conducted for renal laboratory abnormalities using the same criteria described above for serum creatinine, proteinuria, hypophosphatemia, and normoglycemic glycosuria. Confirmed laboratory abnormalities were defined as abnormalities observed at 2 consecutive postbaseline measurements.

2.1.5.1.1.2. Renal SAEs, Discontinuations due to Renal AEs, Renal AEs of Interest, and Association of Renal Events with PRT

No subjects were considered to have renal SAEs in Study GS-US-236-0118.

In the STB cohort, 3 subjects discontinued study drug due to renal AEs of decreased creatinine renal clearance, increased blood creatinine, and abnormal glomerular filtration rate. All 3 subjects had baseline $eGFR_{CG}$ <70 mL/min (baseline $eGFR_{CG}$ values were 50.47, 51.77, and 51.71 mL/min).

In the PI/COBI cohort, 3 subjects discontinued study drug due to renal AEs of abnormal glomerular filtration rate, decreased glomerular filtration rate, and proteinuria and hematuria. All subjects had baseline $eGFR_{CG}$ <70 mL/min (baseline $eGFR_{CG}$ values were 67.57, 51.40, and 59.12 mL/min).

None of the subjects who discontinued study drug had treatment-emergent laboratory findings consistent with PRT.

In addition, 1 subject in the PI/COBI cohort with pre-existing TDF-associated PRT discontinued TDF due to an AE of renal tubular disorder, but continued COBI until Week 48, when the subject discontinued COBI due to lack of efficacy.

Further details for these subjects are provided in Table 6.

Table 6: GS-US-236-0118: Subjects with Renal Events Not Associated with Proximal Renal Tubulopathy

Subject ID	Group	Renal Event Category	Baseline Characteristics[a]	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
0986-1010	STB	DC	4[redacted] yo black/white female; sonographic evidence of medical renal disease; baseline Cr 1.30 mg/dL ($eGFR_{CG}$ 50.47 mL/min)	Creatinine renal clearance decreased, Grade 3 (D227-505)	DC (D240)	At baseline (D1), SAE of blood creatine phosphokinase increased was reported. At Wk2 (D11), AE of hypothyroidism was reported (treated with levothyroxine). At Wk32 (D234), Cr increased to 1.56 mg/dL ($eGFR_{CG}$ 38.82 mL/min) without other findings to suggest PRT, such as hypophosphatemia, proteinuria, or normoglycemic glycosuria. After DC (D240), ddI+3TC+LPV/rtv was started (D241). Cr improved to 0.98 mg/dL ($eGFR_{CG}$ 64.21 mL/min) on D505. On D584 treatment with LPV/rtv discontinued and RAL was started. From D423 to D841, Cr ranged from 0.88 to 1.35 mg/dL ($eGFR_{CG}$ 71.86 to 49.61 mL/min). There were no other renal lab abnormalities. At the 30 day follow-up visit Cr was 0.93 mg/dL ($eGFR_{CG}$ 64.58 mL/min). Hypothyroidism may be the underlying cause of both blood CK increased and Cr increase.

Subject ID	Group	Renal Event Category	Baseline Characteristics[a]	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
4134-1013	STB	DC	6[redacted] yo American Indian or Alaska native male; history of hypertension, renal insufficiency, sonographic evidence of medical renal disease; concomitant amlodipine, atenolol, lisinopril; baseline Cr 1.49 mg/dL ($eGFR_{CG}$ 51.77 mL/min)	Blood creatinine increased, Grade 2 (D15-cont.)	DC (D59)	At Wk 2 (D13), an AE of diarrhea was reported. D20, Cr increased to 2.50 mg/dL ($eGFR_{CG}$ 29.77 mL/min). Study drug interrupted from D21 to D42 inclusive, during which Cr improved to 1.57 mg/dL ($eGFR_{CG}$ 48.78 mL/min) at D36. Study drug was restarted on D43. At Wk8 (D51), Cr increased again to 2.51 mg/dL ($eGFR_{CG}$ 29.74 mL/min). PRT unlikely as no other confirmed findings (hypophosphatemia, proteinuria, or normoglycemic glycosuria) were seen. At the time of DC (D59), Cr improved to 2.12 mg/dL ($eGFR_{CG}$ 35.11 mL/min); urine protein was +1. Subject discontinued the study and no further follow up is available.
5127-1015	STB	DC	7[redacted] yo black male; history of hypertension and hypercholesterolemia; baseline Cr 1.41 mg/dL ($eGFR_{CG}$ 51.71 mL/min)	Glomerular filtration rate abnormal (D1-232)	DC (D159)	At Wk 12 (D85), Cr 1.83 mg/dL ($eGFR_{CG}$ 40.15 mL/min). At Wk24 (D159), Cr improved to 1.55 mg/dL (45.94 mL/min) while continuing study drug. No other findings of PRT (hypophosphatemia, proteinuria, normoglycemic glycosuria) were seen. After DC, Cr improved further to 1.41 mg/dL on D281. Last available Cr at Wk96 (D673) was 1.57 mg/dL ($eGFR_{CG}$ 43.79 mL/min). Post DC regimen DRV/rtv was started on D160.

Subject ID	Group	Renal Event Category	Baseline Characteristics[a]	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
2817-2045	PI/co (TDF+3TC+ ATV/co)	DC	5[redacted] yo White male; history of hypertension; concomitant ramipril; baseline Cr 1.48 mg/dL ($eGFR_{CG}$ 59.12 mL/min), screening and baseline urine protein +1 to +2, baseline urine blood +1	Proteinuria, Grade 2 (D336-cont.); Hematuria, Grade 2 (D336-371)	DC (D343)	While on study drug, Cr ranged from 1.40 to 1.67 mg/dL and $eGFR_{CG}$ from 51.77 to 62.50 mL/min. AE of increased blood creatinine reported on D112 (cont). Urine protein ranged from +1 to +2 and urine blood from trace to +2. Unconfirmed normoglycemic glycosuria at Wk32 (D224) and 48 (D336). AE of glycosuria reported on D336-371. No hypophosphatemia was seen. PRT unlikely. Last available Cr after DC (D371), was 1.50 mg/dL ($eGFR_{CG}$ 57.64 mL/min). Post DC regimen of DRV/rtv was started on D344.
1480-2052	PI/co (ATV/co + FTC/TDF)	DC	7[redacted] yo White male; history of osteopenia and renal stones; baseline Cr 1.29 mg/dL ($eGFR_{CG}$ 51.40 mL/min), baseline urine protein +1	Decreased glomerular filtration rate, Grade 2 (D437-cont.)	DC (D451)	From D339 to D437, Cr increased (range: 1.39 to 1.65 mg/dL; $eGFR_{CG}$ 49.09 to 41.70 mL/min), with +2 normoglycemic glycosuria on D344, and consistent +1 proteinuria. Following DC, Cr decreased to 1.41 mg/dL ($eGFR_{CG}$ 48.80 mL/min) on D458, with +1 proteinuria. From D511 to D820, Cr improved (range 1.29 to 1.19 mg/dL; $eGFR_{CG}$ 54.03 to 59.27 mL/min), with +1 proteinuria at D760. PRT unlikely as no confirmed normoglycemic glycosuria or worsening of proteinuria. At the 30 day follow-up visit (D848), Cr had improved further (1.15 mg/dL, $eGFR_{CG}$ 60.28 mL/min). Post DC regimen of DRV+rtv+3TC was started on D452.

Subject ID	Group	Renal Event Category	Baseline Characteristics[a]	Renal AE (Duration)	Study Drug Status (Last Dose Day)	Clinical Course
0661-2014	PI/co (TVD+ ATV/co)	DC	4[redacted] yo White female; baseline Cr 0.79 mg/dL ($eGFR_{CG}$ 67.57 mL/min)	Glomerular filtration rate abnormal, Grade 2 (D529-cont.)	DC (D529)	At Wk72 (D503, 515), Cr 1.19, 0.96 mg/dL ($eGFR_{CG}$ 40.71, 50.12 mL/min), respectively. PRT unlikely as no other confirmed findings (hypophosphatemia, proteinuria, normoglycemic glycosuria). Unconfirmed +1 urine protein on D419 and 503. After DC (D552), Cr improved to 0.83 mg/dL ($eGFR_{CG}$ 55.35 mL/min) with trace proteinuria; +1 urine protein on D588. Last available Cr on D678 was 1.02 mg/dL ($eGFR_{CG}$ 45.79 mL/min), with +1 proteinuria, and serum phosphate 2.2 mg/dL. Post DC, TVD+ATV was continued and COBI switched to rtv (D552).
1480-2069	PI/co (ABC+TDF+ ATV/co)	DC	5[redacted] yo White male; history of PRT; baseline Cr 1.79 mg/dL ($eGFR_{CG}$ 56.84 mL/min). screening urine protein +2, baseline urine protein +1, baseline normoglycemic glycosuria +2	Renal tubular disorder, Grade 2 (D57-cont.)	DC (D356)	At screening and baseline (D-24 to 1), TDF-associated PRT likely present, given concurrent findings of proteinuria, normoglycemic glycosuria. Until TDF DC, these findings did not worsen, and no hypophosphatemia was seen. Post TDF DC, ABC+ATV/co was continued; TDF switched to MVC. On D356 COBI was discontinued due to lack of efficacy. Post COBI DC regimen of DRV+ETR+RAL+rtv was started on D357.

3TC, lamivudine; ABC, abacavir; AE, adverse event; ATV, atazanavir; CK, creatine kinase; COBI, cobicistat; Cr, serum creatinine; D, study day; DC, discontinuation of study drug; ddI, didanosine; DRV darunavir; $eGFR_{CG}$, estimated glomerular filtration rate (Cockcroft-Gault method); ETR, etravirine, LPV, lopinavir; MVC, maraviroc; PRT, proximal renal tubulopathy; RAL, raltegravir; rtv, low-dose ritonavir; SAE, serious adverse event; STB, Stribild; TDF, tenofovir disoproxil fumarate; TVD, Truvada; Wk, study week; yo, year-old

[a] Includes medical conditions, AEs, laboratory findings, and medications of potential relevance to renal abnormalities.

Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.2.2/Table 7-3

2.1.5.1.1.3. Laboratory Criteria to Identify Subjects with Subclinical Kidney Disease

No subjects met the criteria for treatment-emergent subclinical PRT. One subject receiving metformin for diabetes mellitus at baseline had more than 1 confirmed renal laboratory abnormality. Subject 1407-2035 had elevated serum creatinine (grade 3) with concurrent proteinuria (grade 2) at Week 120. Additionally, the subject had mostly hyperglycemic glycosuria at multiple visits (grades 1 to 3), as well as grade 2 hypophosphatemia at previous visits (Week 48 and Week 84).

2.1.5.1.2. Bone Fractures

Bone fractures were reported for 3 subjects in Study GS-US-236-0118, one of which had a nontraumatic fracture (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.3.4). Subject 0986-1028 (STB cohort) had a traumatic lumbar vertebral fracture on Day 177 with concomitant AEs of spinal osteoarthritis and osteopenia, followed by a nontraumatic spinal compression fracture on Day 433 with a concomitant AE of lordosis. All AEs were nonserious and considered related to study drug by the investigator except lumbar vertebral fracture, which was considered unrelated to study drugs. The nontraumatic spinal compression fracture was probably progression from the original finding of lumbar vertebral fracture. The other 2 fractures were both traumatic.

Additionally, 1 subject (ATV/COBI, non-TDF) had a skull fracture after a seizure; further information regarding trauma is unavailable as the subject was lost to follow-up (the event was an SAE).

2.2. Narratives

Narratives for deaths, SAEs, discontinuations due to AEs, and nontraumatic bone fracture AEs are provided in the CSR (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.2)

3. CLINICAL LABORATORY EVALUATIONS

This section provides an overall summary of laboratory findings in the safety analysis set in Study GS-US-236-0118. Data are provided for laboratory abnormalities and for laboratory assessments related to kidney function, liver function, and lipid parameters.

3.1. Laboratory Abnormalities

STB Cohort

In the STB cohort, graded laboratory abnormalities were reported for all subjects (33 subjects; Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.7.4). The majority of the abnormalities were grade 1 or grade 2 in severity. Grade 3 or 4 abnormalities were reported for 39.4% of subjects (13 subjects), most frequently for glycosuria, amylase (each reported for 3 subjects), and neutrophils, creatine kinase, GGT, hyperglycemia, hematuria (each reported for 2 subjects; Table 7).

PI/COBI Cohort

In the PI/COBI cohort, graded laboratory abnormalities were reported for all subjects with postbaseline laboratory measurements (72 subjects). Grade 3 or 4 abnormalities were reported for 50.0% of subjects (36 subjects; Table 7). The most frequently reported grade 3 or 4 abnormalities overall were hyperbilirubinemia (22 subjects), hematuria (7 subjects), and hyperglycemia (5 subjects).

Table 7: GS-US-236-0118: Grade 3 or 4 Laboratory Abnormalities (Safety Analysis Set)

n (%)	Cohort 1 STB (N=33)	Cohort 2 PI/COBI + 2 NRTIs (N=73)
Maximum Post-Baseline Toxicity Grade[a, b]	33	72
Grade 3 or 4	13 (39.4)	36 (50.0)
Hematology		
Hemoglobin	33	72
Grade 3 or 4	1 (3.0)	0
Neutrophils	33	72
Grade 3 or 4	2 (6.1)	0
Chemistry		
Amylase	33	72
Grade 3 or 4	3 (9.1)	4 (5.6)
Creatine Kinase (CK)	33	72
Grade 3 or 4	2 (6.1)	2 (2.8)
Creatinine	33	72
Grade 3 or 4	1 (3.0)	1 (1.4)
GGT	33	72
Grade 3 or 4	2 (6.1)	1 (1.4)
Lipase[c]	5	9
Grade 3 or 4	0	3 (33.3)
Phosphate (Hypophosphatemia)	33	72
Grade 3 or 4	0	1 (1.4)
Serum Glucose (Hyperglycemia)	33	72
Grade 3 or 4	2 (6.1)	5 (6.9)
Serum Sodium (Hyponatremia)	33	72
Grade 3 or 4	1 (3.0)	0
Total Bilirubin (Hyperbilirubinemia)	33	72
Grade 3 or 4	0	22 (30.6)
Total Cholesterol (Fasting, Hypercholesterolemia)	30	67
Grade 3 or 4	1 (3.3)	2 (3.0)
Uric Acid (Hyperuricemia)	33	72
Grade 3 or 4	1 (3.0)	1 (1.4)
Urinalysis[d]		
Urine Glucose (Glycosuria)	33	72
Grade 3 or 4	3 (9.1)	4 (5.6)
Urine RBC (Hematuria, Quantitative)	33	72
Grade 3 or 4	2 (6.1)	7 (9.7)

[a] Denominator for percentage is the number of subjects in the safety analysis set with at least 1 postbaseline laboratory value (for the test).
[b] Subjects were counted once for the maximum postbaseline severity for each laboratory test.
[c] Lipase test was only performed for subjects with serum amylase >1.5 x upper limit of normal.
[d] For urinalysis (ie, urine glucose and urine RBC), the highest grade is up to grade 3.

