Janssen Research & Development

Clinical Overview

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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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADR	adverse drug reaction
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
APV	amprenavir
ART	antiretroviral therapy
ARV	antiretroviral
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{∞}	area under the plasma concentration-time curve measured from time zero and extrapolated to infinity
AUC_{24h}	area under the plasma concentration-time curve over 24 hours
AUC_{last}	area under the plasma concentration-time curve from time zero to the last quantifiable concentration
C_{0h}	predose plasma concentration
CI	confidence interval
C_{max}	maximum plasma concentration
COBI	cobicistat
CSR	Clinical Study Report
C_{tau}	plasma concentration at the end of the dosing interval tau
CYP	cytochrome P450
DAIDS	Division of AIDS
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
DRV	darunavir
EC_{50}	50% effective concentration
ECG	electrocardiogram
EFV	efavirenz
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	eGFR calculated by the Cockcroft-Gault method
$eGFR_{CC}$	eGFR calculated by cystatin C clearance
$eGFR_{MDRD}$	eGFR calculated using the Modification of Diet in Renal Disease method
ETR	etravirine
EVG	elvitegravir
FC	fold change in EC_{50} values
FDA	Food and Drug Administration
FDC	fixed dose combination
FTC	emtricitabine
GFR	glomerular filtration rate
HDL	high-density lipoprotein
HIV-1	human immunodeficiency virus type 1
IAS	International AIDS Society
IDV	indinavir
IgG	immunoglobulin G
InSTI	integrase strand transfer inhibitor
ITT	intent-to-treat; ITT population: all subject who received at least 1 dose of the study medication
K_d	dissociation constant
LDL	low-density lipoprotein
LOCF	last observation carried forward
LPV	lopinavir
LS	least square
M=E	missing equals excluded
M=F	missing equals failure
MedDRA	Medical Dictionary for Regulatory Activities
MATE1	multidrug and toxin extrusion protein 1
NFV	nelfinavir
NNRTI	non-nucleoside reverse transcriptase inhibitor

non-VF	non-virologic failure
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
P-gp	P-glycoprotein
PD	pharmacodynamic
PI	protease inhibitor
PK	pharmacokinetic(s)
qd	quaque in die, once daily
QTc	QT interval corrected for heart rate
RAM	resistance associated mutation
RNA	ribonucleic acid
rtv	low-dose ritonavir
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SQV	saquinavir
STR	single tablet regimen
TDF	tenofovir disoproxil fumarate
TLOVR	time to loss of virologic response
TMC	Tibotec Medicinal Compound
TMC114-C211	study TMC114-C211, referred to as ARTEMIS
TMC114-C229	study TMC114-TiDP31-C229, referred to as ODIN
TPV	tipranavir
UGT	uridine diphosphate glucuronosyltransferase

1. PRODUCT DEVELOPMENT RATIONALE

1.1. Pharmacologic Class and Targeted Indication

The darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) tablet contains 800 mg of the medicinal product DRV and 150 mg of the medicinal product COBI and is developed by the Applicant in collaboration with Gilead Sciences Inc (Gilead). Darunavir is a registered human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI) and COBI has recently been registered to be concurrently administered as a pharmacokinetic (PK) enhancer of DRV and atazanavir (ATV).

The DRV/COBI FDC 800/150-mg tablet is to be administered once daily and is dosed according to the same once-daily dosage regimen as the single agents.

This tablet is intended to be used in the same adult population for which DRV/low-dose ritonavir (rtv) 800/100 mg once daily (coadministered as single agents) is registered, ie, antiretroviral therapy (ART)-naïve adults and ART-experienced adults with no DRV resistance associated mutations (RAMs) and who have plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L, as described in the proposed indication section of the Summary of Product Characteristics (SmPC) in Module 1. The intended indication for the FDC of DRV/COBI 800/150 mg does not represent a new combination regimen but 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.[11]

1.2. Relevant Scientific Background

An estimated 34.2 million people worldwide are infected with HIV. HIV infection can result in acquired immunodeficiency syndrome (AIDS) which has a significant human and socio-economic impact globally. During 2011, an estimated 2.5 million people became newly infected with HIV-1 and 1.7 million died from AIDS worldwide.[18]

The introduction of combination ART has led to a dramatic reduction in HIV-1 related mortality, and in opportunistic and other related infections in HIV-1 infected individuals. Current treatment options include HIV PIs, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), entry inhibitors (eg, CCR5 antagonist and fusion inhibitor), and integrase strand transfer inhibitors (InSTIs). Protease inhibitors play an important role and are widely used in the treatment of HIV-1 infection. They are most often combined with rtv which serves as a PK enhancer of the PI by inhibiting its metabolism via cytochrome P450 (CYP) 3A isozyme. The use of combination ART can be hampered by high pill burden leading to suboptimal adherence, and subsequent development of viral resistance and treatment failure. These consequences are important drivers for the development of simpler, more convenient antiretroviral (ARV) regimens, including FDCs. Regimen simplicity is recognized by treatment guidelines as an important factor in the selection of an individualized treatment regimen.[11,13,14,22,23,28,31,34,36]

Darunavir (PREZISTA®, also known as TMC114), is an HIV-1 PI, developed by Janssen Research and Development (formerly Tibotec). It is currently indicated for the treatment of HIV-1 infection in adults and in pediatric patients of 3 years of age and above, in combination with rtv and with other ARVs. Low-dose ritonavir is coadministered with DRV (as single agent) for its CYP3A inhibitor properties, in order to enhance (boost) DRV systemic exposure. Darunavir obtained marketing authorization in Europe in February 2007 and is currently registered in more than 100 countries. Once daily and twice daily dosing recommendations of DRV/rtv are available. The dose regimen DRV/rtv 800/100 mg once daily is recommended in ART-naïve adult patients and ART-experienced adult patients with no DRV RAMs,[*] who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100x10^6 cells/L.[30]

In ART-naïve HIV-1 infected subjects this dosing recommendation was registered based on the demonstration of noninferiority in virologic response of the regimen when compared with lopinavir (LPV)/rtv 800/200 mg total daily dose (either 400/100 mg twice daily or 800/200 mg once daily) in the registrational study TMC114-C211 (also referred to as ARTEMIS). In this study, 343 subjects received DRV/rtv 800/100 mg once daily and 346 subjects received a daily dose of LPV/rtv 800/200 mg, both in combination with a fixed background regimen of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC); data up to Week 192 are available (Module 5.3.5.1/TMC114-C211-W192-CRR).[27] 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, in the registrational study TMC114-C229 (also referred to as ODIN). In this study, 294 subjects with a viral load >1,000 HIV-1 RNA copies/mL and a CD4+ cell count >50x10^6 cells/L at screening received DRV/rtv 800/100 mg once daily and 296 subjects received DRV/rtv 600/100 mg twice daily, both in combination with an investigator-selected optimized background regimen of ≥2 NRTIs (Module 5.3.5.1/TMC114-C229-W48-CRR).[3] Based on the review of the clinical efficacy and safety of this study, the benefit-risk balance for DRV was considered positive for the treatment of HIV-1 infection in ART-experienced adults with no DRV RAMs and who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count more than 100x10^6 cells/L. The results of both studies confirmed that DRV/rtv 800/100 mg once daily is generally safe and well tolerated and provides substantial and durable efficacy benefits.

Cobicistat (formerly known as GS-9350) is a new chemical entity developed by Gilead for use as a PK enhancer to increase systemic exposure of coadministered drugs metabolized by CYP3A enzymes, including the HIV-1 InSTI elvitegravir (EVG), and the HIV PIs ATV and DRV. It is a structural analog of rtv and a potent, mechanism-based inhibitor of CYP3A. Inhibition of CYP3A-mediated metabolism by COBI enhances the systemic exposure of CYP3A substrates, such as DRV; this is useful in situations where bioavailability is limited and half-life is shortened by CYP3A-dependent metabolism. Cobicistat itself has no detectable antiviral activity against HIV-1 in vitro and does not directly contribute to the efficacy of an ARV regimen. Its primary pharmacodynamic activity is to enhance the exposure of drugs that are metabolized by CYP3A in order to achieve appropriate therapeutic exposures.[35]

[*] DRV RAMs: V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V and L89V[17]

A single tablet regimen (STR) EVG/COBI/FTC/TDF (STRIBILD®) was approved by the Food and Drug Administration (FDA) on 27 August 2012 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). On 24 May 2013, the European Commission granted marketing authorization for STRIBILD, film-coated tablets intended for treatment of HIV-1 infection in adults aged 18 years and over who are ART-naïve or are infected with HIV-1 without known mutations associated with resistance to any of the 3 ARV agents in STRIBILD.[33]

For the combination with DRV, 2 Phase 1 studies with DRV/COBI coadministered as single agents in healthy subjects were conducted by Gilead as part of the COBI development program. Study GS-US-216-0119 assessed the PK of twice-daily regimens in healthy subjects of COBI alone, DRV/COBI, DRV/rtv, and of tipranavir (TPV)/COBI and TPV/rtv.[7] GS-US-216-0115, a Phase 1 study in 33 healthy subjects, established that COBI 150 mg is the appropriate dose for boosting DRV 800 mg once daily (refer to Module 5.3.1.2/GS-US-216-0115-CSR). In this study, the DRV area under the plasma concentration-time curve over 24 hours (AUC_{24h}) and the maximum plasma concentration (C_{max}), were similar for DRV/COBI 800/150 mg once daily and DRV/rtv 800/100 mg once daily (both regimens coadministered as single agents). The DRV plasma concentration at the end of the dosing interval (C_{tau}) was lower in the COBI group compared to the rtv group (mean [SD]: 1,333 [890] ng/mL versus 1,867 [1,555] ng/mL), but this is not expected to be clinically relevant based on pharmacokinetic/pharmacodynamic (PK/PD) analyses of the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229 with DRV/rtv (refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2/Section 3.4.1.1). Based on these results, it was deemed reasonable to extrapolate the efficacy and safety observed with DRV 800 mg once daily when boosted with rtv to DRV 800 mg once daily when boosted with COBI. As the DRV/COBI FDC 800/150 mg is indicated as a 'substitution indication' of an already approved regimen, no comparative Phase 3 efficacy study was conducted.[11] To further support the registration of COBI as a PK enhancer of DRV, and the registration of the DRV/COBI FDC product, Gilead, in collaboration with the Applicant, conducted a Phase 3b, single-arm clinical study GS-US-216-0130. This study was conducted primarily to generate Week-24 additional safety data on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with 2 NRTIs, but also further provides supportive evidence of the efficacy and PK profile of DRV/COBI in the targeted population (Module 5.3.5.2/GS-US-216-0130-W24-CSR).

1.3. Clinical Development Program of DRV/COBI FDC

The DRV/COBI FDC tablet is developed to provide the combination of DRV and its PK enhancer as one single tablet, and thus provides the option to simplify a DRV-containing ARV regimen. It therefore offers patients convenience as well as the potential for improved adherence and reduced risk of medication errors. The DRV/COBI FDC formulation would be the first coformulation of DRV and a PK enhancer. It is also notable that the DRV/COBI FDC formulation would potentially be one of the first FDCs of a PI not containing rtv and could therefore be used in patients who are intolerant to rtv.

1.3.1. Adults

The clinical development of the DRV/COBI FDC tablet has been built on the information accrued from the development program for DRV in combination with rtv (conducted by the Applicant) and on the development program for COBI (conducted by Gilead), as outlined in Section 1.2. The FDC program aimed at generating PK data that support the development of a FDC formulation and bridge the comprehensive datasets of the individual agents to the FDC formulation. Due to this PK bridging approach, data on the DRV/COBI FDC has not been submitted in several indents of Module 5 but has been replaced by relevant data from the existing development programs of the individual compounds DRV (in combination with rtv) and COBI. The regulatory and scientific rationale for this can be found in Appendix 1.

The target profile for the FDC drug product was a once-daily immediate release oral solid dosage form incorporating 800 mg eq. of DRV (free form) and 150 mg eq. of COBI (non-adsorbed form), while maintaining a maximum core tablet weight of 1600 mg.

Darunavir 800 mg, in combination with 100 mg rtv once daily, is a registered dose regimen. Gilead demonstrated 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 once daily (GS-US-216-0115). The FDC combines 2 products at the same once daily dosage regimen as the selected dose for the single agents; therefore no dose selection study was performed.

The PK data for DRV with the proposed DRV/COBI FDC 800/150-mg tablet were bridged with the existing data for DRV/rtv coadministered as single agents by conducting 2 Phase 1 studies in healthy subjects (relative bioavailability study TMC114IFD1001 and bioequivalence study TMC114IFD1003). The PK results for study TMC114IFD1001 were consistent with those of study GS-US-216-0115. Altogether, these 3 Phase 1 studies showed that DRV exposures achieved with the DRV/COBI FDC are similar to those observed with the rtv- or COBI-boosted DRV single agent. The results allowed the selection of an appropriate DRV/COBI FDC 800/150-mg tablet formulation for the intended commercial use (G006).

The intended indication for the FDC concerns a substitution indication of DRV/COBI registered coadministration and the guideline related to such application does not require a comparative trial with the FDC formulation.[11]

The absence of synergistic toxicity based on the assessment of the preclinical data, the Phase 1 PK bridging results, and the established long-term safety profile of DRV when boosted with rtv, support the extrapolation of the rtv-boosted DRV safety profile to the FDC tablet. The FDC clinical development plan was complemented by a Phase 3b, single-arm study (GS-US-216-0130) to primarily provide evidence of the Week-24 safety profile of DRV/COBI 800/150 mg once daily (coadministered as single agents) in HIV-1 infected subjects, in support of the FDC tablet registration (see Section 5.4.2). Results of the Week-48 interim safety analysis of ongoing study GS-US-216-0130 are discussed in Section 5.7.1.

Further support for the DRV/COBI safety profile is provided by study GS-US-236-0118 performed by Gilead as part of the EVG/COBI program in HIV-1 infected adults with mild to

moderate renal impairment. The study, which includes a cohort treated with DRV/COBI (n=21) or ATV/COBI (n=52) is ongoing; preliminary interim safety data are presented in Section 5.7.

The Applicant obtained Scientific Advice from The Medicines Evaluation Board (MEB), The Netherlands, and Pre-Investigational New Drug (IND) advice from the FDA for the development of the FDC product.[15,24]

All studies included in this application were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonisation Good Clinical Practice guidelines, applicable regulatory requirements.

1.3.2. Pediatrics

The safety and efficacy of a DRV/COBI FDC have not been established in pediatric patients aged from 3 to <18 years; the development of a FDC in this age category is ongoing (see pediatric investigation plan decision number P/0036/2013). The DRV/COBI FDC should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with DRV (see Section 5.1).

2. OVERVIEW OF BIOPHARMACEUTICS

Four completed clinical biopharmaceutical studies (GS-US-216-0115, TMC114IFD1001, TMC114IFD1003, TMC114-C143) evaluated the bioavailability of DRV and COBI as single agents or as DRV/COBI 800/150-mg FDC tablet formulation.

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 Module 2.7.1/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 (standardized breakfast) and fasted conditions. The effect of a high-fat meal relative to fasting was also assessed with the FDC tablet in this study.

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 influence of food on exposure of DRV and COBI is discussed in Section 3.1.1.

The target profile for the drug product was a once-daily immediate release oral solid dosage form incorporating 800-mg eq. of DRV (free form) and 150-mg eq. of COBI (non-adsorbed form), while maintaining a maximum core tablet weight of 1600 mg. A comprehensive overview of the

formulation development process is provided in the Drug Product Formulation Development summary in Module 3.2.P.2.2.1.

2.1. Study GS-US-216-0115

GS-US-216-0115 was an open-label, randomized, 2-period crossover Phase 1 study in 33 healthy subjects to evaluate, under fed conditions, the oral bioavailability of DRV 800 mg when coadministered as single agents with either COBI 150 mg or rtv 100 mg, both of which are PK enhancers of DRV (refer to Module 5.3.1.2/GS-US-216-0115-CSR).

The DRV AUC_{24h} and C_{max}, were similar for DRV/COBI 800/150 mg once daily and DRV/rtv 800/100 mg once daily (both regimens coadministered as single agents); the 90% confidence intervals (CIs) for the least square (LS) means ratios were contained within the 80.00% to 125.00% bounds. The DRV C_{tau} was lower in the COBI group compared to the rtv group (mean [SD]: 1,333 [890] ng/mL versus 1,867 [1,555] ng/mL), but this is not expected to be clinically relevant based on pharmacokinetic/pharmacodynamic (PK/PD) analyses of the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229 with DRV/rtv (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.4.1.1).

For further details on the biopharmaceutical results of study GS-US-216-0115, refer to the Summary of Biopharmaceutical Studies and Associated Analytical Methods in Module 2.7.1/ Section 2.1.1.

2.2. Study TMC114IFD1001

In study TMC114IFD1001, DRV exposures provided by the 2 different DRV/COBI FDC 800/150-mg tablet formulations (G003 and G004) were compared to those of DRV 800 mg coadministered with rtv 100 mg as single agents. The 2 oral tablet formulations G003 and G004 differ only slightly in excipient combinations (refer to Module 2.7.1/Section 2.1.1).

TMC114IFD1001 was an open-label, randomized, 3-way crossover Phase 1 study in 36 healthy subjects to evaluate, under fed and steady-state conditions, the PK and relative bioavailability of these 2 FDC formulations versus DRV/rtv 800/100 mg coadministered as single agents (refer to Module 5.3.1.1/TMC114IFD1001-CSR).

The PK results from this study show that for both DRV/COBI FDC 800/150-mg tablets, at steady-state and when administered under fed conditions, DRV C_{max} and AUC_{24h} values with DRV/COBI FDC were comparable to DRV coadministered with rtv as a single agent; the 90% CIs of the ratios of the LS means for C_{max} and AUC_{24h} were contained within the 80.00% to 125.00% boundaries. Modestly lower predose plasma concentration (C_{0h}) and minimum plasma concentration values were observed in the COBI group compared to when boosted with rtv. These results are consistent with observations in study GS-US-216-0115 (see Section 2.1), and are not expected to be clinically relevant based on PK/PD analyses of the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229 with DRV/rtv (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.4.1.1).

Both formulations were deemed suitable for commercialization but the G004 formulation was selected, because it is closely aligned with the DRV 800-mg tablet formulation and employed the simplest product composition. The G004 FDC tablet formulation was further used in a modified form as the G006 FDC tablet formulation (identical to the G004 tablet except for the nonfunctional coating color; refer to Module 2.7.1/Section 1.1.1).

For further details on the biopharmaceutic results of study TMC114IFD1001, refer to the Summary of Biopharmaceutic Studies and Associated Analytical Methods in Module 2.7.1/ Section 2.1.2.

2.3. Study TMC114IFD1003

Study TMC114IFD1003 tested bioequivalence between the DRV/COBI FDC 800/150-mg tablet formulation G006 and DRV 800 mg coadministered with COBI 150 mg as single agents, both under fed and/or fasted conditions (refer to Module 5.3.1.2/TMC114IFD1003-CSR). TMC114IFD1003 was an open-label, randomized, 3-panel, single-center, single-dose, crossover Phase 1 study and included 133 healthy subjects.

The PK results from this study show that C_{max}, AUC from time zero to the last quantifiable concentration (AUC_{last}), and AUC measured from time zero and extrapolated to infinity (AUC_{∞}) of DRV and COBI were bioequivalent both in fasted and fed conditions for DRV/COBI administered as single agents and as FDC tablet G006; with the 90% CI of the ratios of the LS means for AUC_{last}, AUC_{∞} and C_{max} falling within the 80.00% to 125.00% boundaries of no effect.

The results support the choice of formulation G006 as the proposed commercial formulation of the FDC.

For further details on the biopharmaceutic results of study TMC114IFD1003, refer to the Summary of Biopharmaceutic Studies and Associated Analytical Methods in Module 2.7.1/ Section 2.2.1.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

3.1. Pharmacokinetics

The PK properties of the individual components DRV and COBI have been subject to comprehensive development programs to support their respective Marketing Authorisations.

The development strategy for the DRV/COBI FDC tablet focused on the compatibility of the active ingredients with each other and with the other excipients of the formulation. In addition, the program for the FDC aimed to demonstrate bioequivalence between the FDC tablet and the concurrently administered individual dosage forms.

This section provides a summary of the already available PK data on the individual single agents and details of the additional clinical studies specific for the FDC. For additional information on the clinical pharmacology data related to the single agents and the FDC, refer to the Summary of Clinical Pharmacology Studies in Module 2.7.2.

3.1.1. Absorption and Food Effect

The absolute oral bioavailability of a single 600-mg dose of DRV alone was 37% and increased to 82% in the presence of 100 mg rtv twice daily.[4] The overall PK enhancement effect by rtv was an approximate 14-fold increase in the systemic exposure of DRV when a single dose of 600 mg DRV was given orally in combination with rtv 100 mg twice daily (refer to Module the Summary of Clinical Pharmacology Studies, 2.7.2/Section 3.1.1.1).[4] When administered without food, the relative bioavailability of DRV in the presence of rtv is 30% lower as compared to intake with food (refer to Module 5.3.1.1/TMC114-C143-CRR and Module 2.7.1/Section 2.3.1). Therefore, DRV/rtv should be taken with food.

Following oral administration of COBI with food in HIV-1 infected subjects, C_{max} of COBI was observed 4 hours postdose. The mean (SD) C_{max}, AUC_{24h} and C_{0h} at steady-state following multiple doses of COBI in HIV-1 infected subjects (N=68) were 1.2 (0.3) µg/mL, 10.9 (3.8) µg.h/mL, and 0.07 (0.07) µg/mL, respectively.[35] In clinical studies, COBI was coadministered with ATV or DRV under fed conditions in accordance with the product labeling for these agents. It is recommended that COBI, when coadministered with DRV, is administered with food.

Following a single oral administration of DRV with COBI in healthy subjects, C_{max} of DRV is generally reached within 3 to 4.5 hours (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.3.1) and C_{max} of COBI is observed 2 to 5 hours postdose (Module 2.7.1/Table 15). In study TMC114IFD1003 (Module 5.3.1.2/TMC114IFD1003-CSR), the effect of food (a high-fat breakfast) on the exposure of DRV and COBI when administered as the DRV/COBI FDC (G006 tablet) was assessed. A food effect was observed for DRV; the mean C_{max}, AUC_{last}, and 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 to administration under fasted conditions. Exposure of COBI (C_{max}, AUC_{last}, and AUC_{∞}) with the DRV/COBI FDC was comparable following administration with a high-fat breakfast and under fasted conditions; the 90% CIs for the geometric mean ratios were contained within the 80.00% to 125.00% boundaries. For details, refer to Module 2.7.1/Section 2.2.1 and Module 5.3.1.2/ TMC114IFD1003-CSR.

The effect of different meal types on the oral bioavailability of DRV when coadministered with rtv was investigated in study TMC114-C143. 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. For details, refer to Module 2.7.1/Section 2.3.1 and Module 5.3.1.1/TMC114-C143-CRR.

It is recommended that the DRV/COBI FDC is administered with food. The type of food does not affect the exposure to DRV.