Programming Details: .../version1/prog/t-labtox.sas v9.2 Output file: t-labtox34.out 12MAY2015:10:45
Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 35

3.2. Renal Laboratory Parameters

Renal laboratory parameters were evaluated because renal events have been associated with TDF administration. In addition, COBI inhibits tubular secretion of creatinine, resulting in a small increase in serum creatinine, which results in a small decrease in creatinine-based eGFR (eg, $eGFR_{CG}$), but COBI does not affect aGFR when measured with a probe drug (iohexol) (Study GS-US-216-0121).

3.2.1. Serum Creatinine

STB Cohort

In the STB cohort in Study GS-US-236-0118, increases in median values for serum creatinine were noted as early as Week 2 (baseline median 1.12 mg/dL; the median change from baseline at Week 2 was 0.16 mg/dL; Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.2.3.1), after which they generally stabilized and were nonprogressive through Week 96 (median change from baseline at Week 96 was 0.17 mg/dL). Graded serum creatinine abnormalities were reported for 10 of 33 subjects (30.3%); all but 1 were grade 1 or grade 2 in severity. One subject had a grade 3 serum creatinine abnormality.

PI/COBI Cohort

In the PI/COBI cohort, small increases in median values for serum creatinine were noted as early as Week 2 (baseline median 1.23 mg/dL; the median change from baseline at Week 2 was 0.05 mg/dL), after which they generally stabilized and were nonprogressive through Week 96 (median change from baseline at Week 96 was 0.05 mg/dL). The small changes seen in median values for serum creatinine are not considered clinically relevant. Graded serum creatinine abnormalities were reported for 23 of 72 subjects (31.9%); all but 1 were grade 1 or grade 2 in severity. One subject had grade 3 serum creatinine abnormalities.

3.2.2. eGFR

STB Cohort

In the STB cohort in Study GS-US-236-0118, decreases in median values for $eGFR_{CG}$ were noted as early as Week 2 (baseline median 72.9 mL/min; the median change from baseline at Week 2 was &8.9 mL/min; Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.2.1.1), after which they generally stabilized and were nonprogressive through Week 96 (median changes from baseline: at Week 24, &5.2 mL/min; at Week 48, &7.6 mL/min; at Week 96, &7.9 mL/min; Table 8). The pattern of changes in other creatinine-based eGFR endpoints, ie, $eGFR_{MDRD}$ and $eGFR_{CKD\text{-}EPI,\ creatinine}$, was consistent with that for $eGFR_{CG}$.

There were no notable median changes from baseline in cystatin C-based eGFR endpoints, ie, $eGFR_{CKD\text{-}EPI,\ cysC,\ adjusted}$ (baseline median 76.9 mL/min/1.73 m^2; median changes from baseline: at Week 24, 0.3 mL/min/1.73 m^2; at Week 48, 1.6 mL/min/1.73 m^2; at Week 96, 12.6 mL/min/1.73 m^2) and $eGFR_{CKD\text{-}EPI,\ cysC,\ unadjusted}$ (baseline median 77.6 mL/min/1.73 m^2; median changes from baseline: at Week 24, 0.3 mL/min/1.73 m^2; at Week 48, 1.9 mL/min/1.73 m^2; at Week 96, 12.4 mL/min/1.73 m^2).

PI/COBI Cohort

In the PI/COBI cohort, the small changes seen in eGFR are not considered clinically relevant. The absence of clinically relevant changes was as expected given subjects switched to COBI from low-dose ritonavir (rtv), and the 2 pharmacokinetic enhancers similarly inhibit the tubular secretion of creatinine. Small decreases in median values for $eGFR_{CG}$ were noted as early as Week 2 (baseline median 71.4 mL/min; the median change from baseline at Week 2 was &2.8 mL/min), after which they generally stabilized and were nonprogressive through Week 96 (median changes from baseline: at Week 24, &3.7 mL/min; at Week 48, &3.8 mL/min; at Week 96, &5.0 mL/min; Table 8). The pattern of changes in other eGFR endpoints was consistent with that for $eGFR_{CG}$, both for creatinine- and cystatin C-based endpoints.

Table 8: GS-US-236-0118: Changes from Baseline in GFR (Safety Analysis Set)

	Cohort 1 STB (N=33)						Cohort 2 PI/COBI + 2 NRTIs (N=73)					
	N	Mean	SD	Q1	Median	Q3	N	Mean	SD	Q1	Median	Q3
Creatinine-based Endpoints												
$eGFR_{CG}$ (mL/min)[a]												
Baseline	33	72.6	14.56	64.7	72.9	81.1	73	71.4	12.55	61.9	71.4	80.7
Change at Week 2	32	&7.9	9.19	&11.3	&8.9	&5.8	67	&3.6	8.17	&8.3	&2.8	1.6
Change at Week 4	33	–6.1	11.50	–12.7	–5.5	1.1	72	–3.4	8.32	–8.3	–3.7	1.1
Change at Week 24	30	&5.8	10.18	&13.2	&5.2	1.0	67	&2.3	8.41	&7.4	&3.7	2.0
Change at Week 48	28	&6.9	9.00	&12.2	&7.6	&2.2	63	&4.1	9.50	&9.0	&3.8	0.8
Change at Week 96	25	&9.5	9.65	&14.2	&7.9	&4.1	50	&6.2	9.07	&13.0	&5.0	0.1
$eGFR_{MDRD}$ (mL/min/1.73 m^2)[b]												
Baseline	33	74.7	16.80	64.3	77.1	87.2	73	66.5	14.59	56.2	65.8	75.2
Change at Week 2	32	&10.0	10.51	&14.9	&9.3	&7.0	67	&3.7	8.52	&8.4	&2.5	1.7
Change at Week 4	33	–8.0	13.33	–17.4	–7.8	–3.5	72	–3.9	8.67	–8.5	–3.7	0.6
Change at Week 24	30	–8.8	12.11	–16.3	–7.4	–1.2	67	–2.3	9.08	–7.5	–3.4	1.9
Change at Week 48	28	–11.8	9.92	–17.6	–12.1	–6.5	63	–3.7	9.97	–8.1	–3.9	1.4
Change at Week 96	25	&13.2	10.35	&17.7	&12.9	&5.4	50	&5.5	9.84	&13.7	&2.8	2.2
$eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2)[c]												
Baseline	33	75.2	17.13	65.0	79.2	88.1	73	67.0	15.68	55.3	67.3	77.3
Change at Week 2	32	&10.3	10.67	&15.8	&10.1	&7.5	67	&3.9	9.01	&8.8	&2.6	1.8
Change at Week 4	33	–8.2	13.79	–17.5	–7.5	–3.9	72	–4.1	9.22	–8.7	–4.1	0.7
Change at Week 24	30	–9.2	12.61	–17.4	–6.8	–1.4	67	–2.5	9.49	–8.1	–3.7	1.8
Change at Week 48	28	–12.3	10.02	–17.7	–13.1	–7.0	63	–4.1	10.43	–8.9	–4.4	1.4
Change at Week 96	25	–14.0	10.44	–19.5	–13.2	–6.3	50	–6.2	10.40	–15.0	–3.4	–1.7
Cystatin C-based Endpoints												
$eGFR_{CKD\text{-}EPI,\ cysC,\ adjusted}$ (mL/min/1.73 m^2)[d]												
Baseline	33	77.4	24.04	61.7	76.9	90.1	73	79.9	18.69	67.1	78.2	92.4
Change at Week 2	32	2.9	17.09	&6.1	&0.5	11.0	67	&2.6	8.21	&9.4	&2.2	4.3
Change at Week 4	33	–2.2	10.68	–8.0	–2.3	4.2	72	–1.4	11.34	–10.6	–1.5	6.5
Change at Week 24	30	0.3	13.91	–3.7	0.3	5.7	67	–3.2	9.24	–6.7	–2.8	1.9
Change at Week 48	28	0.8	14.22	–8.0	1.6	6.9	63	–4.4	11.10	–11.7	–4.7	3.9
Change at Week 96	25	14.3	31.62	–0.9	12.6	19.2	50	–0.1	12.61	–7.4	–2.8	8.9

	Cohort 1 STB (N=33)						Cohort 2 PI/COBI + 2 NRTIs (N=73)					
	N	**Mean**	**SD**	**Q1**	**Median**	**Q3**	**N**	**Mean**	**SD**	**Q1**	**Median**	**Q3**
$eGFR_{CKD\text{-}EPI,\ cysC,\ unadjusted}$ (mL/min/1.73 m^2)[e]												
Baseline	33	76.6	23.48	61.7	77.6	90.5	73	81.0	19.00	67.0	78.6	94.4
Change at Week 2	32	3.2	18.39	&6.2	&0.5	10.7	67	&2.8	8.70	&8.9	&2.2	4.5
Change at Week 4	33	–2.5	10.85	–8.1	–2.6	4.3	72	–1.4	11.71	–11.1	–1.5	6.7
Change at Week 24	30	0.1	14.53	–3.3	0.3	6.1	67	–3.2	9.62	–6.8	–2.7	1.9
Change at Week 48	28	0.8	14.43	–7.1	1.9	6.9	63	–4.4	11.44	–12.0	–4.7	4.3
Change at Week 96	25	15.3	33.88	–0.6	12.4	20.4	50	0.4	13.45	–7.3	–2.4	9.4

[a] $eGFR_{CG}$ (mL/min) = [(140 – age (years)) × weight (kg) × (0.85 if female)] / (serum creatinine (mg/dL) × 72)

[b] $eGFR_{MDRD}$ (mL/min/1.73m^2) = 186 × serum creatinine$^{-1.154}$ (mg/dL) × age$^{-0.203}$ (yrs) × (0.742 if female) × (1.21 if Black)

[c] $eGFR_{CKD\text{-}EPI,\ creatinine}$ (mL/min/1.73 m^2) = 141 × min(Scr/κ, 1)$^{\alpha}$ × max(Scr/κ, 1)$^{-1.209}$ × 0.993^{age} × (1.018 if female) × (1.159 if Black); where κ is 0.7 for females and 0.9 for males, α is &0.329 for females and &0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

[d] $eGFR_{CKD\text{-}EPI,\ cysC,\ adjusted}$ (mL/min/1.73 m^2) = 127.7 × cysC$^{-1.17}$ (mg/L) × age$^{-0.13}$ (yrs) × (0.91 if female) × (1.06 if Black)

[e] $eGFR_{CKD\text{-}EPI,\ cysC,\ unadjusted}$ (mL/min/1.73 m^2) = 76.7 × cysC$^{-1.19}$ (mg/L)

Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Tables 8, 9, 10, 11, and 12

3.2.3. Serum Phosphorus

STB Cohort

In the STB cohort in Study GS-US-236-0118, median serum phosphorus values were within normal ranges throughout the study; there were no clinically relevant changes from baseline in median values (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.2.3.3).

Hypophosphatemia was reported for 3 of 33 subjects (9.1%); grade 1 for 2 subjects, and grade 2 for 1 subject. None was reported as an AE, or a confirmed abnormality.

PI/COBI Cohort

In the PI/COBI cohort, median serum phosphorus values were within normal ranges throughout the study; there were no clinically relevant changes from baseline in median values.

Hypophosphatemia was reported as a laboratory abnormality for 10 of 72 subjects (13.9%); all but 1 were grade 1 or grade 2 in severity. One subject had grade 3 hypophosphatemia, in addition to an earlier AE of grade 1 hypophosphatemia. Confirmed hypophosphatemia was reported for 1 subject.

3.2.4. Glycosuria

STB Cohort

In the STB cohort in Study GS-US-236-0118, glycosuria was reported as a graded laboratory abnormality for 5 of 33 subjects (15.2%; Module 5.3.5.2/GS-US-236-0118 Final CSR/ Section 7.2.3.5). Glycosuria was grade 2 in severity for 2 subjects and grade 3 in severity for 3 subjects. All subjects with glycosuria had a history of diabetes, hyperglycemic glycosuria, glycosuria at baseline, or isolated and transient occurrences. One subject had confirmed normoglycemic glycosuria (grade 2).

Glycosuria was reported as an AE for 1 subject (0986-1033) with a medical history of diabetes mellitus; the event began on Day 29, was nonserious, grade 1 in severity, and was not considered related to study drug by the investigator. No action was taken with study drug, and the event resolved (Day 55). Glycosuria was also reported as an AE with onset on Day 169. The event was nonserious, grade 1 in severity, and was considered related to study drug by the investigator. No action was taken with study drug, and the event resolved with medication on Day 225. The subject had +2 urine glucose (grade 1) on Day 29 and +4 urine glucose (grade 3) on Day 169.

PI/COBI Cohort

In the PI/COBI cohort, glycosuria was reported as a graded laboratory abnormality for 12 of 72 subjects (16.7%). Glycosuria was grade 1 in severity for 7 subjects, grade 2 in severity for 1 subject, and grade 3 in severity for 4 subjects. All subjects with glycosuria had a history of diabetes, hyperglycemic glycosuria, glycosuria at baseline, or isolated and transient occurrences. No confirmed normoglycemic glycosuria was reported.

Glycosuria was reported as an AE for 1 subject (2817-2045, ATV/COBI); the event began on Day 336, was nonserious, grade 1 in severity, and was considered related to study drug by the investigator. No action was taken with study drug; however, study drug was discontinued on Day 343 due to concurrent events of proteinuria and hematuria. The event resolved on Day 371. The subject had normal or trace urine glucose values at visits through Day 168, +1 urine glucose on Day 224, and trace urine glucose on Day 280. Urine glucose was +2 (grade 1) on Day 336 when the AE was reported, and was normal on Day 371.

3.2.5. Proteinuria

STB Cohort

In the STB cohort in Study GS-US-236-0118, proteinuria !trace was present at baseline in 18 subjects (54.5%; Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.2.3.6). Treatment-emergent graded proteinuria was reported as a laboratory abnormality for 19 subjects (57.6%). All proteinuria was grade 1 or grade 2 in severity, and tended to be isolated and transient occurrences. Confirmed 2-grade increase from baseline in proteinuria was reported for 1 subject.

Proteinuria was reported as an AE for 1 subject (0986-1010); the event began on Day 15, was nonserious, grade 1 in severity, and was not considered related to study drug by the investigator. The subject had a single occurrence of proteinuria (+2) on Day 15. Urine protein values were negative at baseline, trace on Day 22, and negative on Day 29 and subsequent visits. No action was taken with study drug, and the event resolved (Day 29).