3.1.2. Distribution

Darunavir is bound approximately 95% to plasma proteins. Darunavir binds primarily to plasma α_1-acid glycoprotein (refer to the Summary of Clinical Pharmacology Studies,

Module 2.7.2/Section 3.1.1.2, Module 4.2.2.3/TMC114-NC215-NCPK and Nonclinical Study Report TMC114-NC113-NCDME[25]). This protein binding is concentration dependent indicative for saturation of binding. Therefore, protein displacement of medicinal products highly bound to α_1-acid glycoprotein cannot be ruled out (see Section 3.1.7).

Cobicistat is 97% to 98% bound to human plasma protein and binding is concentration-independent. The mean plasma-to-blood ratio was approximately 2 (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.2.2 and Module 5.3.3.1/GS-US-216-0111-CSR).

3.1.3. Metabolism

In vitro experiments with human liver microsomes indicate that DRV primarily undergoes oxidative metabolism. Darunavir is extensively metabolised by the hepatic CYP system and almost exclusively by CYP3A.[26] At least 3 oxidative metabolites of DRV have been identified in humans; all showed activity that was at least 10-fold less than the activity of DRV against wild-type HIV. A ^{14}C-DRV study in healthy subjects showed that a majority of the radioactivity in plasma after a single 400/100-mg DRV/rtv dose was due to the parent drug (Module 5.3.3.1/TMC114-C109-CRR). Further details are available in the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.1.3.

COBI is metabolized via CYP3A (major) and CYP2D6 (minor)-mediated oxidation and does not undergo glucuronidation. Following administration of ^{14}C-COBI, 99% of circulating radioactivity in plasma was unchanged COBI. Low levels of metabolites were observed in urine and feces and do not contribute to the CYP3A inhibitory activity of COBI. Further details are available in the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.2.3 and in Module 5.3.3.1/GS-US-216-0111-CSR.

3.1.4. Excretion

After a 400/100-mg ^{14}C-DRV/rtv dose (Module 5.3.3.1/TMC114-C109-CRR), approximately 79.5% and 13.9% of the administered dose of ^{14}C-DRV could be retrieved in feces and urine, respectively. Unchanged DRV accounted for approximately 41.2% and 7.7% of the administered dose in feces and urine, respectively (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.1.3.2).

Following oral administration of ^{14}C-COBI, 86% and 8.2% of the dose were recovered in the feces and urine, respectively (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.2.3.2 and Module 5.3.3.1/GS-US-216-0111-CSR). The median terminal plasma elimination half-life of COBI is approximately 3 to 4 hours.[35]

3.1.5. Pharmacokinetics of DRV/COBI or DRV/rtv in Healthy Subjects

The PK results in Phase 1 studies GS-US-216-0115, TMC114IFD1001 and TMC114IFD1003 are presented in Section 2.

Study GS-US-216-0115 showed that DRV exposure (AUC_{24h} and C_{max}) was similar for DRV/COBI 800/150 mg once daily and DRV/rtv 800/100 mg once daily (both regimens

coadministered as single agents). The DRV 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 (refer to Module 5.3.1.2/GS-US-216-0115-CSR and the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.3.2).

Study TMC114IFD1001 (Module 5.3.1.1/TMC114IFD1001-CSR) showed that COBI 150 mg once daily (as part of a DRV/COBI FDC tablet G003 or G004) provides DRV exposures comparable to those obtained when boosted with rtv 100 mg once daily and coadministered as single agents. Darunavir exposures were generally comparable to historical data for DRV exposure following multiple dose administration of DRV/rtv (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.3.2). Similar to previous findings in Gilead study GS-US-216-0115, DRV C_{tau} was lower in the COBI group compared to the rtv group, but this is not expected to be clinically relevant based on PK/PD analyses of the effect of DRV exposure on virologic response in studies TMC114-C211 and TMC114-C229 with DRV/rtv (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.4.1.1).

Study TMC114IFD1003 (Module 5.3.1.2/TMC114IFD1003-CSR) showed that the DRV/COBI FDC 800/150 mg tablet (G006) was bioequivalent to DRV/COBI 800/150 mg coadministered as single agents (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.1.3.1).

These results allow extrapolation of the efficacy observed in registrational studies with DRV 800 mg once daily, when boosted with rtv, to DRV 800 mg once daily, when boosted with COBI. They also support the extrapolation of the data generated with DRV/COBI 800/150 mg administered as single agents to the intended commercial FDC tablet (G006).

3.1.6. Pharmacokinetics of DRV/COBI or DRV/rtv in HIV-1 Infected Subjects

Darunavir exposures based on population PK analyses in study GS-US-216-0130 and in DRV/rtv studies are presented in Table 1. The population PK parameter estimates of DRV (C_{0h} and AUC_{24h}) following multiple-dose administration of DRV/COBI 800/150 mg once daily in study GS-US-216-0130 were comparable to historical values for DRV exposure following multiple-dose administration of DRV/rtv 800/100 mg once daily coadministered as single agents in ART-naïve (study TMC114-C211) and ART-experienced (study TMC114-C229 and integrated PK/PD analysis of studies TMC114-C202* and TMC114-C213*, Module 5.3.4.2/TMC114-C926-CPKPD) HIV-1 infected subjects.

* TMC114-C202 and TMC114-C213: Phase 2 dose-response studies of DRV/rtv in 3-class-experienced HIV-1 infected subjects

Table 1: 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 (Study GS-US-216-0130) or DRV/rtv 800/100 mg Once Daily (Studies TMC114-C211, TMC114-C229, TMC114-C202, and TMC114-C213) Coadministered as Single Agents

	Mean (SD); Median (Range)			
	DRV/COBI Single Agents 800/150 mg qd (ART-naïve and ART-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 [b]	Week 48 TMC114-C229 [b]	Week 24 TMC114-C202 + TMC114-C213[b]
N	298	335	280	118
C_{0h}, ng/mL	2,043 (1,257)	2,281 (1,168)	NA	1,963 (1,003)
	1,875 (70-6,890)	2,041 (368-7,242)	1,896 (184-7,881)	1,840 (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; qd=once daily; NA=not available.

[a] Only 3 subjects were ART-experienced

[b] Historical data from registrational studies with DRV/rtv 800/100 mg once daily coadministered as single agents.

Source: Module 2.7.2/Summary of Clinical Pharmacology Studies/Table 141.

3.1.7. Drug-drug Interaction

No drug-drug interaction studies have been conducted with DRV/COBI (FDC or coadministered as single agents). The drug-drug interaction potential of DRV/COBI is based on the interactions observed with the single agents. The following is a summary of the information most relevant to this combination. Further details are provided in the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.3.2.

Darunavir and COBI are metabolized by CYP3A. Drugs that induce CYP3A activity would be expected to lower plasma concentrations of DRV and COBI. Coadministration of DRV/COBI and other medicinal products that inhibit CYP3A may result in increased systemic exposure of DRV and COBI, which could increase or prolong their therapeutic effect and adverse reactions.

The in vitro drug interaction potential of COBI has been well studied, including the differences with rtv, as summarized in Module 2.7.3/Section 3.3.2.

A comprehensive drug-drug interaction program with DRV/rtv was conducted, including a cocktail study to assess the effects of DRV/rtv on the metabolism of probe substrates.[5] 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 uridine diphosphate glucuronosyltransferase (UGT). A summary of the interactions and recommendations to use DRV/rtv in combination with various drugs is available in the DRV SmPC.[30]

Like rtv, COBI was found to primarily be an inhibitor of CYP3A. Cobicistat is also an inhibitor of CYP2D6, albeit to a lesser extent than rtv. Therefore, most data generated with DRV/rtv 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), 3-hydroxy-3-methylglutary coenzyme A reductase inhibitors (lovastatin, simvastatin), neuroleptics (pimozide, sertindole), sildenafil (when used for treatment of pulmonary arterial hypertension), and sedative/hypnotics (oral midazolam, triazolam). Because DRV is metabolized by CYP3A, potent CYP3A inducers such as LPV/rtv, rifampicin and St John's wort (*Hypericum perforatum*) are also contraindicated. These contraindications also apply to DRV/COBI. In addition, avanafil, colchicine (when used 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 (ETR), efavirenz (EFV), nevirapine (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-glycoprotein (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 whereas COBI is not an inducer of UGT1A1). As COBI has less overall effects on drug metabolizing enzymes and transporters compared to 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. Therefore, caution is needed during the first 2 weeks after switch from rtv to COBI, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of rtv as a PK enhancer (refer to Section 6).

Darunavir/COBI should not be used in combination with another ARV that requires PK enhancement (eg, EVG and other HIV PIs), since dosing recommendations for such combination have not been established. Darunavir/COBI should not be used concurrently with medicinal products containing rtv or regimens containing rtv or COBI.

A table summarizing the theoretical drug-drug interactions for the DRV/COBI FDC as well as more detailed information on the background and extrapolation of drug-drug interactions is presented in the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.3.2.

A summary of interactions with ARVs is provided below. For interactions with other drugs, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Table 143 and Module 2.7.2/ Section 3.3.2.

Interactions With NRTIs

There are no metabolic interactions expected between didanosine and COBI (Module 5.3.3.4/TMC114-C123-CRR). As no clinically relevant interaction is expected with DRV/COBI, DRV/COBI and didanosine can be coadministered without dose adjustments, but their administration should be separated in time due to different meal requirements.

Coadministration of DRV/COBI with TDF may increase concentrations of tenofovir (inhibition of P-gp) (Module 5.3.3.4/TMC114-C124-CRR). The increase in tenofovir is not expected to be clinically relevant. In the Phase 3b study GS-US-216-0130, DRV/COBI was mostly (97%) combined with TDF/FTC and was, in general, safe and well tolerated (Module 5.3.5.2/ GS-US-216-0130-W24-CSR). Darunavir/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.

Based on the different elimination pathways of the other NRTIs (eg, lamivudine, FTC, stavudine, or zidovudine) that are primarily renally excreted, and abacavir for which metabolism is not mediated by CYP, no drug interactions are expected between these NRTIs and DRV/COBI. Darunavir/COBI can be used with these NRTIs without dose adjustment.

For details, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/ Section 3.3.2.1.

Interactions With NNRTIs

NNRTIs for which the interaction with DRV (coadministered with rtv) has been investigated include EFV (Module 5.3.3.4/TMC114-C111-CRR), NVP (Module 5.3.3.4/ TMC114-C119-CRR), ETR (Module 5.3.3.4/TMC125-C176-CRR), and rilpivirine (Module 5.3.3.4/TMC278-C112-CRR), all of which are CYP3A inducers with the exception of rilpivirine. As COBI is a CYP3A substrate, EFV, NVP, and ETR may lower COBI exposure and consequently also its boosting activity on DRV. Coadministration of DRV/COBI with these NNRTIs is not recommended.

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 and no dose adjustment of rilpivirine is needed when coadministered with DRV/COBI.

For details, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/ Section 3.3.2.2.

Interactions With Other HIV Protease Inhibitors

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.

Interactions With CCR5 Coreceptor Antagonists

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. 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). 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 used in combination with DRV/COBI, the recommended dose of maraviroc is 150 mg twice daily.

For details, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.3.2.4.

Interactions With Integrase Strand Transfer Inhibitors

Some clinical studies suggest raltegravir may cause a 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.

Based on theoretical considerations dolutegravir is not expected to affect the PK of DRV/COBI. Darunavir/COBI and dolutegravir can be used without dose adjustments.[32]

For details, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/ Section 3.3.2.5.

3.1.8. Pharmacokinetics of DRV/COBI in Special Populations

3.1.8.1. Pediatric Subjects

The PK of COBI as a single agent and of the DRV/COBI FDC have not been investigated in pediatric subjects <18 years of age (see also Section 5.4.2.10).

3.1.8.2. Older people

Limited information is available with DRV or COBI in older patients (65 years of age and older) and therefore DRV/COBI should be used with caution in patients above 65 years of age. Population PK analysis in HIV-infected subjects showed that DRV PK are not considerably

different in the age range 18 to 75 years evaluated in HIV-infected subjects (refer to Module 5.3.4.2/ TMC114-C926-CPKPD). Pharmacokinetics of COBI have not been fully evaluated in subjects 65 years and older (see also Section 5.4.2.10).

3.1.8.3. Sex

In the population PK analysis of study GS-US-216-0130 in ART-naïve and ART-experienced HIV-1 infected subjects, 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). This result for DRV/COBI was consistent with the situation when DRV was administered as DRV/rtv 800/100 mg once daily in study TMC114-C211 in ART-naïve HIV-1 infected subjects and in study TMC114-C229 in ART-experienced HIV-1 infected subjects. In these studies, population PK analysis indicated that although there was a trend towards a higher (1.10-fold in TMC114-C211; 1.13-fold in TMC114-C229) mean exposure to DRV in females compared with males, this difference was not considered to be clinically relevant (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.2.2).

3.1.8.4. Renal Impairment

The DRV/COBI FDC has not been investigated in patients with renal impairment.

Results from a mass balance study with ^{14}C-DRV/rtv (Module 5.3.3.1/TMC114-C109-CRR) showed that approximately 7.7% of the administered dose of DRV is excreted in the urine unchanged.

Although DRV has not been studied in subjects with renal impairment, population PK analysis showed that the PK of DRV were not significantly affected in HIV-1 infected subjects with moderate renal impairment (creatinine clearance between 30 to 60 mL/min, n=20).

A study to assess the PK of COBI was performed in non-HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min; Module 5.3.3.3/ GS-US-216-0124-CSR). No meaningful differences in COBI PK were observed between subjects with severe renal impairment and healthy subjects, consistent with low renal clearance of COBI. In study GS-US-216-0121 (Module 5.3.3.3/GS-US-216-0121-CSR) in subjects with mild to moderate renal impairment (estimated creatinine clearance 50 to 79 mL/min), higher COBI exposures were observed relative to subjects with normal renal function, which suggests a change in COBI clearance with or without a change in bioavailability. The mechanism for the higher COBI exposures is unknown, however, these exposure differences are not considered to be clinically relevant based on the exposures observed in subjects with severe renal impairment versus healthy subjects as well as the low renal excretion of COBI and low apparent clearance. For details, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.2.5.

The DRV/COBI FDC has not been investigated in HIV-1 infected patients with renal impairment. No dose adjustment is required in patients with renal impairment, including those with severe renal impairment. As DRV and COBI are highly bound to plasma proteins, it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

Darunavir, COBI or the DRV/COBI FDC have not been studied in patients receiving dialysis, and therefore no recommendation can be made for these patients.

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine (see Section 5.3.1).

3.1.8.5. Hepatic Impairment

Darunavir is primarily metabolised and eliminated by the liver. In a multiple-dose study (Module 5.3.3.3/TMC114-C134-CRR) with DRV/rtv 600/100 mg twice daily, it was demonstrated that the total plasma concentrations of DRV in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment were comparable with those in healthy subjects. However, unbound DRV concentrations were approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 2.1.6). Therefore, DRV/rtv should be used with caution. The effect of severe hepatic impairment on the PK of DRV has not been studied (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.2.4).

Cobicistat is primarily metabolized and eliminated by the liver. A study of the PK of COBI (Module 5.3.3.3/GS-US-183-0133) was performed in non-HIV-1 infected subjects with moderate hepatic impairment (Child-Pugh Class B). No clinically relevant differences in COBI PK were observed between subjects with moderate impairment and healthy subjects. No dose adjustment of COBI is necessary for patients with mild to moderate hepatic impairment. The effect of severe hepatic impairment (Child-Pugh Class C) on the PK of COBI has not been studied (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.2.4), therefore, the use of COBI is not recommended in these patients.

The DRV/COBI FDC has not been investigated in patients with hepatic impairment; there are no PK data regarding the use of the DRV/COBI FDC in patients with hepatic impairment. The above studies with DRV/rtv and with COBI single agent suggest no dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, due to an increase in the unbound DRV plasma concentrations, the DRV/COBI FDC should be used with caution in these patients. There are no data regarding the use of DRV or COBI in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of DRV and/or COBI exposure and a worsening of its safety profile. Therefore, the DRV/COBI FDC must not be used in patients with severe hepatic impairment (Child-Pugh Class C).

3.1.8.6. Hepatitis B and/or Hepatitis C Virus Coinfection

Limited information is available on the use of DRV/COBI in patients coinfected with hepatitis B or C. There were insufficient PK data in the clinical studies to determine the effect of hepatitis B and/or C virus coinfection on the PK of the DRV/COBI FDC.

The exposure to DRV in patients coinfected with hepatitis B or C virus receiving DRV/rtv, was comparable to that in patients without coinfection (Module 5.3.5.1/TMC114-C211-W48-CRR

and Module 5.3.5.1/TMC114-C229-W48-CRR). Similar exposure is expected with the DRV/COBI FDC.

3.2. Pharmacokinetic/Pharmacodynamic Relationships

PK/PD relationships evaluated for the association between DRV PK parameters and efficacy are described in Section 4.3.2.

PK/PD relationships evaluated for the association between DRV PK parameters and safety are described in Section 5.4.2.8.

3.3. Dosing Recommendation

The DRV/COBI FDC 800/150-mg tablet is intended to be used in the same adult population for which DRV/rtv 800/100 mg once daily is registered, ie, ART-naïve HIV-1 infected subjects and ART-experienced HIV-1 infected subjects with no DRV RAMs, who have plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L.

The DRV/rtv 800/100 mg once daily dosing recommendation was approved based on the demonstration of noninferiority in virologic response of the regimen in registrational studies TMC114-C211 and TMC114-C229.

During the clinical development of COBI, Gilead demonstrated that a 150-mg dose of COBI led to similar DRV exposures (C_{max} and AUC_{24h}) as a 100-mg dose of rtv, in each case when coadministered with DRV 800 mg once daily (study GS-US-216-0115). These results were later confirmed by the Phase 1 study TMC114IFD1001 conducted by the Applicant (see Section 2.2).

In line with guideline EMEA/CHMP/EWP/240/95 on the clinical development for FDC (Section 6.4),[11] no dose selection study was performed.

The bioequivalence study TMC114IFD1003 confirmed that the results obtained with the coadministration of the single agents DRV 800 mg and COBI 150 mg can be extrapolated to the intended commercial DRV/COBI FDC 800/150-mg tablet (see Section 2.3).

4. OVERVIEW OF EFFICACY

The efficacy profile of the DRV/COBI FDC in HIV-1 infected adult subjects is driven by DRV, as COBI has no detectable antiviral activity against HIV-1.

The same dosage regimen as established for the single agents DRV and COBI is proposed for the DRV/COBI FDC formulation. With the DRV/COBI FDC 800/150 mg once daily, similar DRV exposures are targeted as with the reference treatment DRV/rtv 800/100 mg once daily used in the TMC114-C211 and TMC114-C229 studies, in order to achieve comparable outcomes in HIV-1 infected ART-naïve adults and ART-experienced adults without DRV RAMs.

The efficacy of DRV/rtv 800/100 mg once daily was established in 2 registrational Phase 3 studies (TMC114-C211 and TMC114-C229). These studies formed the basis of approval of the DRV/rtv 800/100 mg once daily regimen. These data are summarized in Section 4.1.

The efficacy of DRV/COBI 800/150 mg once daily coadministered as single agents in the Phase 3b study GS-US-216-0130 is presented in Section 4.2.

Based on the clinical development strategy (see Section 1.3), and the PK results from the Phase 1 studies (see Section 3.1.5), these data support the registration of the DRV/COBI FDC 800/150 mg once daily for the treatment of HIV-1 infected adult subjects.

4.1. Efficacy of DRV/rtv 800/100 mg Once Daily

Treatment with DRV/rtv 800/100 mg once daily in combination with other ARVs has been shown to provide substantial and durable efficacy benefits, with a high genetic barrier to the development of resistance, both in ART-naïve subjects and in ART-experienced HIV-1 infected subjects without DRV RAMs.

4.1.1. ART-naïve Subjects

The evidence of efficacy of DRV/rtv 800/100 mg once daily in ARV treatment-naïve HIV-1 infected subjects is based on data from the randomized, active-controlled, open-label Phase 3 study TMC114-C211 comparing 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 300 mg once daily and FTC 200 mg once daily.

HIV-1 infected patients eligible for this study had plasma HIV-1 RNA >5,000 copies/mL. Randomization was stratified by screening plasma viral load and screening CD4+ cell count. Stratification factors were screening plasma viral load (<100,000, ≥100,000 HIV-1 RNA copies/mL) and screening CD4+ cell count (<200, ≥200x10^6 cells/L). Virologic response was defined as a confirmed plasma HIV-1 RNA viral load of <50 copies/mL.

Demographics and baseline characteristics were balanced between the DRV/rtv and the LPV/rtv arm. The 343 subjects on DRV/rtv 800/100 mg once daily had a median age of 34 years (range 18 to 70), 70% were male, 40% white, 23% black, 23% Hispanic, and 13% Asian. The mean baseline plasma HIV-1 RNA value was 4.86 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228x10^6 cells/L (range 4 to 750x10^6 cells/L).

Table 2 shows the efficacy outcomes (virologic response <50 copies/mL, time to loss of virologic response [TLOVR] and immunologic change) at Week 48 and Week 96 in study TMC114-C211.

Table 2: Efficacy Outcomes in the Week-48 and Week-96 Analyses of Study TMC114-C211

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	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	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 <200x10^6 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 ≥200x10^6 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 analysis at Week 48.
[b] Data based on analysis 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, the virologic response rate defined as the percentage of patients with plasma HIV-1 RNA level <50 copies/mL (TLOVR, primary efficacy parameter) was 83.7% in the DRV/rtv arm and 78.3% in the LPV/rtv arm. The noninferiority of DRV/rtv versus LPV/rtv was demonstrated (at the predefined 12% noninferiority margin, p<0.001). This outcome was also supported by the results of the secondary virologic parameters, including virologic response at other time points, the time to reach first virologic response, the percentage of subjects with plasma viral load <400 HIV-1 RNA copies/mL, percentage of subjects with a ≥2.0 $\log_{10}$ drop in plasma viral load (compared to baseline) at each time point, the change in $\log_{10}$ viral load at each time point, virologic response (all definitions) based on the non-virologic failure (non-VF) censored approach using the TLOVR algorithm, and the time averaged difference of $\log_{10}$ plasma viral load over 48 weeks. These Week-48 results were confirmed in the analysis of data at 96 weeks of treatment in this study. The Week-192 analysis demonstrated sustained efficacy of the DRV/rtv arm: virologic response was 68.8% and 57.2% in the DRV/rtv and LPV/rtv arms, respectively. Further details are available in the Clinical Study Reports (CSRs) (Module 5.3.5.1/TMC114-C211-W48-CRR, TMC114-C211-W96-CRR and Module 5.3.5.1/ TMC114-C211-W192-CRR).

4.1.2. ART-experienced Subjects

The evidence of efficacy of DRV/rtv 800/100 mg once daily in treatment-experienced subjects with no DRV RAMs is based on the Week-48 analysis of the Phase 3 study TMC114-C229. Study TMC114-C229 was a randomized, open-label study comparing DRV/rtv 800/100 mg once daily to DRV/rtv 600/100 mg twice daily in HIV-1 infected treatment-experienced subjects with screening genotype resistance testing showing no DRV RAMs, a viral load of >1,000 HIV-1 RNA copies/mL and a CD4+ cell count >50x10^6 cells/L at screening. Both arms used an optimized background regimen consisting of ≥2 NRTIs selected by the investigator. Randomization was stratified for screening viral load (≤50,000 and >50,000 HIV-1 RNA copies/mL).