PI/COBI Cohort

In the PI/COBI cohort, proteinuria !trace was present at baseline in 37 subjects (50.7%). Treatment-emergent graded proteinuria was reported as a laboratory abnormality for 33 of 72 subjects (45.8%). All proteinuria was grade 1 or grade 2 in severity, and tended to be isolated and transient occurrences. Confirmed 2-grade increase from baseline in proteinuria was reported for 2 subjects (0661-2021 and 1407-2035).

Proteinuria was reported as an AE for 2 subjects. Subject 2817-2045 (ATV/COBI) had an event of proteinuria on Day 336, which was nonserious, grade 2 in severity, and considered related to study drug by the investigator. Study drug was discontinued due to the event (and concurrent hematuria; there was also a concurrent AE of glycosuria) on Day 343; the event was ongoing. The subject had +1 (grade 1) proteinuria at screening, +2 (grade 2) proteinuria at baseline, and +1 or +2 proteinuria at all visits (+2 on Day 336 when the AE was reported). Subject 1480-2069 (abacavir +ATV/COBI+TDF) had an event of proteinuria on Day 85, which was nonserious, grade 1 in severity, and considered unrelated to study drug by the investigator.

3.2.6. Urine Fractional Excretion of Phosphate

STB Cohort

In the STB cohort in Study GS-US-236-0118, small increases in median values for urine fractional excretion of phosphate ($FEPO_4$) were noted as early as Week 2 (baseline median 12.2%; the median change from baseline at Week 2 was 4.1%), after which they generally stabilized and were nonprogressive through Week 96 (median change from baseline at Week 96 was 3.8%; Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.2.3.4). The small changes in $FEPO_4$ are not considered clinically relevant; they are unlikely to represent a true increase in renal phosphate excretion as the formula used to calculate $FEPO_4$ is influenced by serum creatinine.

PI/COBI Cohort

In the PI/COBI cohort, small increases in median values for $FEPO_4$ were noted as early as Week 2 (baseline median 15.9%; the median change from baseline at Week 2 was 2.2%), after which they generally stabilized and were nonprogressive through Week 96 (median change from baseline at Week 96 was 1.9%). The small changes in $FEPO_4$ are not considered clinically relevant; they are unlikely to represent a true increase in renal phosphate excretion as the formula used to calculate $FEPO_4$ is influenced by serum creatinine.

3.3. Liver-Related Laboratory Tests

In the STB cohort in Study GS-US-236-0118, no subjects had elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >3 × upper limit of the normal range (ULN) along with elevations in total bilirubin >2 × ULN but alkaline phosphatase ≤1.5 × ULN (Module 5.3.5.2/ GS-US-236-0118 Final CSR/Section 7.7.3).

In the PI/COBI cohort, 1 subject who received ATV/COBI had elevations in AST or ALT >3 × ULN along with elevations in total bilirubin >2 × ULN but alkaline phosphatase ≤1.5 × ULN. This subject entered the study with hyperbilirubinemia and elevated ALT (both grade 2 at screening and grades 3 and 1 at baseline, respectively), and completed the study.

No Hy's law cases were identified.

3.4. Fasting Glucose and Lipid Parameters

There were no clinically relevant changes from baseline in fasting glucose and lipid parameters in either cohort in Study GS-US-236-0118 (Module 5.3.5.2/GS-US-236-0118 Final CSR/ Section 7.7.2).

4. VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY

Clinically significant electrocardiogram (ECG) abnormalities were infrequent in Study GS-US-236-0118 (Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 7.8.2).

5. SAFETY IN SPECIAL GROUPS AND SITUATIONS

5.1. Intrinsic Factors

No new information is submitted.

5.2. Extrinsic Factors

No new information is submitted.

5.3. Drug Interactions

No new information is submitted.

5.4. Use in Pregnancy and Lactation

No new information is submitted.

5.5. Overdose

No new information is submitted.

5.6. Drug Abuse

No new information is submitted.

5.7. Withdrawal and Rebound

No new information is submitted.

5.8. Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No new information is submitted.

6. POSTMARKETING DATA

No new information is submitted.

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APPENDIX

Appendix 1: Tabular Summary of Study GS-US-236-0118

Type of Study	Study Number	Study Objective(s)	Study Design	Study and Control Drug Regimens	Duration of Treatment	Number of Subjects by Treatment	Study Population/ Entry Criteria	Study Status; Type of Report
Safety and Efficacy	GS-US-236-0118	Primary objective: To evaluate the effect of COBI-containing regimens on renal parameters at Week 24 Secondary objectives: To evaluate the safety and tolerability of COBI-containing regimens To evaluate the long-term effect of COBI-containing regimens on renal parameters To measure the proportion of subjects achieving virologic response at Weeks 24, 48, and 96 (HIV-1 RNA < 50 copies/mL, snapshot analysis)	Phase 3, open-label, multicenter, multiple-cohort	Cohort 1 (STB): coformulated EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg, orally, once daily with food at approximately the same time each day Cohort 2 (PI/co): 1 × 150-mg COBI tablet orally, once daily with food at approximately the same time each day. All other regimen components (ATV or DRV + 2 NRTIs) were as prescribed by the investigator	96 weeks. Subjects who completed at least 96 weeks of study treatment continued to take their study regimen and attend visits every 12 weeks until all subjects discontinued from the study, or STB or COBI were commercially available in the applicable country.	Planned: 100 (33 subjects/cohort) Analyzed: Safety and full analysis sets: 106 subjects (33 STB; 73 PI/co [51 ATV/co+2NRTIs; 22 DRV/co+2NRTIs]); Week 96 full analysis set: 27 STB, 54 PI/co	HIV-1 infected adults with mild to moderate renal impairment ($eGFR_{CG}$ of 50 to < 90 mL/min), with stable renal function, meeting the following criteria: STB: ARV treatment-naive with HIV-1 RNA ! 1000 copies/mL at screening PI/co: ARV treatment-experienced, receiving a regimen of ATV 300 mg/rtv 100 mg, + 2 NRTIs or DRV 800 mg/rtv 100 mg + 2 NRTIs for ≥ 6 mo prior to screening; with stable virologic suppression (HIV-1 RNA < 50 copies/mL)	Study completed; Module 5.3.5.2, Final CSR

Janssen Research & Development

Clinical Summary
Literature References

Darunavir/Cobicistat 800/150 mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

Status: Approved
Date: 16 October 2013
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
Document no. & version: EDMS-ERI-70745344; 2.0

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REFERENCES

All literature references are considered supportive but have been included for the convenience of the reviewer.

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Janssen Research & Development

Clinical Summary
Literature References

Cobicistat-containing Highly Active Antiretroviral Regimens in HIV-1 Infected Patients with Mild to Moderate Renal Impairment

DRV/COBI (darunavir/cobicistat)

Status: Approved
Date: 25 September 2015
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
Document no. & version: EDMS-ERI-112194951, 1.0

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*Available on Request

Approved, Date: 25 September 2015

Janssen Research & Development

Tabular Listing of All Clinical Studies

Darunavir/Cobicistat 800/150 mg Fixed Dose Combination Tablet for the Treatment of HIV-1 Infection in Adults

DRV/COBI (darunavir/cobicistat)

Status: Approved
Date: 10 April 2014
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
EDMS no. and version: EDMS-ERI-70622875, 3.0

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5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C102 (Belgium: 1)	Open-label, randomized, 2-way crossover study. To investigate the effect of food on relative bioavailability of darunavir (DRV).	Healthy volunteers N=12	- DRV, oral solution, single dose, 800 mg. - Fasted - Fed	Completed Full report (available upon request) 5.3.1.1
1	TMC114-C114 (France: 1)	Open-label, randomized, 4-way crossover study. To establish absolute bioavailability of DRV.	Healthy volunteers N=8	- DRV: single 1-hour intravenous infusion of 150 mg. - DRV: single oral dose of 600 mg. - DRV: single 1-hour intravenous infusion of 150 mg on Day 3 + ritonavir 100 mg twice daily, oral, Days 1 to 6. - DRV: single oral dose of 600 mg on Day 3 + ritonavir 100 mg twice daily, oral, Days 1 to 6.	Completed Full report (available upon request) 5.3.1.1
1	TMC114-C118 (Belgium: 1)	Open-label, randomized, 4-way crossover study. To assess the relative bioavailability for 2 formulations of DRV with low-dose ritonavir, and the effect of food.	Healthy volunteers N=16	- DRV: single dose, 400 mg, oral solution on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 4. - Fasted - Fed - DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, Days 1 to 4. - Fasted - Fed	Completed Full report (available upon request) 5.3.1.1

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C143 (Belgium: 1)	Open-label, 2-panel, randomized, 3-way crossover study. To investigate the effect of food on the relative bioavailability of DRV (F014) coadministered with low-dose ritonavir.	Healthy volunteers N=24	In all treatments, a single oral dose of DRV (F014) 400 mg was administered on Day 3; ritonavir oral dose of 100 mg twice daily on Days 1 to 5. - Treatment A: after a standard breakfast - Treatment B: in fasted state - Treatment C: after a high-fat breakfast - Treatment D: after a nutritional drink - Treatment E: after a croissant with coffee	Completed Synopsis Full report 5.3.1.1
1	TMC114IFD1001 (Belgium: 1)	Open-label, randomized, 3-way crossover study. To assess the relative bioavailablity for 2 formulations of the darunavir/cobicistat (DRV/COBI) fixed dose combination tablet (G003 and G004) compared to coadministration of DRV and low-dose ritonavir as single agents.	Healthy volunteers N=36	- Treatment A: DRV oral dose of 800 mg in combination with 100 mg ritonavir once daily for 10 consecutive days, under fed conditions. - Treatment B: DRV/COBI oral dose of 800/150 mg administered as tablet G003 once daily for 10 consecutive days, under fed conditions. - Treatment C: DRV/COBI oral dose of 800/150 mg administered as tablet G004 once daily for 10 consecutive days, under fed conditions. There was a washout of at least 7 days between subsequent treatment sessions.	Completed Synopsis Full report 5.3.1.1

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.1 Bioavailability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-236-0105 (United States: 1)	Randomized, open-label, single-center, single-dose, 6-sequence, 3-treatment, 3-period crossover study. To evaluate the effect of food (a high-calorie/high-fat meal or a light meal) on the pharmacokinetics of elvitegravir (EVG), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and COBI when administered as a single tablet regimen containing EVG/COBI/FTC/ TDF.	Healthy volunteers N=24	An oral single dose of a single tablet regimen containing EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg, administered under the following meal conditions: Treatment A: fasted Treatment B: light meal Treatment C: high-calorie/high-fat meal	Completed Synopsis Full report 5.3.1.1

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C103 (Belgium: 1)	Open-label, randomized, 3-way crossover study. To assess the effect on food on systemic exposure of DRV.	Healthy volunteers N=27	- Treatment A: DRV (TF019): single dose, 800 mg, oral solution, fasted. - Treatments B (fasted) and C (fed): - DRV (TF036): single dose, 800 mg, oral tablet. - DRV (TF041): single dose, 800 mg, oral suspension (powder). - DRV (TF038): single dose, 800 mg, oral capsules.	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C116 (France: 1)	Open-label, 2-panel, randomized, 2-way crossover study. To assess the effect of food on relative bioavailability of DRV (TF014) coadministered with low-dose ritonavir.	Healthy volunteers N=49	Panel 1: - DRV (F002): single oral 600-mg dose. - DRV (F016): single oral 600-mg dose. Panel 2: - DRV (F001): single oral 1200-mg dose. - DRV (F016): single oral 1200-mg dose. In each treatment period: ritonavir 100 mg twice daily, oral, on Days 1 to 5, DRV is administered on Day 3 in fasted state.	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C117 (Belgium: 1)	Open-label, randomized, 4-way crossover study. To determine the relative bioavailability for 4 formulations of DRV with low-dose ritonavir.	Healthy volunteers N=16	- DRV (TF019): single 300-mg dose as oral solution. - DRV (TF042): single oral 300-mg dose as capsule. - DRV (TF043): single oral 300-mg dose as capsule. - DRV (TF044): single oral 300-mg dose as capsule. In each treatment period: ritonavir 100 mg twice daily, oral, on Days 1 to 4, DRV is administered on Day 3 in fasted state.	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C136 (Belgium: 1)	Open-label, randomized, 3-way crossover study. To determine the relative bioavailability for 3 formulations of DRV with low-dose ritonavir.	Healthy volunteers N=15	- DRV (TF019): single oral 300-mg dose as oral solution. - DRV (TF051): single oral 300-mg dose as capsule. - DRV (TF052): single oral 300-mg dose as capsule. In each treatment period: rionavir 100 mg twice daily, oral, on Days 1 to 4, DRV is administered on Day 3 in fasted state.	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C144 (Belgium: 1)	Open-label, randomized, 4-way crossover study. To determine the relative bioavailability for 4 formulations of DRV with low-dose ritonavir.	Healthy volunteers N=16	- DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 5; Formulations: F001, F011, F012, F013.	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C148 (Belgium: 1)	Open-label, randomized, 4-way crossover study. To determine the relative bioavailability for 4 formulations of DRV with low-dose ritonavir.	Healthy volunteers N=16	- DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 5. Formulations: TF036A, TF036B, TF036C, TF036.	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C154 (Belgium: 1)	Open-label, randomized, 3-way crossover study. To assess the effect of different particle size distributions of drug substance on relative bioavailability of DRV in the presence of low-dose ritonavir.	Healthy volunteers N=24	- DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 5. Formulations: F002 (Batch X), F002 (Batch Y), F002 (Batch Z).	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C156 (Belgium: 1)	Open-label, randomized, 2-way crossover study. To determine the relative bioavailability of DRV formulated as tablets using 2 different batches of drug substance.	Healthy volunteers N=16	- DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 5. Formulations: F002, F009.	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD

1	TMC114-C162
	(France: 8)
		Open-label, randomized, 2-panel, 2-way crossover study.
		To assess the rate and extent of absorption of DRV following administration of 2 tablet strengths (in presence of low-dose ritonavir) under fasted or fed conditions.
			Healthy volunteers
			N=96
				- DRV: 2 x 300 mg (F016), oral tablet, on Day 3 + ritonavir 100 mg twice daily, oral, Days 1 to 5.
				  - Fasted
				  - Fed
				- DRV: single oral dose of 600 mg (F032) on Day 3 + ritonavir 100 mg twice daily, oral, Days 1 to 5.
				  - Fasted
				  - Fed
					Completed
					Full report (available upon request)
					5.3.1.2

1	TMC114-C166 (The Netherlands: 1)	Open-label, randomized, crossover study. To assess the relative bioavailability of 4 formulations of DRV with low-dose ritonavir.	Healthy volunteers N=56	DRV (Treatment A, B, C, D, E, F, G): single oral dose on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 5. <u>Panel 1:</u> - Treatment A: 400 mg, F001 tablet. - Treatment B: 400 mg, F021 tablet. <u>Panel 2:</u> - Treatment C: 600 mg, F002 tablet. - Treatment D: 600 mg, F001 + F002 tablets . - Treatment E: 600 mg, F016 tablet. <u>Panel 3:</u> - Treatment F: 800 mg, F001 tablet. - Treatment G: 800 mg, F021 tablet. Formulations: as F001, F002, F016, and F021.	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C167 (The Netherlands: 1)	Open-label, randomized, crossover study. To compare the oral bioavailability of an improved tablet formulation of DRV (F026) to that of the Phase 3/commercial tablet formulation (F016) in the presence of low-dose ritonavir and under fasted conditions.	Healthy volunteers N=32	In all panels, ritonavir was administered at an oral dose of 100 mg twice daily from Day 1 to Day 5: <u>Panel 1:</u> - Treatment A: single, oral dose of 600 mg DRV (F016) on Day 3. - Treatment B: single, oral dose of 600 mg DRV (F026, batch PD1684) on Day 3. <u>In Panel 2:</u> - Treatment B - Treatment C: single, oral dose of 600 mg DRV (F026, batch PD1752 with larger particle size) on Day 3.	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C168 (Belgium: 1)	Open-label, randomized, 2-way crossover study. To assess the relative bioavailability of 4 formulations of DRV with low-dose ritonavir.	Healthy volunteers N=48	DRV (Treatment A, B, C, D): single oral dose on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1 to 5. <u>Panel 1:</u> - Treatment A: 600 mg, F002 tablet. - Treatment B: 600 mg, F016 tablet. <u>Panel 2:</u> - Treatment C: 1200 mg, F001 tablet. - Treatment D: 1200 mg, F016 tablet.	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C169 (The Netherlands: 1)	Open-label, randomized, crossover study. To compare the oral bioavailability of a suspension formulation of DRV to that of the commercial 300 mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions, and to assess multiple dose pharmacokinetics of the suspension formulation of DRV in the presence of low-dose ritonavir.	Healthy volunteers N=23	- Treatment A: Days 1 to 5 ritonavir 100 mg twice daily + single dose of 600 mg DRV (2 x F016) on Day 3 (fed conditions). - Treatment B: Days 1 to 5 ritonavir 100 mg twice daily + single dose of 600 mg DRV (F051) on Day 3 (fasted conditions). - Treatment C: Days 1 to 5 ritonavir 100 mg twice daily + single dose of 600 mg DRV (F051) on Day 3 (fed conditions). - Treatment D: Days 1 to 9 ritonavir 100 mg twice daily and 600 mg DRV (F051) twice daily on Days 1 to 6, and an additional morning dose on Day 7 (fed conditions).	Completed Full report (available upon request) 5.3.1.2
1	TMC114-C176 (Germany: 1)	Open-label, randomized, 2-panel, 2-way crossover study. To establish the bioequivalence of a 800-mg tablet formulation of DRV to that of the commercial 400-mg tablet formulation in the presence of low-dose ritonavir, under fasted and fed conditions.	Healthy volunteers N=128	DRV (Treatment A, B, C, D): single oral dose on Day 3 + ritonavir 100 mg once daily on Days 1 to 5. Panel 1: fasted conditions: - Treatment A: 800 mg DRV (2 x 400 mg oral tablet [F030]). - Treatment B: 800 mg DRV (800 mg oral tablet [G002]). Panel 2: fed conditions: - Treatment C: 800 mg DRV (2 x 400 mg oral tablet [F030]). - Treatment D: 800 mg DRV (800 mg oral tablet [G002]).	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C182 (Poland: 1)	Open-label, randomized, single dose crossover study. To compare the oral bioavailability of a prototype tablet formulation of DRV 800 mg (G002) to that of the commercial 400 mg tablet formulation (F030) under fed and fasted conditions and in the presence of low-dose ritonavir.	Healthy volunteers N=32	DRV (Treatments A, B, C, D): single oral dose on Day 3 + ritonavir 100 mg once daily on Days 1 to 5. <u>Panel 1:</u> fed conditions: - Treatment A: 800 mg DRV (2 x 400 mg oral tablet [F030]). - Treatment B: 800 mg DRV (800 mg oral tablet [G002]). <u>Panel 2:</u> fasted conditions: - Treatment C: 800 mg DRV (2 x 400 mg oral tablet [F030]). - Treatment D: 800 mg DRV (800 mg oral tablet [G002]).	Completed Full report (available upon request) 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114IFD1003 (Belgium: 1)	Open-label, randomized, 3-panel crossover study. To assess bioequivalence between the DRV/COBI fixed dose combination (FDC) tablet (G006) and DRV/COBI coadministered as single agents. To assess effect of food on systemic exposure of DRV and COBI.	Healthy volunteers N=133	Panel 1 (N=74): Treatment A (Reference): a single oral dose of 800 mg DRV and 150 mg COBI administered as single agents, under fasted conditions; Treatment B (Test): a single oral dose of 800 mg DRV and 150 mg COBI administered as a FDC tablet (G006), under fasted conditions. Panel 2 (N=40): Treatment C (Reference): a single oral dose of 800 mg DRV and 150 mg COBI administered as single agents, under fed conditions (standardized breakfast); Treatment D (Test): a single oral dose of 800 mg DRV and 150 mg COBI administered as a FDC tablet (G006), under fed conditions (standardized breakfast). Panel 3 (N=19): Treatment E (Reference): a single oral dose of 800 mg DRV and 150 mg COBI administered as FDC tablet (G006), under fasted conditions. Treatment F (Test): a single oral dose of 800 mg DRV and 150 mg COBI administered as FDC tablet (G006), under fed conditions (high-fat breakfast). There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.1.2

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.2 Comparative Bioavailability and Bioequivalence Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0115 (United States: 1)	Randomized, open-label, single-center, multiple-dose, 2-sequence, 2-period crossover study. To evaluate the relative bioavailibility and pharmacokinetics of DRV when coadministered with COBI versus ritonavir.	Healthy volunteers N=33	Treatment A: an oral dose of DRV/COBI 800/150 mg once daily. Treatment B: an oral dose of DRV/rtv 800/100 mg once daily There was a washout of 4 days between subsequent treatments.	Completed Synopsis Full report 5.3.1.2

5.3.1.3 In Vitro - In Vivo Correlation Study Reports and Related Information

As the drug product is a fixed dose combination tablet, in vitro - in vivo correlation studies were not performed. Therefore, no report is available.

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Report Number	Report Title	Status Study Location in the FDC CTD
TMC114-BA10396	Validation of a method for the determination of TMC114 in human plasma samples – stability in the presence and in the absence of cobicistat.	Completed Full report 5.3.1.4
TMC114-BA1119	Validation (partial) of an LC-MS/MS method for the determination of JNJ-25875382 (TMC114, R319064) and JNJ-16382028 (R115891) in human heparin plasma.	Completed Full report 5.3.1.4
TMC114-BA1389	Validation of a method for the determination of TMC114 and ritonavir in human plasma samples.	Completed Full report 5.3.1.4
TMC114-BA10243	Partial validation of a method for the determination of TMC114 and ritonavir in human K2-EDTA plasma samples.	Completed Full report 5.3.1.4
[redacted] 60-0949 Method Validation Report Cobicistat ([redacted] Study Number: 60-0949)	Validation of a Method for the Determination of GS-9137 and GS-9350 in K2EDTA Human Plasma by LC-MS/MS.	Completed Full report 5.3.1.4
Document No. 20137v2	Validation of a Method for the Determination of GS-9350 in Human Plasma using HPLC with MS/MS Detection. Final Validation Report, Addendum No. 1.	Completed Full report 5.3.1.4
Document No. 20238v1	Validation (partial) of an LC-MS/MS Method for the Determination of JNJ25875382 (TMC114, R319064) and JNJ-16382028 (R115891) in Human Heparin Plasma	Completed Full report 5.3.1.4
Document No. 20219v1	Abbreviated Validation of a Method for the Determination of GS-9350 and GS-9612 in Human Plasma by HPLC with MS/MS Detection. Final Validation Report.	Completed Full report 5.3.1.4

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Report Number	Report Title	Status Study Location in the FDC CTD
TMC114-ABL1982	Validation of the determination of TMC114 in human plasma using LC-MS/MS.	Completed Full report (available upon request) 5.3.1.4
TMC114-ABL3021	Validation of the combined determination of TMC114 and ritonavir in human plasma using LC-MS/MS.	Completed Full report (available upon request) 5.3.1.4
TMC114-ABL3173	The validation of the free TMC114 in human plasma by centrifugal filtration with a 10.000 MW filter.	Completed Full report (available upon request) 5.3.1.4
TMC114-ABL5150	The cross-validation of the determination of TMC114 and ritonavir in human plasma using an API-4000 LC-MS/MS system.	Completed Full report (available upon request) 5.3.1.4
TMC114-ABL1983	Validation of the determination of TMC114 in human urine using LC-MS/MS.	Completed Full report (available upon request) 5.3.1.4
TMC114-PRD-BA502-NCAV-Compl	Validation (full) of an LC-MS/MS method for the determination of R319064 (TMC114) and R115891 (ritonavir) in human heparin plasma.	Completed Full report (available upon request) 5.3.1.4
TMC114-PBR040553	Validation of a method for the determination of TMC114 and ritonavir in human heparin plasma samples.	Completed Full report (available upon request) 5.3.1.4
TMC114-BA819	Validation of an LC-MS/MS method for the determination of TMC114 (R319064)/R115891/R366619 in human heparin plasma.	Completed Full report (available upon request) 5.3.1.4

5.3.1 Reports of Biopharmaceutic Studies

5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies

Report Number	Report Title	Status Study Location in the FDC CTD
BA1513	Validation of an LC-MS/MS method for the determination of TMC435350 in human EDTA plasma samples.	Completed Full report 5.3.1.4

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials
5.3.2.1 Plasma Protein Binding Study Reports
These reports are available in Module 4.2.2.
5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies
These reports are available in Module 4.2.2.
5.3.2.3 Reports of Studies Using Other Human Biomaterials
These reports are available in Module 4.2.2.

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C101 (Belgium: 1)	Randomized, double-blind, placebo-controlled, dose escalation study. To assess the pharmacokinetics of single doses of DRV (oral solution).	Healthy volunteers N=27	- DRV: single dose, oral solution, of 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, 1600 mg, 2400 mg, 3200 mg, fasted.	Completed Full report (available upon request) 5.3.3.1
1	TMC114-C104 (Belgium: 1)	Randomized, double-blind, placebo-controlled, multiple dose escalation study. To assess the pharmacokinetics after repeated 2 or 3 times daily doses of DRV (oral solution).	Healthy volunteers N=36	- DRV: oral 400 mg twice daily for 13 days, single dose on Day 14. - DRV: oral 800 mg twice daily for 13 days, single dose on Day 14. - DRV: oral 800 mg three times daily for 13 days, single dose on Day 14. - DRV: oral 1200 mg three times daily for 13 days, single dose on Day 14.	Completed Full report (available upon request) 5.3.3.1
1	TMC114-C109 (Belgium: 1)	Open-label, randomized study. Mass balance trial with C-14 radiolabelled DRV with and without ritonavir to characterize excretion and metabolic profile.	Healthy volunteers N=8	- Treatment A:, a single dose of oral solution ^{14}C-DRV 400 mg on Day 1. - Treatment B: a single dose of oral solution ^{14}C-DRV 400 mg on Day 1 + an oral dose of ritonavir 100 mg twice daily on Days -2 to 7.	Completed Synopsis Full report 5.3.3.1

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C137 (Belgium: 1)	Open-label, parallel group, dose-ranging study. To assess the pharmacokinetics of various multiple dose regimens of DRV with low-dose ritonavir.	Healthy volunteers N=40	- DRV/rtv: oral 400/100 mg once daily for 7 days. - DRV/rtv: oral 800/100 mg once daily for 7 days. - DRV/rtv: oral 1200/100 mg once daily for 7 days. - DRV/rtv: oral 400/100 mg twice daily for 6 days, single dose on Day 7. - DRV/rtv: oral 800/100 mg twice daily for 6 days, single dose on Day 7. For all regimens, ritonavir 100 mg (once daily and twice daily as for DRV), oral, was taken on Days 1 to 11.	Completed Full report (available upon request) 5.3.3.1
1	GS-US-216-0111 (United States: 1)	Open-label, single-center, multiple-dose, mass-balance study. To determine the mass-balance of COBI at steady-state using a tracer dose of ^{14}C-COBI.	Healthy volunteers N=8	An oral dose of COBI 150 mg once daily on Days 1 to 6. An oral dose of COBI 150 mg (148.5 mg nonradiolabeled COBI plus 100 µCi [1.5 mg] ^{14}C-radiolabeled COBI) administered on Day 7.	Completed Synopsis Full report 5.3.3.1
1	GS-US-216-0113 (United States: 1)	Open-label, single-center, single- and multiple-dose, staggered dose-escalation cohort study. To evaluate the pharmacokinetics of COBI following oral administration at single and multiple doses.	Healthy volunteers N=24	- Cohort 1 (N=12): an oral dose of COBI 300 mg once daily for 7 days. - Cohort 2 (N=12): a single oral dose of COBI 400 mg.	Completed Synopsis Full report 5.3.3.1

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.1 Healthy Subject PK and Initial Tolerability Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-236-0101 (United States: 1)	Randomized, double-blind, single-centre, placebo- and active-controlled, single and multiple dose-ranging study. Evaluating the relative bioavailability of EVG, FTC, and TDF plus pharmacoenhancer GS-9350; fixed-dose combination tablet vs. the individual components.	Healthy volunteers N=44	- Treatment A: EVG 150 mg + ritonavir 100 mg, once daily, oral. - Treatment B: Single tablet regimen containing EVG 150 mg/ COBI 100 mg/FTC 200 mg/ TDF 300 mg once daily, oral. - Treatment C: FTC 200 mg + TDF 300 mg, once daily, oral. - Treatment D: Single tablet regimen containing EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg once daily, oral.	Completed Full report (available upon request) 5.3.3.1

5.3.3.2 Patient PK and Initial Tolerability Study Reports

This information is available in Module 5.3.4.2 Patient PD and PK/PD Study Reports.