Demographics and baseline characteristics were balanced between the DRV/rtv once daily arm and the DRV/rtv twice daily arm. The 590 subjects in total had a median age of 40 years (range 18 to 77), 64% were male, 36% white, 26% black, 18% Hispanic, and 15% Asian. The mean baseline plasma HIV-1 RNA value was 4.16 $\log_{10}$ copies/mL and the median baseline CD4+ cell count was 228x10^6 cells/L (range 24 to 1306x10^6 cells/L).

Table 3 shows the efficacy data (virologic response [<50 copies/mL, TLOVR]) and immunologic change at Week 48 in study TMC114-C229.

Table 3: Efficacy Outcomes in the Week-48 Analysis of Study TMC114-C229

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			
All Subjects,% (n/N)	72.1% (212/294)	70.9% (210/296)	1.2% (-6.1; 8.5)
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			
Mean (SD) Change in CD4+ Cell Count, x10^6 Cells/L[e]	+108 (112.9)	+112 (130.1)	-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 and Display GEN.11.

In the primary analysis, the virologic response rate defined as the percentage of patients with plasma HIV-1 RNA level <50 copies/mL (TLOVR) at Week 48 with DRV/rtv was 72.1% in the once daily arm and 70.9% in the twice daily arm. The noninferiority of DRV/rtv once daily versus DRV/rtv twice daily was demonstrated (at the predefined 12% noninferiority margin; p<0.001). The results of the secondary efficacy analyses were supportive of this finding. Further details are available in the CSR (Module 5.3.5.1/TMC114-C229-W48-CRR).

4.2. Efficacy of DRV/COBI 800/150 mg Once Daily

Information on the efficacy of DRV/COBI 800/150 mg once daily in combination with other ARVs in HIV-1 infected adults is provided by the Week-24 analysis of study GS-US-216-0130. In this ongoing, single-arm, multicenter, Phase 3b study, 313 HIV-1 infected adult subjects (295 ART-naïve and 18 ART-experienced with no DRV RAMs) are treated for a period of at least 48 weeks with DRV/COBI 800/150 mg once daily coadministered as single agents, and 2 fully active NRTIs.

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 counts at Weeks 24 and 48. After 48 weeks of treatment, subjects were given the option to participate in an open-label extension of the study to receive COBI until it becomes commercially available, or until termination of COBI development for any reason.

Results of the Week-24 efficacy 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. The primary efficacy endpoint was the proportion of subjects who reached HIV-1 RNA <50 copies/mL at Week 24 using the FDA-defined 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. For detailed information on the study design and efficacy analyses for this study, refer to the Summary of Clinical Efficacy in Module 2.7.3/Section 2.3 and the CSR in Module 5.3.5.2/GS-US-216-0130-W24-CSR.

4.2.1. Population Studied and Extent of Exposure

Details on demographic parameters, baseline disease characteristics, baseline resistance and ARV use in study GS-US-216-0130 are provided in Module 2.7.3/Section 2.2 and in the CSR, located in Module 5.3.5.2/GS-US-216-0130-W24-CSR.

A total of 314 HIV-1 infected adult subjects were enrolled; 313 subjects received at least 1 dose of both study medications DRV and COBI 800/150 mg once daily as single agents and constitute the intent-to-treat (ITT) population. Of these 313 subjects, 295 (94.3%) were ART-naïve and 18 (5.7%) 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. Per prespecified statistical analysis plan, data are presented by subgroup. However, the small sample size in the treatment-experienced subgroup precludes any meaningful comparisons or firm conclusions on this subgroup.

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, 265 (89.8%) treatment-naïve subjects and 16 (88.9%) of the treatment-experienced subjects.

The majority of subjects were male (90.2% in the treatment-naïve subgroup, 72.2% in the treatment-experienced subgroup) and most were white (59.7% and 61.1%, respectively) or black (34.2% and 38.9%, respectively). The median age was 34 years (range 18 to 72 years) for treatment-naïve subjects and 48 years (range 22 to 69 years) for treatment-experienced subjects.

Table 4 summarizes the relevant baseline disease and resistance characteristics of the subjects included in study GS-US-216-0130.

For subjects 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 15.9% of subjects had a CD4+ cell count $\leq 200x10^6$ cells/L. The majority of subjects (81.7%) had asymptomatic HIV-1 infection, 8.8% of subjects had symptomatic HIV-1 infection, and 9.5% were diagnosed with AIDS.

The baseline disease characteristics in the treatment-experienced subgroup reflected a more advanced stage of HIV-1 disease, 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 66.7% of subjects had a CD4+ cell count $\leq 200x10^6$ cells/L. The median number of years since HIV diagnosis was 8.5 years (range 2 to 24 years); approximately half of the subjects (55.6%) had asymptomatic HIV-1 infection, and 6 (33.3%) were diagnosed with AIDS.

According to the GenoSure™ MG assay, most study subjects (96.2%) had subtype B HIV-1 virus (refer to Module 2.7.3/Table 4).

The majority of subjects received TDF-based ARV medication during the study (99.7% of treatment-naïve subjects and 94.4% of treatment-experienced subjects), with coformulated FTC/TDF, being the most common TDF-based regimen (99.0% of treatment-naïve subjects and 61.1% of treatment-experienced subjects) (refer to Module 2.7.3/Table 5).

As expected in the treatment-naïve subjects, only 3.1% had 1 primary PI RAM, with the M46I/L and Q58E mutations found in 3 and 4 subjects, respectively. The majority of subjects (95.9%) had one or more secondary PI RAM(s), 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 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 NVP and 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 cohort had the M184V mutation, also suggesting some transmitted resistance (M184V and I are major NRTI RAMs with a potential to reduce lamivudine 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 RAMs (M46I/L and I54V) at baseline, the other 17 subjects had none. One or more secondary PI RAMs 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.

In line with the selection criteria defined in the protocol, 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 4: Baseline Disease and Baseline Resistance Characteristics – GS-US-216-0130 Week-24 Analysis

	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Baseline Disease Characteristics			
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)
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)
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)
Subjects with CD4+ Cell Count, n (%)			
<$100x10^6$ Cells/L	26 (8.8)	9 (50.0)	35 (11.2)
≤$200x10^6$ Cells/L	47 (15.9)	12 (66.7)	59 (18.8)
>200 to ≤$500x10^6$ Cells/L	179 (60.7)	3 (16.7)	182 (58.1)
>$500x10^6$ Cells/L	69 (23.4)	3 (16.7)	72 (23.0)
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)
Baseline Mutations[a]			
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; NA=not applicable; SD=standard deviation.
[a] International AIDS Society (IAS)-USA 2011 list[16] and additional protease/reverse transcriptase 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 2.7.3/Table 5 and Table 6.

4.2.2. 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, the mean percentage adherence to the prescribed DRV 800 mg and COBI 150 mg pills 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/

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.

4.2.3. Antiviral Activity

The main efficacy parameter was virologic response defined as plasma viral load <50 copies/mL according to the FDA-defined snapshot analysis (Table 5).

In the treatment-naïve subgroup, virologic response at Week 24 was reached 24 by 247 subjects (83.7%; 95% CI: 79.0% to 87.8%). There were 29 subjects (9.8%) with virologic failure. Of the 17 subjects with virologic failure due to HIV-1 RNA ≥50 copies/mL at Week 24, 14 were still receiving study medication at Week 36 with HIV-1 RNA levels available in 10 subjects. Of these 10 subjects, 6 had HIV-1 RNA levels <50 copies/mL (Module 5.3.5.2/ GS-US-216-0130-W24-CSR/Section 9.1.1). The percentage of subjects with no virologic data in the Week-24 window was 6.4% (19 subjects); the reasons for virologic failure and the absence of virologic data are presented in Table 5.

Few treatment-experienced subjects were enrolled in the study (n=18), and virologic response at Week 24 in this subgroup was reached by 11 subjects (61.1%; 95% CI 35.7% to 82.7%). There were 7 subjects (38.9%) with virologic failure and no subjects had missing virologic data in the Week-24 window (Table 5). Of the 5 subjects with virologic failure at Week 24 due to HIV-1 RNA levels ≥50 copies/mL, 1 subject was lost to follow-up after the Week-24 visit but within the Week-24 analysis window, 3 subjects did not have additional HIV-1 RNA data after Week 24 at the cut-off date for this analysis, and 1 subject had HIV-1 RNA <50 copies/mL at Week 36 (Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 9.1.1).

Table 5: 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 Adverse Event/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 2.7.3/Table 8.

Sensitivity analyses (including confirmed virologic response defined as HIV-1 RNA <50 copies/mL, TLOVR, virologic response <50 copies/mL with missing equals failure [M=F], a missing equals excluded [M=E], and a last observation carried forward [LOCF] method) demonstrated that the results for virologic response defined as confirmed plasma viral load <50 copies/mL were generally consistent across the different imputation methods used (Table 6), confirming that the observed results are representative of the true effect of DRV/COBI 800/150 mg once daily and are not the result of biases.

Table 6: Sensitivity Analyses for the Proportion of Subjects With HIV-1 RNA Levels <50 Copies/mL – 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 2.7.3/Table 9.

In the TLOVR analysis, where a viral load <50 copies/mL at 2 consecutive visits is required, 78.6% of treatment-naïve subjects and 44.4% of treatment-experienced subjects reached and maintained confirmed HIV-1 RNA !50 copies/mL through Week 24 and were responders (Table 7). Among the treatment-naïve subjects, 10.2% of subjects were classified as virologic failure and no subjects were considered nonresponders as a result of drug discontinuation due to lack of efficacy or death. In the small subgroup of treatment-experienced subjects, 7 subjects (38.9%) were classified as virologic failure (all due to no viral suppression through Week 24) and 3 subjects (16.7%) discontinued due to other reasons (lost to follow-up, subject withdrawal, protocol noncompliance, protocol violation and other reasons) (Table 7).