5.3.3.3 Intrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C134 (Germany: 1)	Open-label, parallel, controlled, sequential study. To assess the steady-state pharmacokinetics and safety/tolerability of DRV/rtv in subjects with hepatic impairment.	Subjects with mild and moderate hepatic impairment N=32	An oral dose of DRV 600 mg twice daily on Days 1 to 6, and once daily on Day 7. An oral dose of ritonavir 100 mg twice daily on Days 1 to 9.	Completed Synopsis Full report 5.3.3.3

5.3.3.3 Intrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0121 (United States: 4 Germany: 1)	A 2-cohort study. - Cohort 1 was a randomized, double-blind, placebo (negative)- controlled, single-center, multiple-dose, parallel-group cohort. To evaluate renal function and renal creatinine handling before, during, and following completion of administration of COBI or ritonavir in healthy subjects. - Cohort 2 was a single-treatment, open-label, multicenter, multiple-dose cohort. To evaluate renal function and renal creatinine handling in stable mild/moderate renal impairment before, during, and following completion of administration of COBI, and assess the pharmacokinetics and safety of COBI in stable mild/moderate renal impairment.	Cohort 1: Healthy subjects with normal renal function (estimated glomerular filtration rate [$eGFR_{CG}$] ≥80 mL/min). N=36 Cohort 2: Subjects with stable mild/ moderate renal impairment N=18	Cohort 1 - On Days 1 to 7: Treatment 1 (N=12): an oral dose of COBI 150 mg + ritonavir 100 mg placebo, OR Treatment 2 (N=12): ritonavir 100 mg + COBI 150 mg placebo, OR Treatment 3 (N=12): COBI 150 mg placebo + ritonavir 100 mg placebo. - On Days 0, 7, and 14: Probe drug administered (IV iohexol) Cohort 2 - On Days 1 to 7: an oral dose of COBI 150 mg - On Days 0, 7, and 14: Probe drug administered (IV iohexol)	Completed Synopsis Full report 5.3.3.3

5.3.3.3 Intrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0124 (United States: 3 Germany: 1)	Open-label, parallel-group, multiple-dose study. To evaluate the pharmacokinetics, safety, and renal function prior to, during, and after dosing with EVG/COBI in subjects with severe renal impairment.	Subjects with severe renal impairment N=13 Matched control subjects with normal renal function N=11	An oral dose of EVG/COBI 150/150 mg once daily on Days 1 to 7.	Completed Synopsis Full report 5.3.3.3
1	GS-US-183-0133 (United States: 1 Germany: 1)	Open-label, parallel-group, multiple-dose study. To evaluate any differences in the pharmacokinetics and safety of EVG/COBI by evaluating subjects with moderate impairment of hepatic function (Child-Pugh Classification B) compared to matched subjects with normal hepatic function.	Subjects with moderate hepatic impairment (CPT Classification B) N=10 Healthy matched control subjects N=10	An oral dose of EVG/COBI 150/150 mg once daily on Days 1 to 10.	Completed Synopsis Full report 5.3.3.3

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C105 (Belgium: 1)	Open-label, single dose, interaction study. To investigate the effect of repeated doses of ritonavir on pharmacokinetics of a single dose of DRV.	Healthy volunteers N=10	- DRV, oral solution, single dose, 800 mg. - DRV, oral solution, single dose, 800 mg on Day 4 + ritonavir, oral, repeated doses (titrated: 300 mg twice daily on Day 1, 400 mg twice daily on Day 2, 500 mg twice daily on Day 3 and 600 mg twice daily on Days 4 to 6).	Completed Full report (available upon request) 5.3.3.4
1	TMC114-C107 (The Netherlands: 1)	Open-label, randomized, crossover study. To investigate the interaction between repeated dosing of DRV and rifabutin both in combination with low-dose ritonavir.	Healthy volunteers N=16	Panel 1: - An oral dose of DRV/rtv 400/100 mg twice daily for 9 days and single dose on Day 10. - An oral dose of rifabutin 300 mg once daily on Days 1 to 10, followed by rifabutin 150 mg once daily + an oral dose of DRV/rtv 400/100 mg twice daily on Days 11 to 20. Panel 2: - An oral dose of DRV/rtv 400/100 mg twice daily for 9 days and single dose on Day 10. - An oral dose of rifabutin 150 mg once daily + and oral dose of DRV/rtv 400/100 mg twice daily on Days 1 to 10, followed by rifabutin 300 mg once daily on Days 11 to 20.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C110 (Belgium: 1)	Open-label, 1-sequence, crossover study. Interaction between repeated doses of DRV and a single dose of saquinavir.	Healthy volunteers N=12	- saquinavir, single oral dose of 1200 mg. - DRV, oral solution, twice daily, 1200 mg, on Days 1 to 14 + saquinavir, oral, single dose, 1200 mg on Day 14.	Completed Full report (available upon request) 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C111 (Belgium: 1)	Open-label, 1-sequence, crossover study. To assess the interaction between DRV with low-dose ritonavir and efavirenz.	Healthy volunteers N=12	Session 1: - An oral dose of DRV/rtv 300/100 mg twice daily on Days 1 to 6 and a single dose on Day 7. Session 2: - An oral dose of DRV/rtv 300/100 mg twice daily on Days 11 to 16 and a single dose on Day 17 + efavirenz 600 mg once daily on Days 1 to 18. There was a washout of at least 7 days between subsequent sessions.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C112 (Belgium: 1)	Open-label, parallel groups, 1-sequence, crossover, multiple dose escalating study. To assess the interaction between different dosages of DRV and different dosages of ritonavir.	Healthy volunteers N=40	- DRV, oral, 200 mg once daily on Days 1 to 14 + ritonavir, oral, 100 mg once daily on Days 2 to 16. - DRV, oral, 400 mg once daily on Days 1 to 14 + ritonavir, oral, 100 mg once daily on Days 2 to 16. - DRV, oral, 300 mg twice daily on Days 1 to 13 + 300 mg once daily on Day 14 + ritonavir, oral, 100 mg twice daily on Days 2 to 16. - DRV, oral, 600 mg once daily on Days 1 to 14 + ritonavir, oral, 200 mg once daily on Days 2 to 16. - DRV, oral, 1200 mg once daily on Days 1 to 14 + ritonavir, oral, 200 mg once daily on Day 2 to 16.	Completed Full report (available upon request) 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C119 (United Kingdom: 1)	Open-label, randomized, 1-sequence, crossover study. To assess the interaction between repeated dosing of DRV in combination with low-dose ritonavir and nevirapine.	HIV-1 infected subjects N=19	Subjects continued their current HIV therapy consisting of nevirapine (200 mg twice daily) and at least 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). In addition, subjects received either - An oral solution of DRV 300 mg in combination with a capsule of rtv 100 mg twice daily on Days 1 to 13 + a single dose on Day 14 on top of current HIV therapy. - An oral tablet of DRV 400 mg in combination with a capsule of rtv 100 mg twice daily on Days 1 to 13 + a single dose on Day 14 on top of current HIV therapy.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C120 (Belgium: 1)	Open-label, randomized, one-sequence, crossover study. To assess the interaction between DRV in combination with low-dose ritonavir and a single dose of pravastatin.	Healthy volunteers N=14	- Treatment A: a single oral dose of pravastatin 40 mg. - Treatment B: an oral dose of DRV/rtv 600/100 mg twice daily on Days 1 to 7 + a single oral dose of pravastatin 40 mg on Day 7.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C121 (United States: 1)	Open-label, randomized, crossover study. To determine the interaction between DRV/rtv and paroxetine or sertraline.	Healthy volunteers N=36	<u>Panel 1:</u> - Treatment A: an oral dose of DRV/rtv 400/100 mg twice daily for 6 days and single dose on Day 7. - Treatment B: an oral dose of paroxetine 20 mg once daily for 7 days. - Treatment C: an oral dose of paroxetine 20 mg once daily and an oral dose of DRV/rtv 400/100 mg twice daily for 7 days. <u>Panel 2:</u> - Treatment A: an oral dose of DRV/rtv 400/100 mg twice daily for 6 days and single dose on Day 7. - Treatment D: an oral dose of sertraline 50 mg once daily for 7 days. - Treatment E: an oral dose of sertraline 50 mg once daily and an oral dose of DRV/rtv 400/100 mg twice daily for 7 days. There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C122 (United States: 1)	Open-label, randomized, 3-way crossover study. To determine the interaction between DRV/rtv with ranitidine and omeprazole.	Healthy volunteers N=17	- Treatment A: an oral dose of DRV/rtv 400/100 mg twice daily for 4 days and a single dose on Day 5. - Treatment B: an oral dose of ranitidine 150 mg twice daily and an oral dose of DRV/rtv 400/100 mg twice daily for 4 days and a single dose on Day 5. - Treatment C: an oral dose of omeprazole 20 mg once daily and an oral dose of DRV/rtv 400/100 mg twice daily for 4 days and a single dose on Day 5. There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C123 (The Netherlands: 1)	Open label, randomized, 3-way crossover study. To determine the interaction between DRV/rtv and didanosine (ddI).	Healthy volunteers N=18	- Treatment A: an oral dose of DRV/rtv 600/100 mg twice daily for 6 days and single dose Day 7. - Treatment B: an oral dose of ddI 400 mg once daily for 7 days. - Treatment C: an oral dose of DRV/rtv 600/100 mg twice daily and an oral dose of ddI 400 mg once daily for 7 days. There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C124 (Belgium: 1)	Open-label, one-sequence, crossover study. To determine the interaction between DRV boosted with low-dose ritonavir and tenofovir.	Healthy volunteers N=13	Session 1 (N=13): - An oral dose of DRV/rtv 300/100 mg twice daily on Days 1 to 6 and a single dose on Day 7. Session 2 (N=12): Group 1 (N=6) - An oral dose of DRV/rtv 300/100 mg twice daily on Days 8 to 14 and an oral dose of tenofovir 300 mg once daily for 14 days. Group 2 (N=6) - An oral dose of DRV/rtv 300/100 mg twice daily on Days 1 to 7 and an oral dose of tenofovir 300 mg once daily for 14 days. There was a washout of at least 6 days between subsequent sessions.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C125 (Belgium: 1)	Open-label, randomized, 4-way crossover study. To assess the interaction between DRV and lopinavir (LPV) both in combination with low-dose ritonavir.	Healthy volunteers N=16	- LPV/rtv, oral, 400/100 mg twice daily for 6 days and single dose on Day 7. - DRV/rtv, oral, 300/100 mg twice daily for 6 days and single dose on Day 7. - DRV/rtv, oral, 300/100 mg twice daily for 6 days and single dose on Day 7 + LPV/rtv 400/100 mg, oral, twice daily for 6 days and single dose on Day 7. - DRV, oral, 300 mg twice daily for 6 days and single dose on Day 7 + LPV/rtv, oral 400/100 mg twice daily for 6 days and single dose on Day 7.	Completed Full report (available upon request) 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C127 (The Netherlands: 1)	Open label, add-on study. To determine the interaction between methadone and DRV/rtv.	Subjects on stable methadone maintenance therapy N=16	An oral dose of DRV/rtv 600/100 mg twice daily for 7 days as add-on to the subject's current stable methadone therapy.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C128 (United States: 1)	Open-label, randomized, 2-way crossover study. To determine the interaction between DRV coadministered with low-dose ritonavir and sildenafil.	Healthy volunteers N=16	- Treatment A: a single oral dose of sildenafil 100 mg. - Treatment B: an oral dose of DRV/rtv 400/100 mg twice daily on Days 1 to 8 + an oral dose of sildenafil 25 mg once daily on Day 7. There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C129 (Belgium: 1)	Open-label, controlled, randomized, crossover study. To investigate the interaction between DRV with and without low-dose ritonavir and ketoconazole.	Healthy volunteers N=26	Panel 1 (N=8) - Treatment A: an oral dose of DRV 400 mg twice daily for 6 days and single dose on Day 7. - Treatment B: an oral dose of DRV 400 mg + an oral dose of ketoconazole 200 mg; twice daily for 6 days and single dose on Day 7. Panel 2 (N=18) - Treatment C: an oral dose of DRV/rtv 400/100 mg twice daily for 6 days and single dose on Day 7. - Treatment D: an oral dose of ketoconazole 200 mg twice daily for 6 days and a single dose on Day 7. - Treatment E: an oral dose of DRV/rtv 400/100 mg + an oral dose of ketoconazole 200 mg; twice daily for 6 days and single dose on Day 7. There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C131 (United States: 1)	Open-label, randomized, 2-way crossover study in women. To investigate the interaction between DRV with low-dose ritonavir, and ethinyl estradiol and norethindrone.	Healthy volunteers N=18	- Treatment A: an oral dose of ethinyl estradiol 35 µg and norethindrone 1 mg on Days 1 to 21, no medication on Days 22 to 28. - Treatment B: an oral dose of ethinyl estradiol 35 µg and norethindrone 1 mg on Days 1 to 21, an oral dose of DRV/rtv 600/100 mg twice daily on Days 1 to 14, no medication on Days 22 to 28.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C133 (United States: 1)	Open-label, randomized, 1-way crossover study. To determine the effect of DRV with low-dose ritonavir on the pharmacokinetics of atorvastatin and its metabolites atorvastatin lactone and 2-and 4-hydroxy-atorvastatin.	Healthy volunteers N=16	- Treatment A: an oral dose of atorvastatin 40 mg once daily on Days 1 to 4. - Treatment B: an oral dose of DRV/rtv 300/100 mg twice daily on Days 1 to 9 + an oral dose of atorvastatin 10 mg once daily on Days 4 to 7. There was a washout of 6 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C138 (Belgium: 1)	Open-label, randomized, crossover study. To investigate the interaction between DRV and saquinavir with low-dose ritonavir.	Healthy volunteers N=32	Session 1: - Panel 1: DRV/rtv, oral, 400/100mg twice daily on Days 1 to 13 and single dose on Day 14. - Panel 2: saquinavir/rtv, oral, 1000/100 mg twice daily on Days 1 to 13 and single dose on Day 14. Session 2 (Panel 1 and 2): - DRV/rtv/saquinavir, oral, 400/100/1000 mg twice daily on Days 1 to 13 and single dose on Day 14.	Completed Full report (available upon request) 5.3.3.4
1	TMC114-C141 (United States: 1)	Open-label, randomized, 3-way crossover study. To assess the interaction between repeated dosing of DRV and indinavir both in combination with low-dose ritonavir.	Healthy volunteers N=17	- DRV/rtv, oral, 400/100 mg twice daily for 6 days and single dose on Day 7. - indinavir/rtv, oral, 800/100 mg twice daily for 6 days and single dose on Day 7. - indinavir/DRV/rtv, oral, 800/400/100 mg twice daily for 7 days and single dose on Day 7.	Completed Full report (available upon request) 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C142 (Belgium: 1)	Open-label, randomized, 3-way crossover study. To determine the interaction between DRV and low-dose ritonavir and clarithromycin.	Healthy volunteers N=18	- Treatment A: an oral dose of DRV/rtv 400/100 mg twice daily for 6 days and single dose on Day 7. - Treatment B: an oral dose of clarithromycin 500 mg twice daily for 6 days and single dose on Day 7. - Treatment C: an oral dose of clarithromycin 500 mg twice daily for 6 days and single dose on Day 7 + an oral dose of DRV/rtv 400/100 mg twice daily for 7 days. There was a washout of at least 7 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C149 (United States: 1)	Open-label, randomized, 3-way crossover study. To assess the interaction between repeated dosing of DRV and atazanavir both in combination with low-dose ritonavir.	Healthy volunteers N=23	- DRV/rtv, oral, 400/100 mg twice daily for 6 days and single dose on Day 7. - atazanavir/rtv, oral, 300/100 mg once daily for 7 days. - atazanavir, oral, 300 mg once daily + DRV/rtv, oral, 400/100 mg twice daily for 7 days.	Completed Full report (available upon request) 5.3.3.4
1	TMC114-C150 (United States: 1)	Open-label, randomized, 2-way crossover study. To determine the interaction between DRV with low-dose ritonavir and digoxin.	Healthy volunteers N=17	- Treatment A: single dose, 0.4 mg digoxin, oral tablet. - Treatment B: DRV/rtv, oral, tablets, 600/100 mg twice daily on Days 1 to 11 + 0.4 mg digoxin, single dose, capsule, on Day 8. There was a washout of at least 2 weeks between subsequent treatments.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C151 (International, multicentre)	Open-label, randomized, 3-way crossover study. To assess the interaction between DRV and LPV/rtv in combination with 2 NRTIs with or without enfuvirtide.	HIV-1-infected subjects N=32	Panel 1: Treatments A, B, D; Panel 2: Treatments A, C, D. - Treatment A: current HIV therapy including LPV/rtv 400/100 mg twice daily for 14 days. - Treatment B: current HIV therapy including LPV/rtv 400/100 mg twice daily + DRV/rtv 1200/100 mg twice daily for 14 days. - Treatment C: current HIV therapy including LPV/rtv 400/100 mg twice daily + DRV 1200 mg twice daily + additional LPV/rtv 133.3/33.3 mg twice daily for 14 days. - Treatment D: current HIV therapy without LPV/rtv + DRV/rtv 1200/600 mg twice daily for 14 days.	Completed Full report (available upon request) 5.3.3.4
1	TMC114-C163 (France: 1)	Open-label, randomized, 3-way crossover study. To investigate the interaction between rifabutin and DRV in combination with low-dose ritonavir, at steady-state.	Healthy volunteers N=27	In 3 sessions, each subject received Treatment A, B and C. - Treatment A: 600/100 mg DRV/rtv twice daily, oral, for 12 days with an additional morning dose on Day 13. - Treatment B: 300 mg rifubatin once daily, oral, on Days 1 to 13. - Treatment C: 600/100 mg DRV/rtv twice daily and rifabutin 150 mg every other day, oral, on Days 1 to 13. There was a washout of at least 14 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C171 (United States: 1)	Open-label, add-on study. To determine the drug interaction potential of DRV/rtv with buprenorphine/ naloxone at steady state.	Subjects on stable buprenorphine/ naloxone therapy N=17	Subjects received DRV/rtv for 7 days, which was added onto their current buprenorphine/naloxone maintenance therapy: - Buprenorphine/naloxone at a maximum of 24/6 mg once daily (individualized dose) from Day –14 until Day 8. - DRV/rtv 600/100 mg twice daily from Day 1 until Day 7.	Completed Synopsis Full report 5.3.3.4
1	TMC114-C172 (Belgium: 1)	Open-label, 2-panel, crossover study. To determine the drug interaction potential of DRV/rtv with the anticonvulsant carbamazepine (CBZ) following multiple dosing of these drugs.	Healthy volunteers N=32	<u>Panel 1:</u> - Days 1 to 7: DRV/rtv 600/100 mg twice daily alone. - Days 8 to 10: DRV/rtv 600/100 mg twice daily plus CBZ 200 mg once daily. - Days 11 to 29: DRV/rtv 600/100 mg twice daily plus CBZ 200 mg twice daily. - Day 30: morning dose of DRV/rtv 600/100 mg plus CBZ 200 mg. <u>Panel 2:</u> - Days 1 to 3: CBZ 200 mg once daily alone. - Days 4 to 23: CBZ 200 mg twice daily alone. - Days 24 to 29: CBZ 200 mg twice daily plus DRV/rtv 600/100 mg twice daily. - Day 30: morning dose of CBZ 200 mg plus DRV/rtv 600/100 mg.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C173 (Germany: 1)	Open-label, randomized, crossover study. To assess the drug interaction potential of DRV coadministered with low-dose ritonavir with a drug "cocktail" representative for CYP2C9, CYP2C19 and CYP2D6 substrates.	Healthy volunteers N=12	Subjects received Treatment A and Treatment B in 2 sessions: - Treatment A: Single, oral dose of a drug cocktail consisting of 10 mg warfarin supplemented with 10 mg vitamin K1, 30 mg dextromethorphan, and 40 mg omeprazole, oral. - Treatment B: DRV/rtv 600/100 mg twice daily, oral, for 7 days and the drug cocktail single, oral dose on Day 7.	Completed Full report (available upon request) 5.3.3.4
1	TMC114-C181 (United States: 1)	Open-label, randomized, 3-way crossover study. To assess the pharmacokinetics of DRV given once-daily with different doses of ritonavir.	Healthy volunteers N=21	Subjects received Treatments A, B, and C: - Treatment A: DRV/rtv 800/100 mg once daily for 7 days. - Treatment B: DRV/rtv 800/50 mg once daily for 7 days. - Treatment C: DRV/rtv 800/20 mg once daily for 7 days.	Completed Full report (available upon request) 5.3.3.4
1	TMC114-MK0518 (United States: 2)	Open-label, sequential, 2-period study. To assess the pharmacokinetics of raltegravir coadministered with DRV and ritonavir.	Healthy volunteers N=18	Period 1: - An oral dose of raltegravir 400 mg twice daily for 4 days. Period 2: - An oral dose of raltegravir 400 mg twice daily coadministered with DRV/rtv 600/100 mg twice daily for 12 days. Period 2 immediately followed Period 1.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-A4001052 (Singapore: 1)	Open-label, randomized, 2-way crossover study. To investigate the effect of DRV/rtv on the pharmacokinetics of maraviroc.	Healthy volunteers N=16	Treatment A: an oral dose of maraviroc 150 mg twice daily and an oral dose of DRV/rtv 600/100 mg twice daily on Days 1 to 9 and a single dose on the morning of Day 10. Treatment B: an oral dose of maraviroc 150 mg twice daily and an oral dose of placebo twice daily on Days 1 to 9 and a single dose on the morning of Day 10. There was a washout of at least 14 days between subsequent treatments.	Completed Synopsis Full report 5.3.3.4
1	TMC278-C112 (Belgium: 1)	Randomized, open-label, 2-way crossover, multiple-dose, drug-drug interaction study. To determine the steady-state interaction between DRV/rtv and rilpivirine.	Healthy volunteers N=16	Subjects received Treatment A/B or B/A: - Treatment A: an oral dose of rilpivirine 150 mg once daily on Days 1 to 11. - Treatment B: an oral dose of DRV/rtv 800/100 mg once daily on Days 1 to 22 plus an oral dose of rilpivirine 150 mg once daily on Days 12 to 22. Treatments A and B were separated by a washout of 14 days.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	VX-950-C124 (The Netherlands: 1)	Randomized, open-label, 2-way crossover, multiple-dose drug-drug interaction study. To determine the steady-state interaction between DRV/rtv and telaprevir.	Healthy volunteers N=40	Panel 1: Treatment A/B or B/A; Panel 2: Treatment C/D or D/C: - Treatments A and C: an oral dose of telaprevir 750 mg every 8 hours on Days 1 to 10 and 1125 mg every 12 hours on Days 11 to 13 with a morning dose on Day 14. - Treatment B: an oral dose of DRV/rtv 600/100 mg twice daily on Days 1 to 23 with a morning dose on Day 24 and coadministration of an oral dose of telaprevir 750 mg every 8 hours on Days 11 to 20 and 1125 mg every 12 hours on Days 21 to 23 with a morning dose on Day 24. - Treatment D: an oral dose of fosamprenavir/rtv 700/100 mg twice daily on Days 1 to 23 with a morning dose on Day 24 and coadministration of an oral dose of telaprevir 750 mg every 8 hours on Days 11 to 20 and 1125 mg every 12 hours on Days 21 to 23 with a morning dose on Day 24. All treatment sessions were separated by a washout of at least 13 days.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC125-C139 (The Netherlands: 1)	Open-label, randomized, 2-way crossover study. To study the interaction between steady state concentrations of DRV/rtv and etravirine (ETR).	Healthy volunteers N=24	Two panels consisting of 2 sessions: - Session A: ETR, oral, 800 mg twice daily for 7 days and single dose on Day 8. - Session B1: DRV/rtv, oral, 600/100 mg twice daily for 15 days and single dose on Day 16 + ETR, oral, 800 mg twice daily on Days 9 to 15 and single dose on Day 16. - Session B2: DRV/rtv, oral, 600/100 mg twice daily for 15 days and single dose on Day 16 + ETR, oral, 800 mg twice daily on Days 1 to 7 and single dose on Day 8.	Completed Full report (available upon request) 5.3.3.4
1	TMC125-C176 (The Netherlands: 1)	Open-label, randomized, 2-way crossover study. To investigate the pharmacokinetic interaction between DRV/rtv and ETR at steady-state.	Healthy volunteers N=32	Panel 1: Treatments A and B1; Panel 2: Treatments A and B2: - Treatments A: an oral dose of ETR 100 mg twice daily on Days 1 to 7 and a morning dose on Day 8. - Treatment B1: an oral dose of DRV/rtv 600/100 mg twice daily on Days 1 to 15 and a morning dose on Day 16 + ETR 100 mg twice daily on Days 9 to 15 and a morning dose on Day 16. - Treatment B2: an oral dose of DRV/rtv 600/100 mg twice daily on Days 1 to 15 and a morning dose on Day 16 + ETR 200 mg twice daily on Days 9 to 15 and a morning dose on Day 16. All treatments were separated by a washout of at least 14 days.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC125VIR1001[*] (Poland: 1)	Open-label, partially randomized, 2-way, 2-period crossover study. To investigate the pharmacokinetic interaction between ETR or DRV/rtv and artemether/lumefantrine at steady-state.	Healthy volunteers (Panel 2) N=16	Subjects received Treatment A/B or B/A: - Treatment A: 3 days of treatment with an oral dose of artemether/lumefantrine 80/480 mg (6 doses of 4 tablets [20/120 mg] at 0, 8, 24, 36, 48, and 60 hours. - Treatment B: an oral dose of DRV/rtv 600/100 mg twice daily from Day 1 to Day 21 with a single oral dose of DRV/rtv 600/100 mg in the morning on Day 22. From Day 8, 3 days of treatment with an oral dose of artemether/lumefantrine 80/480 mg (6 doses of 4 tablets [20/120 mg] at 0, 8, 24, 36, 48, and 60 hours. Treatments A and B were separated by a washout of at least 4 weeks.	Completed Synopsis Full report 5.3.3.4
1	TMC435-TiDP16-C115[†] (Belgium: 1)	Open-label, randomized, 2-panel, 3-way crossover study. To investigate the effect of steady-state concentrations of DRV/rtv on the steady-state pharmacokinetics of TMC435 (simeprevir) 50 mg once daily.	Healthy volunteers (Panel 2) N=25	Subjects received Treatments D, E, and F: - Treatment D: an oral dose of simeprevir 150 mg once daily for 7 days. - Treatment E: an oral dose of DRV/rtv 800/100 mg once daily for 7 days. - Treatment F: an oral dose of simeprevir 50 mg once daily + DRV/rtv 800/100 mg once daily for 7 days. There was a washout period of at least 7 days between subsequent sessions.	Completed Synopsis Full report 5.3.3.4

[*] Panel 1, in which the drug-drug interaction between etravirine and artemether/lumefantrine is investigated, is not described in this table.

[†] Panel 1, in which the drug-drug interaction between simeprevir and erythromycin is investigated, is not described in this table.