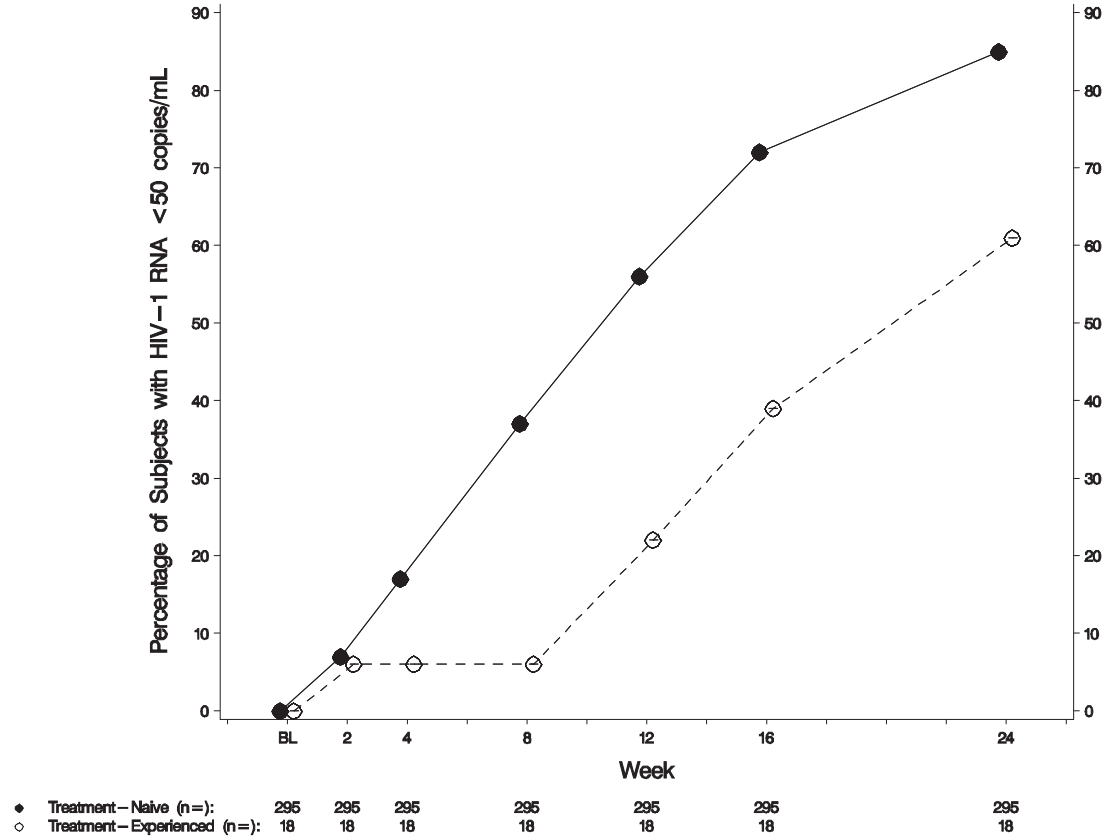
Table 7: Virologic Outcome (TLOVR Analysis) and Immunologic Outcome– GS-US-216-0130 Week-24 Analysis

	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
HIV-1 RNA Category, Number of Subjects, n (%)			
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 Adverse Event(s)	**15 (5.1)**	**0**	**15 (4.8)**
Drug Discontinuation due to Other Reasons[c]	**18 (6.1)**	**3 (16.7)**	**21 (6.7)**
HIV-1 RNA log Change From Baseline			
Mean log_{10} Copies/mL (SD)	-3.00 (0.788)	-2.56 (1.459)	-2.98 (0.842)
CD4+ Cell Count[d]			
Mean Change From Baseline (SD)	+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 2.7.3/Table 10, Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 9.1.4 and/Section 9.1.5).

The percentage of subjects achieving HIV-1 RNA levels <50 copies/mL continued to increase with continued treatment and had not reached a plateau by Week 24 (Figure 1, M=F). 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 1: Percentage of Subjects With Plasma HIV-1 RNA ¦50 Copies/mL Over Time (M=F) - GS-US-216-0130 Week-24 Analysis



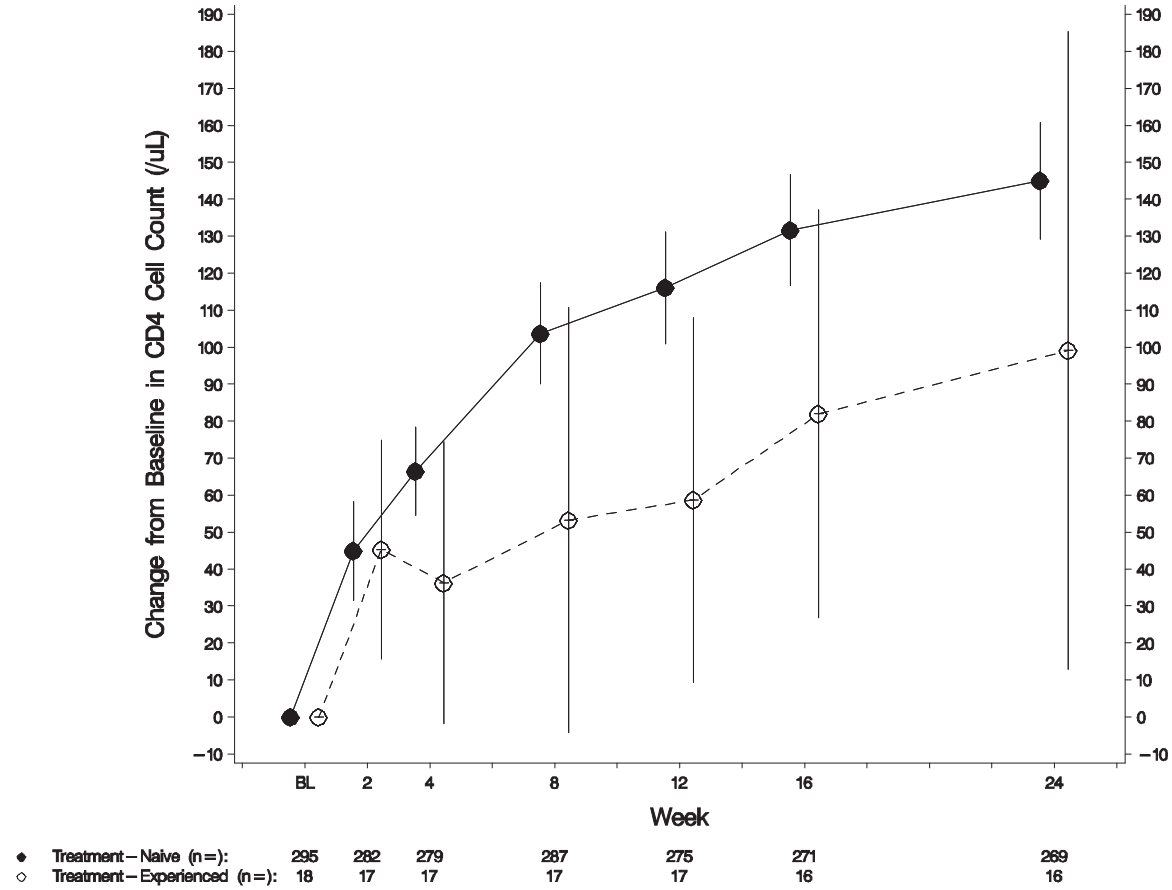
Source: Module 2.7.3/Figure 2.

These Week-24 virologic response results were supported by those of the other virologic parameters. In both subgroups, a steep drop in viral load was seen in the first 2 weeks of treatment, followed by a continued gradual decrease up to Week 24 (refer to Module 2.7.3/Figure 3). The mean (SD) change from baseline in $\log_{10}$ HIV-1 RNA level at Week 24 was #3.0 (0.79) copies/mL in the treatment-naïve subgroup and #2.6 (1.46) $\log_{10}$ copies/mL in the treatment-experienced subgroup.

4.2.4. Immunologic Response

The beneficial effect of the DRV/COBI 800/150 mg once daily regimen, plus 2 fully active NRTIs, on restoration of the immune function was shown by a steady increase in CD4+ cell counts throughout treatment (Figure 2). At Week 24, the mean (SD) increase from baseline in CD4+ cell count was +133 (135.4) $x10^6$ cells/L in the treatment-naïve subgroup, and +88 (155.4) $x10^6$ cells/L in the treatment-experienced subgroup (LOCF analysis) (refer to Module 2.7.3/Section 2.3.2.2).

Figure 2: Mean (95% CIs) Change From Baseline in CD4+ Cell Count Over Time (M=E) – GS-US-216-0130 Week-24 Analysis



Source: Module 2.7.3/Figure 4.

4.3. Efficacy Results Across Studies

4.3.1. Comparative Efficacy Results

The Week-24 results of study GS-US-216-0130 are compared with DRV/rtv data from registrational studies TMC114-C211 (ART-naïve subjects) and TMC114-C229 (ART-experienced subjects with no DRV RAMs), used as historical controls. In order to compare efficacy results after similar treatment duration, results after 24 weeks of treatment with DRV/rtv in TMC114-C211 and TMC114-C229 were used. Baseline viral load was similar for ART-naïve patients between the GS-US-216-0130 and TMC114-C211 studies (mean $\log_{10}$ viral load of 4.8 copies/mL versus 4.9 copies/mL). Mean baseline CD4+cell count was 378×10^6 cells/L versus 245×10^6 cells/L, respectively (refer to Module 2.7.3/Table 11). The treatment-experienced subjects in study GS-US-216-0130 (N=18) had a higher baseline viral load (mean $\log_{10}$ viral load of 4.8 copies/mL) than those in study TMC114-C229 (mean $\log_{10}$ viral load 4.2 copies/mL) with half of the subjects (9/18) in study GS-US-216-0130 with >100,000 copies/mL HIV-1 RNA versus 13.3% in study TMC114-C229. Baseline CD4+ cell count was slightly lower in study GS-US-216-0130 than in study TMC114-C229 (mean cell count 198×10^6 cells/L versus 250×10^6 cells/L) (refer to Module 2.7.3/Table 11). Comparisons

between these studies are to be interpreted with caution given the inherent limitations associated with the use of historical data as control.

The efficacy results at Week 24 of the GS-US-216-0130, TMC114-C211, and TMC114-C229 studies are summarized in Table 8.

In treatment-naïve subjects, response rates in study GS-US-216-0130 were comparable to those in study TMC114-C211. In the Week-24 snapshot analysis, 83.7% of treatment-naïve subjects administered DRV/COBI in study GS-US-216-0130 and 81.6% of subjects administered DRV/rtv in historical study TMC114-C211 reached virologic response. In treatment-experienced subjects, response rates were 61.1% in study GS-US-216-0130 and 70.1% in study TMC114-C229 (Table 8). The small number of treatment-experienced subjects in study GS-US-216-0130 results in a wide 95% CI around the 61.1% point estimate (35.7% to 82.7%, Table 5), and hence, any interpretation in the comparison with study TMC114-C229 is not meaningful.

Table 8: 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, n (%)	280 (81.6)	247 (83.7)	206 (70.1)	11 (61.1)
Virologic Response (TLOVR)				
HIV-1 RNA <50 Copies/mL, n (%)	273 (79.6)	232 (78.6)	201 (68.4)	8 (44.4)
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 2.7.3/Table 12.

4.3.2. Pharmacokinetic/Pharmacodynamic Relationships

The PK/PD relationship between DRV exposure (AUC_{24h} or C_{0h}) and virologic response (ie, change in viral load from baseline and plasma viral load <50 copies/mL) were analysed in the registrational studies TMC114-C211 and TMC114-C229 after 48 weeks of treatment with DRV/rtv 800/100 mg once daily (ie, the time point for primary efficacy analysis).

In HIV-infected treatment-naïve subjects of study TMC114-C211 there was no apparent relationship between DRV exposure and virologic response (refer to Module 5.3.5.1/ TMC114-C211-W48-CRR).

In HIV-infected treatment-experienced subjects of study TMC114-C229, there was no clinically relevant relationship between DRV exposure and virologic response, although the decrease in

viral load tended to be smaller in subjects with higher DRV exposures (refer to Module 5.3.5.1/TMC114-C229-W48-CRR). Possible reasons for this trend for an inverse PK/PD relationship could include the higher plasma alpha-1 acid glycoprotein 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 (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.4.1.1.1).

The PK/PD relationship between DRV exposure (AUC_{24h} or C_{0h}) and antiviral activity (ie, change in viral load from baseline and virologic response) with DRV/COBI 800/150 mg once daily were analyzed in study GS-US-216-0130 after 24 weeks of treatment. In HIV-infected treatment-naïve subjects, there was no apparent relationship between the decrease in log_{10} plasma viral load from baseline at Week 24 and DRV exposure. Virologic response was comparable across the first to third DRV exposure quartiles and was lower in the fourth (ie, highest) DRV exposure quartile. The lowest quartile of DRV exposure (AUC_{24h} and C_{0h}) was associated with the highest virologic response. Similar results were found in study TMC114-C211 where DRV was coadministered with rtv. In the treatment-experienced subgroup of study GS-US-216-0130, there was a trend towards higher virologic response and a greater change in log_{10} HIV-1 RNA viral load with higher DRV exposures. The sample size of treatment-experienced HIV-1 infected subjects in this study is too limited to reliably evaluate the relationship between DRV exposure and efficacy in this subgroup (n ranged from 1 to 9 per exposure quartile, refer to Module 5.3.4.2/GS-US-216-0130-CPK-W24/Table 4 and Table 5).