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-201-0104 (United States: 1)	Randomized, open-label, single- and multiple-dose, 2-way crossover study. To evaluate the single-dose pharmacokinetics of GS-8374 and DRV, and evaluate the multiple-dose pharmacokinetics of GS-8374, DRV, and EVG following administration of GS-8374 or DRV, each in combination with EVG/COBI.	Healthy volunteers N=18	In Sequence 1 subjects received Treatments A/C/D. In Sequence 2 subjects received Treatments B/D/C. - Treatment A: an oral single dose of GS-8374 600 mg. - Treatment B: an oral single dose of DRV 800 mg. - Treatment C: an oral dose of GS-8374 600 mg + EVG 150 mg + COBI 150 mg for 10 days. - Treatment D: an oral dose of DRV 800 mg + EVG 150 mg + COBI 150 mg for 10 days. Treatments C and D were separated by a washout of 2 days.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0112 (United States: 1)	Open-label, single-center, multiple-cohort, crossover study. To evaluate the effects of COBI on cytochrome P450 (CYP) isoforms 2B6 and 2D6, and on the drug efflux transporter Pgp using validated phenotyping probes.	Healthy volunteers. N=53 Cohort 1 was limited to individuals who were intermediate, extensive, or ultra-rapid CYP2D metabolizers. Cohort 3 was limited to individuals who were intermediate or extensive CYP2B6 metabolizers.	Cohort 1 (CYP2D6) - Treatment A: a single oral dose of desipramine 50 mg. - Treatment B: an oral dose of COBI 150 mg once daily for 10 days + a single oral dose of desipramine 50 mg on Day 10. Cohort 2 (Pgp) - Treatment C: an oral single dose of digoxin 0.5 mg. - Treatment D: an oral dose of COBI 150 mg once daily for 10 days + a single oral dose of digoxin 0.5 mg on Day 10. Cohort 3 (CYP2B6) - Treatment E: a single oral dose of EFV 600 mg. - Treatment F: an oral dose of COBI 150 mg once daily for 10 days + a single oral dose of EFV 600 mg on Day 10.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0120 (United States: 1)	Randomized, open-label, single-center, multiple-dose, 3-sequence, 4-treatment, 2-period crossover study. To evaluate the relative bioavailability and pharmacokinetics of EVG/COBI after coadministration with a representative H_2-receptor antagonist or a representative proton pump inhibitor.	Healthy volunteers. N=33	Subjects received Treatments A/B, A/C, or A/D. - Treatment A: an oral dose of EVG/COBI 150/150 mg once daily in the morning with food on Days 1 to 8 and on Day 16. - Treatment B: an oral dose of EVG/COBI 150/150 mg once daily in the morning with food on Days 1 to 8 + an oral dose of famotidine 40 mg once daily in the afternoon with food 12 hours after EVG/COBI on Days 9 to 15. - Treatment C: an oral dose of EVG/COBI 150/150 mg once daily in the morning with food on Days 1 to 8 + an oral dose of omeprazole 20 mg, once daily in the morning in a fasted state 2 hours before EVG/COBI on Days 9 to 15. - Treatment D: an oral dose of EVG/COBI 150/150 mg once daily in the morning with food on Days 1 to 8 + an oral dose of omeprazole 20 mg once daily in the afternoon in a fasted state 12 hours after EVG/COBI on Days 9 to 15.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0122 (United States: 1)	Randomized, open-label, single-center, multiple-dose, 2-way crossover study. To determine whether simultaneous coadministration of EVG/COBI with a representative H_2-receptor antagonist reduces the relative bioavailability of EVG/COBI.	Healthy volunteers. N=16	Subjects received Treatments A/B or B/A. - Treatment A: an oral dose of EVG/COBI 150/150 mg once daily in the morning with food for 8 days. - Treatment B: an oral dose of EVG/COBI 150/150 mg once daily + an oral dose of famotidine 40 mg once daily in the morning with food for 8 days. There was no washout between treatments.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0123 (United States: 1)	Partially randomized, open-label, single-center, single- and multiple-dose, multiple-cohort, crossover study. To evaluate the pharmacokinetics and safety of EVG/COBI coadministered once daily with ATV, rosuvastatin, or rifabutin versus once-daily administration of EVG/COBI, ATV/rtv, single dose of rosuvastatin alone, or once-daily administration of rifabutin alone.	Healthy volunteers. N=34	Cohort 1 (N=12): - Treatment A: a single oral dose of rosuvastatin 10 mg on Day 1. - Treatment B: an oral dose of EVG 85 mg + COBI 150 mg + ATV 300 mg, once daily on Days 4 to 13. - Treatment C: an oral dose of EVG/COBI 150/150 mg once daily on Days 15 to 24. - Treatment D: a single oral dose of EVG/COBI 150/150 mg + a single oral dose of rosuvastatin 10 mg on Day 25. There was a washout of 2 days between Treatments A and B, and of 1 day between Treatments B and C. Cohort 2 (N=10): - Treatment B: an oral dose of EVG 85 mg + COBI 150 mg + ATV 300 mg, once daily on Days 4 to 13. - Treatment E: an oral dose of ATV/rtv 300/100 mg once daily on Days 15 to 24. There was a washout of 1 day between Treatments B and E. Cohort 3 (N=12): - Treatment C: an oral dose of EVG/COBI 150/150 mg once daily on Days 1 to 10. - Treatment F: an oral dose of EVG/COBI 150/150 mg once daily + an oral dose of rifabutin 150 mg every other day on Days 11 to 23. - Treatment G: an oral dose of rifabutin 300 mg once daily on Days 35 to 46. There was a washout of 10 days between Treatments F and G.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.4 Extrinsic Factor PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0125 (United States: 2)	Open-label, crossover, 2-cohort, multiple-dose study. To evaluate the drug interaction potential between once-daily COBI-boosted alvitegravir and methadone or buprenorphine/naloxone (BUP/NLX).	Healthy volunteers on stable oral methadone or sublingual BUP/NLX once daily for at least 2 weeks N=28	Cohort 1: - Treatment A: methadone 80 to 120 mg on Day 1 (Period 1), and - Treatment B: methadone + COBI 150 mg + EVG 150 mg on Days 2 through 11 (Period 2). Cohort 2: - Treatment C: BUP/NLX 16 mg/4 mg – 24 mg/6 mg on Day 1 (Period 1), and - Treatment D: BUP/NLX + COBI 150 mg + EVG 150 mg on Days 2 through 11 (Period 2).	Completed Full report (available upon request) 5.3.3.4
1	GS-US-236-0106 (United States: 1)	Fixed-sequence, open-label, single-center, multiple-dose study. To determine effect of the QUAD single tablet regimen on the pharmacokinetics of norgestimate/ethinyl estradiol (NGM/EE)	Healthy adult women of childbearing potential N=21	Part A (Lead-In) (1 menstrual cycle): - An oral dose of NGM/EE once daily for 28 days (21 days active + 7 days inert). Part B (2 menstrual cycles): - An oral dose of NGM/EE once daily for 39 days (21 days active, 7 days inert, 11 days active). - An oral dose of QUAD single tablet regimen (EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg) once daily + an oral dose of NGM/EE (active) once daily for 10 days. - An oral dose of NGM/EE (inert) once daily for 7 days. There was no washout between Parts A and B.	Completed Synopsis Full report 5.3.3.4

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1 - 2	TMC114-C925 (Not applicable)	Population pharmacokinetics - Empirical Bayes' estimation of pharmacokinetic parameters.	Healthy volunteers + 3-class-experienced, HIV-1 infected subjects N=108 + 468	See individual study TMC114-C129. For study TMC114-C137: - DRV/rtv: oral 400/100 mg once daily for 7 days. - DRV/rtv: oral 800/100 mg once daily for 7 days. - DRV/rtv: oral 1200/100 mg once daily for 7 days. - DRV/rtv: oral 400/100 mg twice daily for 6 days, single dose on Day 7. - DRV/rtv: oral 800/100 mg twice daily for 6 days, single dose on Day 7. For all regimens, ritonavir 100 mg (once and twice daily as for DRV), oral, was taken on Days 1-11. For study TMC114-C138: Session 1: - Panel 1: DRV/rtv, oral, 400/100mg twice daily on Days 1-13 and single dose on Day 14. - Panel 2: saquinavir/rtv, oral, 1000/100 mg twice daily on Days 1-13 and single dose on Day 14. Session 2 (Panel 1 and 2): - DRV/rtv/saquinavir, oral, 400/100/1000 mg twice daily on Days 1-13 and single dose on Day 14.	Completed Full report 5.3.3.5

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
				For study TMC114-C154: - DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1-5. Formulations: F002 (Batch X), F002 (Batch Y), F002 (Batch Z). For study TMC114-C156: - DRV: single dose, 400 mg, oral tablet on Day 3 + ritonavir 100 mg twice daily, oral, on Days 1-5. Formulations: F002, F009. For study TMC114-C202: - Control: optimized background regimen (OBR), oral, 24 weeks. - DRV/rtv: oral, 400/100 mg once daily or 800/100 mg once daily, or 400/100 mg twice daily, or 600/100 mg twice daily for 24 weeks. For study TMC114-C213: - Control: OBR, oral, 24 weeks. - DRV/rtv: oral, 400/100 mg once daily, or 800/100 mg once daily, or 400/100 mg twice daily, or 600/100 mg twice daily, for 24 weeks.	

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1 - 2	TMC114-C927a (Not applicable)	Population pharmacokinetic and covariate analysis of DRV.	Healthy volunteers + 3-class-experienced, HIV-1 infected subjects N=111 + 468	See report TMC114-C925	Completed Full report 5.3.3.5
1 - 2	TMC114-C927b (Not applicable)	Emperical Bayesian feedback for studies TMC114-C202, TMC114-C213, and TMC114-C215.	Healthy volunteers + 3-class-experienced, HIV-1 infected subjects N=702	For study TMC114-C202: - Control: OBR, oral, 24 weeks. - DRV/rtv: oral, 400/100 mg once daily or 800/100 mg once daily, or 400/100 mg twice daily, or 600/100 mg twice daily for 24 weeks. For study TMC114-C213: - Control: OBR, oral, 24 weeks. DRV/rtv: oral, 400/100 mg once daily, or 800/100 mg once daily, or 400/100 mg twice daily, or 600/100 mg twice daily, for 24 weeks. For study TMC114-C215: - DRV/rtv, oral, 400/100mg twice daily, for 96 weeks. After approval of amendment to switch to the recommended dose, subjects received DRV/rtv, oral, 600/100 mg twice daily. + OBR of at least 2 antiretrovirals (ARVs) (NRTIs with/without enfuvirtide).	Completed Full report 5.3.3.5

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	TMC114-C922 (Not applicable)	Bayesian feedback for study TMC114-C214	Treatment-experienced (ie, have been on a highly active antiretroviral therapy (HAART) regimen for at least 12 weeks) HIV-1 infected subjects N=285	- Oral dose of DRV/rtv 600/100 mg twice daily for 96 weeks. - Oral dose of LPV/rtv 400/100 mg twice daily (or 533/133 mg twice daily in case non-nucleoside reverse transcriptase [NNRTI] is included in OBR) for 96 weeks. + OBR of at least 2 ARVs (NRTIs with or without NNRTIs)	Completed Full report 5.3.3.5
3	TMC114-C923 (Not applicable)	Intra-individual variability in apparent intrinsic clearance of DRV.	Treatment-experienced (ie, have been on a HAART regimen for at least 12 weeks) HIV-1 infected subjects N=285	- Oral dose of DRV/rtv 600/100 mg twice daily for 96 weeks. - Oral dose of LPV/rtv 400/100 mg twice daily (or 533/133 mg twice daily in case NNRTI is included in OBR) for 96 weeks. + OBR of at least 2 ARVs (NRTIs with or without NNRTIs)	Completed Full report 5.3.3.5

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	TMC114-C935 (Not applicable)	TMC114-C211 modeling techniques (48 weeks)	Treatment-naïve HIV-1 infected subjects N=660	See study TMC114-C211	Completed Full report 5.3.3.5
3	TMC114-C947 (Not applicable)	Bayesian feedback analysis of DRV/rtv.	HIV-1 infected early treatment-experienced subjects with a viral load of >1,000 HIV-1 RNA copies/mL N=558	See study TMC114-C229	Completed Full report 5.3.3.5

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	GS-US-216-0130 Population PK (Not applicable)	Open-label, single-arm study. Model development, 24-week parameter re-estimation and Bayesian feedback for DRV.	HIV-1 infected antiretroviral treatment (ART)-naïve and ART–experienced adult subjects with 0 DRV resistance associated mutations N=60[a] N=303[b]	DRV oral dose of 800 mg in combination with 150 mg COBI once daily administered as single agents for 24 weeks, under fed conditions.	Completed Full report 5.3.3.5

[a] N=60 for model development and parameter re-estimation.

[b] N=303 for the Bayesian feedback.

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	TMC114-C153 (France: 1)	Open-label, randomized, active controlled, placebo-controlled, 4-way crossover study. To evaluate ECG intervals in healthy volunteers receiving DRV/rtv.	Healthy volunteers N=40	All subjects received Treatments A, B, C, and D. - Treatment A: an oral dose of DRV/rtv 1600/100 mg once daily for 7 days. - Treatment B: an oral dose of DRV/rtv 800/100 mg twice daily for 7 days. - Treatment C: an oral dose of moxifloxacine 400 mg once daily for 7 days (control). - Treatment D: an oral dose of placebo once daily for 7 days. There was a washout of at least 7 days between treatments.	Completed Synopsis Full report 5.3.4.1
1	GS-US-216-0107 (United States: 1)	Randomized, partially blinded, single-dose, placebo- and positive (moxifloxacin)-controlled, 8-sequence, 4-period crossover, thorough QT/QTc study. To evaluate the effects of COBI on time-matched, baseline-adjusted, placebo-corrected QTcF.	Healthy volunteers N=48	All subjects received Treatments A, B, C, and D - Treatment A: an oral dose of COBI 250 mg. - Treatment B: an oral dose of COBI 400 mg. - Treatment C: an oral dose of placebo. - Treatment D: an oral dose of moxifloxacin 400 mg There was a washout of 7 days between treatments.	Completed Synopsis Full report 5.3.4.1

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0101 (United States: 1)	Randomized, double-blind, placebo- and active-controlled, single and multiple dose-ranging study. To evaluate the safety and tolerability of escalating single and multiple oral doses of COBI, and to characterize the single-dose pharmacokinetics and steady-state pharmacokinetics and pharmacodynamics (anti-CYP3A activity) of COBI.	Healthy volunteers N=60	Part A - Cohort 1, Periods 1 (single dose for 1 day) and 2 (multiple-dose for 14 days): an oral dose of COBI 50 mg, ritonavir 100 mg, or matching placebo(s). - Cohort 2, Periods 1 (single dose for 1 day) and 22 (multiple-dose for 14 days): an oral dose of COBI 100 mg, ritonavir 100 mg, or matching placebo(s). Part B - Cohort 3: an oral dose of COBI 200 mg, ritonavir 100 mg, or matching placebo(s) for 14 days.	Completed Synopsis Full report 5.3.4.1

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0116 (United States: 1)	Two-cohort, randomized, open-label, multiple-dose, crossover study. To evaluate multiple-dose pharmacokinetics of a new formulation of COBI, administered alone; to evaluate multiple-dose pharmacokinetics of EVG as a stand-alone tablet administered with a new formulation of COBI tablet.	Healthy volunteers N=62	Cohort 1: Subjects in Cohort 1 received Treatments A/B or B/A - Treatment A: an oral dose of COBI 150 mg Formulation 2 (new formulation) once daily for 10 days. - Treatment B: an oral dose of COBI 150 mg Formulation 1 (original formulation) once daily for 10 days. Single oral dose of midazolam 5 mg on Days 10 and 20 (metabolic probe) (for both Treatments A and B) Cohort 2: Subjects in Cohort 2 received Treatments C/D or D/C - Treatment C: an oral dose of EVG 150 mg + COBI 150 mg Formulation 2 (new formulation), once daily for 10 days - Treatment D: an oral dose of EVG/rtv 150/100 mg once daily for 10 days.	Completed Synopsis Full report 5.3.4.1