For further details on exposure-response relationships, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.4.1.1.

4.4. Resistance Determinations

Cobicistat has no antiviral activity in cell culture against HIV-1 and does not antagonize the antiviral activity of DRV (refer to Module 4.2.1.2/PC-216-2002, Module 4.2.1.2/PC-216-2005, Module 4.2.1.2/PC-216-2011 and Module 2.7.2/Summary of Virology). 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.

Section 4.4.1 briefly summarizes in vitro virology data of DRV, ie, mechanism of drug action, in vitro antiviral activity, and in vitro drug resistance. Section 4.4.2.1 summarizes the established clinical virology data of DRV/rtv 800/100 mg once daily regimen in the 2 Phase 3 studies TMC114-C211 and TMC114-C229. Supporting clinical resistance data from Phase 3b study GS-US-216-0130 with the combined use of DRV and COBI as single agents are presented in Section 4.4.2.2. Section 4.4.2.3 provides a comparison of the historical clinical resistance data with resistance data from study GS-US-216-0130.

4.4.1. In Vitro Virology

4.4.1.1. Mechanism of Action

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (K_d of $4.5x10^{-12}$ M).[20,21] It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins

in virus infected cells, thereby preventing the formation of mature infectious virus particles. For more details also refer to Module 2.7.2/Summary of Virology.

4.4.1.2. Antiviral Activity In Vitro

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 and human monocytes/macrophages 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 (more information can be found in Module 4.2.1.1/TMC114-20050011-VRR, TMC114-20050012-VRR and TMC114-20050014-VRR). The EC_{50} value of DRV increased by a median factor of 5.4 in the presence of human serum (more information can be found in Module 4.2.1.1/ TMC114-20050010-VRR). For more details also refer to Module 2.7.2/Summary of Virology.

4.4.1.3. Resistance In Vitro

The results of in vitro selection studies (along with the high binding affinity of DRV with HIV-1 protease and its resilience to the effects of PI RAMs) provided evidence of a high genetic barrier to the development of resistance to DRV.

In vitro selection of DRV-resistant virus from wild-type HIV-1 was lengthy (>3 years). The selected viruses were unable to grow in the presence of DRV concentrations above 400 nM. Viruses selected in these conditions and showing decreased susceptibility to DRV (range: 23 to 50-fold) harboured 2 to 4 amino acid substitutions in the protease gene (more information can be found in Module 4.2.1.1/TMC114-20050013-VVR). For more details also refer to Module 2.7.2/Summary of Virology.

4.4.1.4. Cross-Resistance In Vitro

Darunavir fold change in EC_{50} values (FC) was less than 10 for 90% of 3,309 clinical isolates resistant to amprenavir (APV), ATV, indinavir (IDV), LPV, nelfinavir (NFV), RTV, saquinavir (SQV) and/or TPV showing that viruses resistant to most PIs remain susceptible to DRV (more information can be found in Module 4.2.1.1/TMC114-20050005-VRR).

Cross-resistance between DRV and the NRTIs, NNRTIs, entry inhibitors or integrase inhibitor, is unlikely because the viral targets for those inhibitors are different.

For more details also refer to Module 2.7.2/Summary of Virology.

4.4.2. Clinical Resistance Data

Of note, 11 protease mutations associated with DRV resistance (V11I, V32I, L33F, I47V, I50V, I54L or M, T74P, L76V, I84V or L89V)[17] were previously identified based on an analysis of a pooled dataset of studies with ARV treatment-experienced subjects who received treatment including DRV/rtv 600/100 mg twice daily. The clinical study data from ART-experienced

subjects 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, respectively, were determined.[9,10]

4.4.2.1. Clinical Resistance Data With DRV/rtv 800/100 mg Once Daily

4.4.2.1.1. Phase 3 Study TMC114-C211 – Week-192 Analysis

In the Week-192 analysis of the TMC114-C211 study, the proportion of virologic failures (based on viral load ≥50 copies/mL; ITT – TLOVR non-VF censored) in the group of subjects receiving DRV/rtv 800/100 mg once daily was 16.0% (n=55), of which 11.4% (n=39) subjects were rebounders and 4.7% (n=16) were never suppressed subjects. In these virologic failures with available genotypes/phenotypes at baseline and endpoint (n=10), 4 subjects with developing (IAS-USA) PI RAMs were identified. None of the developing mutations were primary (ie, major) PI mutations. In 4 virologic failures a maximum of 2 developing (IAS-USA) NRTI RAMs were observed. The development of the NRTI RAM M184V/I (n=4) was associated with a decreased susceptibility to FTC included in the background regimen. No cross-resistance with other PIs was observed in virologic failures of the TMC114-C211 study (refer to Module 5.3.5.1/TMC114-C211-W192-CRR).

4.4.2.1.2. Phase 3 Study TMC114-C229 – Week-48 Analysis

The presence of DRV RAMs at screening was an exclusion criterion for subjects participating in the TMC114-C229 study.

In the Week-48 analysis of the TMC114-C229 study, the proportion of virologic failures (based on viral load ≥50 copies/mL; ITT – TLOVR non-VF censored) was comparable in the DRV/rtv 800/100 mg once daily group and the DRV/rtv 600/100 mg twice daily group. Out of the 294 DRV/rtv 800/100 mg once daily subjects, 65 (22.1%) experienced virologic failure versus 54 (18.2%) out 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 virologic failures with available genotypes/phenotypes at baseline and endpoint, 7 of 60 subjects (12%) in the DRV/rtv 800/100 mg once daily group with developing (IAS-USA) PI RAMs were identified compared to 4 of 42 subjects (9.5%) in the DRV/rtv 600/100 mg twice daily group. One virologic failure in the DRV/rtv 800/100 mg once daily group developed primary (ie, major) PI mutations, which included 3 DRV RAMs, resulting in decreased susceptibility to DRV. All the virologic failures from the DRV/rtv 600/100 mg twice daily group retained susceptibility to DRV. Four (6.7%) and 3 (7.1%) virologic failures developed 1 or 2 (IAS-USA) 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 virologic failures 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. Of the viruses isolated from subjects receiving DRV/rtv 800/100 mg once daily and experiencing virologic failure in the TMC114-C229 study, 98%

remained susceptible to DRV after treatment. In the same group of subjects, 96% to 100% that were susceptible at baseline to APV, ATV, IDV, LPV, SQV or TPV remained susceptible to these PIs after treatment. In the virologic failures receiving DRV/rtv 600/100 mg twice daily, no cross-resistance with other PIs was observed (more information can be found in Module 5.3.5.1/TMC114-C229-W48-CRR).

4.4.2.2. Clinical Resistance Data With DRV/COBI 800/150 mg Once Daily

Supporting clinical resistance data with DRV and COBI, coadministered as single agents, are generated in the Week-24 analysis of study GS-US-216-0130.

4.4.2.2.1. Influence of Baseline Genotype on Response

The effect of 5 baseline genotype characteristics on virologic 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 virologic response (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Table 9-4).

4.4.2.2.2. Development of Resistance

Resistance development to DRV or other PIs and to NRTIs was rare in study GS-US-216-0130. 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 treatment-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 treatment-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. 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.

For details on the resistance analyses for this study, refer to the Summary of Virology in Module 2.7.2, Module 5.3.5.2/GS-US-216-0130-W24-CSR and Module 5.3.5.2/GS-US-216-0130-SAP-W24-Virology).

4.4.2.3. Clinical Resistance Data Across Studies

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

[*] 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.

[†] 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.

800/100 mg once daily has been established in the study TMC114-C211 (ART-naïve subjects) and in study TMC114-C229 (ART-experienced subjects).

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 study and the TMC114-C229 study. Comparable low rates of resistance development were observed in study GS-US-216-0130 (Week-24 analysis). Phenotypic resistance to DRV and other PIs and NRTIs included in the background regimen was not or rarely observed in these 3 studies. These results confirm the clinical resistance profile of DRV/rtv 800/100 mg once daily in ART-naïve subjects and ART-experienced subjects without DRV RAMs, and the high genetic barrier of DRV whether boosted with COBI or rtv (refer to Module 2.7.2/Summary of Virology).

4.4.3. Recommendations for Resistance Testing

When considering a DRV/COBI FDC 800/150 mg once daily regimen for ARV treatment-experienced subjects, genotypic resistance testing is recommended to confirm the absence of DRV RAMs. This is consistent with the current treatment guidelines that recommend resistance testing prior to initiating therapy or when changing ARV regimen.[13,34,36]

4.5. Long-term Efficacy

The ongoing study GS-US-216-0130 will provide efficacy data up to 48 weeks and beyond. After 48 weeks of treatment, subjects will be given the option to participate in an open-label extension to receive COBI until it becomes commercially available, or until termination of COBI development for any reason. The final analysis of the study will be performed after all subjects complete the study or experience early discontinuation of study drug.

The long-term efficacy of the DRV/rtv 800/100 mg once daily treatment regimen has been 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 (see Section 4.1).

4.6. Efficacy in Special Populations

No subgroup analyses in special populations are done in the efficacy analyses of studies with DRV/COBI.

Assessment of the efficacy of DRV/rtv 800/100 mg once daily in special populations was done by subgroup analysis of the Week-192 results in the TMC114-C211 study (refer to Module 5.3.5.1/TMC114-C211-W192-CRR) and by subgroup analysis of the Week-48 results in the TMC114-C229 study (refer to Module 5.3.5.1/TMC114-C229-W48-CRR). The outcome of these analyses is reflected in the DRV SmPC[30] to which the DRV/COBI FDC should be aligned.

The efficacy of the DRV/COBI FDC have not been established in pediatric patients aged from 3 to <18 years. The DRV/COBI FDC should not be used in children below 3 years of age.

Limited information is available with DRV or COBI in older patients (65 years of age and older) and therefore DRV/COBI should be used with caution in patients above 65 years of age.

For PK and safety data of DRV and COBI in special populations, see Section 3.1.8 and Section 5.4.2.10, respectively.

5. OVERVIEW OF SAFETY

The safety profile of the DRV/COBI FDC is based on the data from the Phase 3b study GS-US-216-0130 in HIV-1 infected subjects, Phase 1 studies in healthy subjects (TMC114IFD1001 and TMC114IFD1003) and on the safety profiles of the individual agents, DRV (in combination with rtv) and COBI.

The overall number of subjects exposed to DRV/COBI once daily in new clinical studies part of the FDC clinical development plan and included in this application is provided in Table 9.

Table 9: Number of Subjects Exposed to DRV/COBI in Studies Conducted by the Applicant or Gilead and Included in This Application

Type of Study	Study Number	Population	Number of Subjects	Study Status
Phase 1:				
Single dose PK	TMC114IFD1003	Healthy subjects	133	Completed
Multiple dose PK	TMC114IFD1001	Healthy subjects	36	Completed
Phase 3b:				
Safety	GS-US-216-0130[a]	HIV-1 infected subjects	313	Ongoing
Total			**482**	

Number of subjects includes all subjects that were treated in studies.
[a] Conducted by Gilead in collaboration with the Applicant.
Source: Module 5.3.1.1/TMC114IFD1001-CSR; Module 5.3.1.2/TMC114IFD1003-CSR; Module 5.3.5.2/GS-US-216-0130-W24-CSR.

The overall number of subjects exposed to DRV/COBI once daily in clinical studies conducted by Gilead and not included in this application is provided in Table 10. Per safety data exchange agreement,[29] Gilead provided information on related serious adverse events (SAEs) from studies with DRV/COBI on an ongoing basis.