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0119 (United States: 1)	Partially randomized, open-label, single-centre, multiple-dose, multiple-cohort, crossover study. To evaluate the safety, tolerability, and pharmacokinetics of COBI administered twice daily and the potential of COBI to boost plasma concentrations of coadministered DRV or tipranavir (all administered twice daily) relative to ritonavir; DRV/COBI treatments incorporating EVG or ETR were also evaluated versus DRV/rtv.	Healthy volunteers N=48	Cohort 1 - Treatment A: COBI 150 mg twice daily, oral (Days 1 to 10). Cohort 2: - Treatment B: DRV/r 600/100 mg twice daily, oral (Days 1 to 10). - Treatment C: DRV/COBI 600/150 mg twice daily, oral (Days 17 to 26). - Treatment D: DRV/COBI 600/150 mg twice daily + EVG 150 mg once daily, oral (Days 27 to 36). - Treatment E: DRV/COBI 600/150 mg + ETR 200 mg, twice daily, oral (Days 27 to 36). Cohort 3: - Treatment F: tipranavir/rtv 500/200 mg twice daily, oral (Days 1 to 10). - Treatment G: tipranavir/COBI 500/150 mg, twice daily, oral (Days 17 to 26).	Completed Full report (available upon request) 5.3.4.1
1	GS-US-216-0134 (United States: 1)	Multiple-dose, randomized study. To evaluate the pharmacokinetics and safety of COBI and TDF administered alone or in combination.	Healthy volunteers N=46	Cohort 1: - Treatment A: COBI 150 mg once daily for 7 days. - Treatment B: COBI 150 mg once daily + TDF 300 mg once daily for 7 days. Cohort 2: - Treatment B: COBI 150 mg coadministered once daily with TDF 300 mg once daily for 7 days. - Treatment C: TDF 300 mg once for 7 days.	Completed Full report (available upon request) 5.3.4.1

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-236-0130 (United States: 1)	Randomized, blinded, placebo controlled study. To evaluate the effect of COBI and TDF, each administered alone, in combination or as part of the QUAD single tablet regimen (EVG/COBI/FTC/ TDF) versus placebo on renal function.	Healthy volunteers N=71	Treatment 1: COBI 150 mg, plus TDF placebo, plus QUAD placebo to match for 30 days, oral. Treatment 2: TDF 300 mg, plus COBI placebo, plus QUAD placebo for 30 days, oral. Treatment 3: COBI 150 mg plusTDF 300 mg, plus QUAD placebo for 30 days, oral. Treatment 4: QUAD, plus COBI placebo, plus TDF placebo for 30 days, oral. Treatment 5: TDF placebo, plus COBI placebo, plus QUAD placebo for 30 days, oral.	Completed Full report (available upon request) 5.3.4.1

5.3.4.2 Patient PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1 - 2	TMC114-C926 (Not applicable)	Subject PK/PD study report	3-class-experienced, HIV-1 infected subjects N=468	- Control: OBR, oral, 96 weeks - DRV/rtv: oral, 400/100 mg once daily, or 800/100 mg once daily, or 400/100 mg twice daily, or 600/100 mg twice daily, for 96 weeks	Completed Full report 5.3.4.2
3	TMC114-C0000009 (Not applicable)	Subject PK/PD study report	Treatment-naïve HIV-1 infected subjects and early treatment-experienced subjects with a viral load of >1,000 HIV-1 RNA copies/mL N=335+280	See individual studies TMC114-C211 and TMC114-C229.	Completed Full report 5.3.4.2

5.3.4.2 Patient PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	GS-US-216-0130 PK/PD (Not applicable)	Open-label, single-arm study. Pharmacokinetic and Pharmacodynamic Analyses of DRV at Week 24 in Study GS-US-216-0130.	HIV-1 infected antiretroviral treatment (ART)-naïve and ART–experienced adult subjects with 0 DRV resistance associated mutations N=281	DRV oral dose of 800 mg in combination with 150 mg COBI once daily administered as single agents for 24 weeks, under fed conditions.	Completed Full report 5.3.4.2

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
2a	TMC114-C207 (International, multicentre)	Randomized, open-label, controlled, dose-finding study. To investigate the antiviral activity of DRV formulated as an oral solution coadministrated with low-dose ritonavir in patients with multiple protease inhibitor (PI) resistant strains (Proof-of-principle).	HIV-1-infected, PI-experienced subjects N=50	- Control: remain on failing therapy. - DRV/rtv: oral, 300/100 mg twice daily, or 600/100 mg twice daily, or 900/100 mg once, for 13 days followed by a single intake on Day 14	Completed Full report (available upon request) 5.3.5.1
3	TMC114-C211 (International: multicenter)	Randomized, controlled (LPV/rtv), open-label study. The primary objective: demonstrate non-inferiority with DRV/rtv versus LPV/rtv, in a confirmed plasma viral load <50 copies/mL at 48 weeks.	Treatment-naïve HIV-1 infected subjects N=689	- An oral dose of DRV/rtv 800/100 mg once daily for maximum 192 weeks. - An oral dose of LPV/rtv 800/200 mg once daily or 400/100 mg twice daily (depending on approval of once-daily use of LPV/rtv), for maximum 192 weeks. + Fixed background of tenofovir/FTC, oral, 300/200 mg once daily for maximum 192 weeks.	Completed - Reports of SAEs. - Data up to cut-off date of primary efficacy analyses, [redacted]: Full report 48 Weeks - Data up to [redacted]: Full report 96 Weeks - Data up to [redacted]: Full report 192 Weeks 5.3.5.1

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	TMC114-C214 (International, multicentre)	Randomized, controlled (LPV/rtv), open-label study. The primary objective: demonstrate non-inferiority with DRV/rtv versus LPV/rtv, in a confirmed plasma viral load < 400 copies/mL at 48 weeks.	Treatment-experienced (ie, have been on a HAART regimen for at least 12 weeks) HIV-1 infected subjects N=595	- DRV/rtv, oral, 600/100 mg twice daily, for 96 weeks. - LPV/rtv, oral, 400/100 mg twice daily (or 533/133 mg twice daily in case NNRTI is included in OBR), for 96 weeks. + OBR of at least 2 ARVs (NRTIs with or without NNRTIs)	Completed Full report (available upon request) 5.3.5.1
3	TMC114-C229 (International: multicenter)	Randomized, open-label study. To compare the efficacy, safety and tolerability of DRV, formulated as an oral tablet, administered with low-dose ritonavir (rtv) over a 48-week treatment period.	HIV-1 infected early treatment-experienced subjects with a viral load of >1,000 HIV-1 RNA copies/mL N=590	- An oral dose of DRV/rtv 800/100 mg once daily for 48 weeks. - An oral dose of DRV/rtv 600/100 mg twice daily for 48 weeks. + OBR of at least 2 investigator selected NRTIs	Completed - Reports of SAEs - Data up to [redacted]: Full report 48 Weeks 5.3.5.1

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.1 Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	GS-US-236-0118 (International, multicentre)	Open-label study. To characterize the effect of COBI-based regimens on parameters of renal function in HIV-infected patients with mild to moderate renal impairment.	HIV-1 infected subjects with mild to moderate renal impairment N=100 (planned)	Cohort 1: - Single tablet regimen of EVG 150mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg for 96 weeks, oral. Cohort 2: - COBI-boosted atazanavir + 2 NRTIs for 96 weeks, or COBI-boosted DRV + 2 NRTIs for 96 weeks, oral	Ongoing Interim report (available upon request) 5.3.5.1

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.2 Study Reports of Uncontrolled Clinical Studies (Pertinent to the Claimed Indication)

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	GS-US-216-0130 (United States: 56)	Open-label, single-arm study. To assess safety and efficacy of a regimen of COBI-boosted DRV (coadministered as single agents) + 2 fully active NRTIs in HIV-1 infected ART-naïve and ART–experienced adult subjects with 0 DRV RAMs.	HIV-1 infected ART-naïve and ART–experienced adult subjects with 0 DRV RAMs N=313	DRV oral dose of 800 mg in combination with 150 mg COBI once daily administered as single agents for 24 weeks, under fed conditions.	Completed (data up to cut-off of Week-24 interim analysis) Synopsis Full report 5.3.5.2

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.2 Study Reports of Uncontrolled Clinical Studies (Pertinent to the Claimed Indication)

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
2	TMC114-C228[*] (International, multicenter)	Open-label study. To evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV in combination with low-dose ritonavir (rtv) and to support dose recommendations of DRV/rtv in this population.	HIV-1 infected pediatric (3 to <6 years) subjects N=27[†]	Before dose adjustment[‡] DRV, oral, suspension (F052), 20 mg/kg twice daily with rtv, oral solution 3 mg/kg twice daily + OBR. After dose adjustment[†] - children weighing 10 to <15 kg: DRV, oral, suspension (F052), 25 mg/kg twice daily with rtv, oral solution 3 mg/kg twice daily + OBR. - children weighing 15 to <20 kg: DRV, oral, suspension (F052), 375 mg twice daily with rtv, oral solution 50 mg twice daily + OBR. Total treatment duration: 48 weeks.	Completed - Reports of SAEs - Data up to [redacted]: Full report 24 Weeks - Data up to [redacted]: Full report 48 Weeks 5.3.5.2
2	TMC114-C230[§] (International, multicenter)	Open-label study. To evaluate pharmacokinetics, safety, tolerability and antiviral activity of DRV/rtv once daily.	Treatment-naïve HIV-1 infected adolescents N=12	DRV/rtv, oral, 800/100 mg once daily + OBR for 48 weeks.	Completed - Reports of SAEs - Data up to [redacted]: Full report 24 Weeks - Data up to [redacted]: Full report 48 Weeks 5.3.5.2

[*] Study TMC114-C228 is included as part of the developed pediatric investigation plan (PIP) for the FDC (PIP decision number P/0036/2013).

[†] Twenty-seven treatment-experienced HIV-1 infected children from 3 to <6 years of age and weighing between 10 and <20 kg were recruited for inclusion in study TMC114-C228. Due to critical inspection findings at Site KE00004 (involving 6 subjects), the analyses in the main body of the report reflect analyses performed without the data from this site (ie, with a sample size of 21).

[‡] F052: oral suspension containing 100 mg eq. DRV/mL, rtv: oral solution containing 80 mg eq. rtv/mL.

[§] Study TMC114-C230 is included as part of the developed PIP for the FDC (PIP decision number P/0036/2013).

5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.3 Reports of Analyses of Data from More Than One Study

No pooling of data from clinical safety or efficacy studies was performed. Therefore, no reports of analyses of data from more than one study are available.

5.3.5.4 Other Clinical Study Reports

These reports are available in Module 4.2.1.

5.3.6 Reports of Postmarketing Experience

The DRV/COBI FDC tablet has not yet been marketed. Therefore, no reports of postmarketing experience are available.

5.3.7 Case Report Forms and Individual Patient Listings

Janssen commits to providing Case Report Forms as well as individual patient listings for Deaths, other Serious Adverse Events (SAE) and withdrawals due to (S)AEs within 48 hours upon request. Other random samples of CRFs can be made available upon request, within 5 to 10 working days. If the number of random samples of CRFs is substantial, timelines for delivery will be discussed and agreed upon.

Janssen Research & Development

Tabular Listing of All Clinical Studies - Addendum

Physiologically-based Pharmacokinetic Modeling of Interactions of CYP3A4 Inhibitors with Cobicistat

DRV/COBI (darunavir/cobicistat)

Status: Approved
Date: 1 April 2015
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
EDMS no. and version: EDMS-ERI-102342825, 1.0

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5.3.2 Reports of Studies Pertinent to Pharmacokinetics Using Human Biomaterials

5.3.2.2 Reports of Hepatic Metabolism and Drug Interaction Studies

Report Number	Report Title	Status Study Location in the FDC CTD
AD-216-2113	Physiologically-based pharmacokinetic modeling of interactions of CYP3A inhibitors with cobicistat	Completed Full report 5.3.2.2

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.3.5 Population PK Study Reports

Report Number	Report Title	Status Study Location in the FDC CTD
N/A	Population pharmacokinetics of cobicistat Supplemental population pharmacokinetic modeling data	Completed Full report 5.3.3.5

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.4.1 Healthy Subject PD and PK/PD Study Reports

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
1	GS-US-216-0119 (United States: 1)	Partially randomized, open-label, single-centre, multiple-dose, multiple-cohort, crossover study. To evaluate the safety, tolerability, and pharmacokinetics of COBI administered twice daily and the potential of COBI to boost plasma concentrations of coadministered DRV or tipranavir (all administered twice daily) relative to ritonavir; DRV/COBI treatments incorporating EVG or ETR were also evaluated versus DRV/rtv.	Healthy volunteers N=48	Cohort 1 - Treatment A: COBI 150 mg twice daily, oral (Days 1 to 10). Cohort 2: - Treatment B: DRV/r 600/100 mg twice daily, oral (Days 1 to 10). - Treatment C: DRV/COBI 600/150 mg twice daily, oral (Days 17 to 26). - Treatment D: DRV/COBI 600/150 mg twice daily + EVG 150 mg once daily, oral (Days 27 to 36). - Treatment E: DRV/COBI 600/150 mg + ETR 200 mg, twice daily, oral (Days 27 to 36). Cohort 3: - Treatment F: tipranavir/rtv 500/200 mg twice daily, oral (Days 1 to 10). - Treatment G: tipranavir/COBI 500/150 mg, twice daily, oral (Days 17 to 26).	Completed Synopsis Full report 5.3.4.1

Janssen Research & Development

Tabular Listing of All Clinical Studies - Addendum

Cobicistat-containing Highly Active Antiretroviral Regimens in HIV-1 Infected Patients with Mild to Moderate Renal Impairment

DRV/COBI (darunavir/cobicistat)

Status: Approved
Date: 25 September 2015
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
EDMS no. and version: EDMS-ERI-111366618, 1.0

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5.3.5 Reports of Clinical Efficacy and Safety Studies

5.3.5.2 Uncontrolled Studies (Phase III or Other)

Study Phase	Study (Country and Number of Centers)	Design Study Objectives	Subjects Total Number of Subjects	Dosage Regimen Route of Administration Duration of Treatment	Status Type of Report Study Location in the FDC CTD
3	GS-US-236-0118 (United States: 23; Puerto Rico: 2; United Kingdom: 5; Australia: 3; Austria: 2; Canada: 2; Mexico: 1; Dominican Republic: 1; Germany: 1)	Open-label, multicenter, multiple-cohort study. To evaluate the effect of COBI-containing regimens on renal parameters at Week 24. To evaluate the safety and tolerability of COBI-containing regimens. To evaluate the long-term effect of COBI-containing regimens on renal parameters. To measure the proportion of subjects achieving virologic response at Weeks 24, 48, and 96 (HIV-1 RNA <50 copies/mL, snapshot analysis).	HIV-1 infected adults with mild to moderate renal impairment ($eGFR_{CG}$ of 50 to <90 mL/min), with stable renal function N=106	- Cohort 1 (STB): coformulated EVG 150 mg/ COBI 150 mg/ FTC 200 mg/ TDF 300 mg, orally, once daily with food at approximately the same time each day for 96 weeks. - Cohort 2 (PI/co): 1 × 150-mg COBI tablet orally, once daily with food at approximately the same time each day. All other regimen components (ATV or DRV + 2 NRTIs) were as prescribed by the investigator for 96 weeks.	Completed Synopsis Full report 5.3.5.2