Table 10: Number of Subjects Exposed to DRV/COBI in Studies Conducted by Gilead Included in the Marketing Application for COBI

Type of Study	Study Number	Population	Number of Subjects on DRV/COBI	Study Status
Phase 1:				
Multiple dose PK (800/150 qd)	GS-US-216-0115	Healthy subjects	33	Completed
Multiple dose PK (600/150 bid)	GS-US-216-0119	Healthy subjects	24	Completed
Phase 2-3:				
Safety in renal impaired	GS-US-236-0118	HIV-1 infected subjects	21	Ongoing
Total			**78**	

Number of subjects includes all subjects that were treated in studies.
qd=once daily; bid=twice daily.
Source: Module 5.3.1.2/GS-US-216-0115-CSR and CSRs of studies GS-US-216-0119[7] and GS-US-236-0118.[6]

Nonclinical safety data with DRV and COBI, relevant to the DRV/COBI FDC, are summarized in Section 5.1.

The safety of DRV/rtv 800/100 mg once daily is discussed in Section 5.2.

The safety profile of COBI in healthy subjects and HIV-1 infected subjects, resulting from the clinical development by Gilead and relevant for the FDC, is discussed in Section 5.3.1 and Section 5.3.2, respectively.

Safety data on DRV/COBI obtained in healthy subjects and HIV-1 infected subjects in studies conducted to support the DRV/COBI FDC registration are discussed in Section 5.4.1 and Section 5.4.2, respectively.

The Week-24 safety profile of DRV/COBI 800/150 mg once daily versus that of DRV/rtv 800/100 mg is discussed in Section 5.5.

Long-term safety data relevant to the DRV/COBI FDC are discussed in Section 5.6.

Available Week-48 safety information of study GS-US-216-0130 (cut-off date [redacted]), selected safety data (SAEs considered to be related to DRV/COBI) reported in ongoing studies up to the cut-off date of [redacted], and relevant safety information from ongoing study GS-US-236-0118 are discussed in Section 5.7.

Selected safety data from postmarketing experience are discussed in Section 5.8.

5.1. DRV and COBI Nonclinical Safety Relevant to DRV/COBI FDC

A comprehensive package of nonclinical safety data is available for DRV, including toxicity studies of DRV in combination with rtv. Similarly, an extensive nonclinical program has been carried out by Gilead documenting the nonclinical pharmacology, PK, and toxicology of COBI, both as single agent and in coadministration with ATV or EVG.

A brief summary of the nonclinical safety profile of DRV and COBI is given below. For details, refer to the Nonclinical Overview in Module 2.4.

Darunavir Nonclinical Safety

Repeated dose toxicity studies, up to 3 months in mice, 6 months in rats and 12 months in dogs, identified only limited effects of treatment with DRV. The key target organs identified in rodents after administration of DRV were the hematopoietic system, the blood coagulation system, liver and thyroid. The effects seen in the liver and thyroid (cellular hypertrophy with increase in organ weight) were consistent with the liver enzyme inducing property of DRV. Limited changes in liver were observed in dogs after 12 months of treatment. In a 6-month study in rats, the combination of DRV with rtv showed no unexpected toxicities. The hematological and thyroid changes were not observed during clinical studies or postmarketing experience with DRV in combination with rtv.

Darunavir did not show any effects on fertility or early embryonic development and showed no teratogenic potential, nor effects on pre- and postnatal development when dosed alone, and in combination with rtv. In juvenile rats directly dosed with DRV (from 20 mg/kg to 1000 mg/kg) up to days 23 to 26 of age, mortality was observed and, in some of the animals, convulsions. Within this age range, exposures in plasma, liver and brain were dose and age dependent and

were considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of the CYP450 liver enzymes involved in the metabolism of DRV and the immaturity of the blood brain barrier. No treatment related mortalities were noted in juvenile rats dosed at 1000 mg/kg DRV (single dose) on day 26 of age or at 500 mg/kg (repeated dose) from day 23 to 50 of age, and the exposures and toxicity profile were comparable to those observed in adult rats. Due to uncertainties regarding the rate of development of the human blood brain barrier and liver enzymes, DRV/rtv should not be used in pediatric patients below 3 years of age. Refer to Module 2.4/Non Clinical Overview.

No immunotoxicity of DRV with and without rtv was found in rats.

Genotoxicity tests have shown DRV to be free of genotoxic potential. Carcinogenicity studies with DRV showed an increase in the incidence of hepatocellular adenomas and carcinomas in mice and rats and thyroid follicular cell adenomas in male rats, at exposure levels below those observed in humans at the recommended therapeutic doses. These findings are considered to be of limited to no relevance to humans based on mechanistic and epidemiological data. There were no effects of DRV on cardiovascular parameters in dogs and no effects in rats on neurobehavior and motor activity, or on gastrointestinal and pulmonary safety.

Cobicistat Nonclinical Safety

In repeated-dose toxicity studies up to 3 months in mice, up to 6 months in rats and up to 9 months in dogs, the liver (mouse, rat and dog) and thyroid (rat) were identified as target organs for COBI. Slight, non-adverse hematological changes were noted in rats, slight clinical chemistry changes were observed in mice, rats and dogs, and increases in urine volume and urine chemistry changes were noted primarily at high doses in rats and dogs. In rats, the thyroid changes are considered rodent-specific, secondary to microsomal enzyme induction and thyroid imbalance. Liver changes in mice, rats, and dogs included microsomal enzyme induction, increased weights, and hepatocellular hypertrophy and/or vacuolation. Combination toxicity studies of COBI with EVG or ATV in rats did not result in unexpected or additive toxicity.

Cobicistat did not affect fertility in male or female rats at daily exposures approximately 4-fold higher than human exposures at the recommended 150 mg daily dose. Fertility was normal in the offspring of rats exposed daily from before birth (in utero) through sexual maturity at daily exposures of approximately 1.2-fold higher than human exposures at the recommended 150 mg daily dose. There was no evidence of an effect on embryonic development and COBI showed no teratogenic potential.

Other potential toxicities related to COBI that were observed in nonclinical studies included PR interval prolongation, decreases in left ventricular function and decreased immunoglobulin G (IgG) levels in female rats, only. Ex vivo rabbit studies and in vivo dog studies suggest that COBI has a low potential for QT prolongation, and may slightly prolong the PR interval and decrease left ventricular function at mean concentrations at least 10-fold higher than the human exposure at the recommended 150 mg daily dose. In female rats, a significantly decreased T-dependent IgG antibody response to keyhole limpet hemocyanin injection was observed in an

immune function test. In this study, lymphoid depletion of germinal centers in the spleen was also observed. In other nonclinical studies (13-week mouse, 26-week rat and 39-week dog), no indications for immunotoxicity were observed. No clinically relevant changes in left ventricular function or serum IgG levels have been observed in Phase 1 or Phase 2 studies conducted to date. Dose-related increases in PR interval, which were not considered to be clinically significant, have been observed in a clinical study (thorough QT/QTc study GS-US-216-0107; see Section 5.3.1).

COBI did not show a genotoxic potential in genotoxicity tests. A long term carcinogenicity study of COBI in rats revealed tumourigenic potential specific for this species that is regarded as of no relevance for humans. A long term carcinogenicity study in mice did not show any carcinogenic potential.

DRV/COBI FDC

In consideration of the established nonclinical safety profiles of the single compounds DRV and COBI and the extent of the available clinical data, no additional nonclinical studies were performed to support the use and registration of the DRV/COBI FDC. This is in line with Section 4.2.1 of guideline EMEA/CHMP/SWP/258498/2005 on the nonclinical evaluation of an FDC of compounds already approved as free combination therapy.[12]

There are no anticipated clinically relevant pharmacologic or toxicologic interactions expected with DRV and COBI beyond the PK enhancing effect of COBI on DRV. Although both DRV and COBI result in rodent specific hepatic microsomal enzyme induction and thyroid hormone changes, these changes are not considered clinically relevant.

There are no shared clinical effects of concern that cannot readily be monitored in clinical studies. No adverse effects on hematological, coagulation, thyroid function parameters or on IgG levels that could be indicative of immunosuppression have been observed in clinical Phase 1 or Phase 2 studies with COBI conducted by Gilead. Immune status (CD4+ count), the occurrence of infections, and the possible potentiation of liver toxicity (increases of bilirubin and liver enzymes) due to the combined use of DRV and COBI is carefully monitored in clinical studies.

Moreover, the concern for unexpected or additive toxicities has further been mitigated based on the Phase 3b study GS-US-216-0130, where combination treatment with DRV 800 mg and COBI 150 mg was generally well tolerated and did not raise concerns.

5.2. Safety Profile of DRV/rtv

5.2.1. Relevant Safety Studies of DRV/rtv in Healthy Subjects

The thorough QT study TMC114-C153 was interpreted as negative according to the E14 ICH Guidelines since the results demonstrated that administration of DRV/rtv 1600/100 mg or 800/100 mg for 7 days is not associated with a clinically relevant increase in QT interval (refer to Module 5.3.4.1/TMC114-C153-CRR).

5.2.2. Safety of DRV/rtv 800/100 mg Once Daily in HIV-1 Infected Subjects

The safety profile of DRV/rtv 800/100 mg once daily is established in TMC114-C211 up to 192 weeks (refer to Module 5.3.5.1/TMC114-C211-W192-CRR)[27] and in TMC114-C229 up to 48 weeks (refer to Module 5.3.5.1/TMC114-C229-W48-CRR)[3], and through the extensive postmarketing experience (see Section 5.8). The safety findings from the clinical studies with DRV/rtv demonstrated that DRV/rtv was generally safe and well tolerated in HIV-1 infected subjects.[30]

In the Week-48 safety analysis of study TMC114-C211, no new safety signals were identified in the treatment-naïve population in addition to the knowledge gained with DRV/rtv twice daily in the treatment-experienced 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 patients 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 adverse events (AEs) were observed compared to the Week-48 data. In the Week 192 safety analysis, the safety profile was in general comparable to that of Week 48 and Week 96. The Week-192 analysis identified additional adverse drug reactions (ADRs) of at least grade 2 compared to the Week-24 analysis (lipodystrophy, osteonecrosis, and diabetes). These ADRs are expected to also occur when DRV is boosted with COBI.

The safety profile for DRV/rtv in study TMC114-C229 was in line with the known safety profile for DRV. Overall, the clinical safety profile of the DRV/rtv 800 mg once daily dosing regimen in ART-experienced adult patients with 0 DRV RAMs was considered acceptable.

Additional DRV ADRs were identified in other DRV studies, including study TMC114-C229 (abdominal distension and gynaecomastia, both uncommon), or during postmarketing experience (toxic epidermal necrolysis and acute generalized exanthematous pustulosis, both very rare) and are likewise expected to occur when DRV is boosted with COBI.

Table 11 presents all DRV/rtv ADRs identified in the TMC114-C211 Week-192 analysis.

Table 11: Adverse Drug Reactions to DRV/rtv 800/100 mg Once Daily (TMC114-C211 Week-192 Analysis)

System Organ Class	Frequency category	Adverse Drug Reactions
Immune System Disorders	Common	(Drug) Hypersensitivity
	Uncommon	Immune Reconstitution Syndrome
Metabolism and Nutrition Disorders	Common	Anorexia, Hypercholesterolaemia, Hyperglycaemia, Hyperlipidaemia, Hypertriglyceridaemia, Lipodystrophy[a], Low Density Lipoprotein Increased
	Uncommon	Diabetes Mellitus
Psychiatric Disorders	Uncommon	Abnormal Dreams
Nervous System Disorders	Very Common	Headache
Gastrointestinal Disorders	Very Common	Abdominal Pain, Diarrhoea, Nausea
	Common	Abdominal Distension, Dyspepsia, Flatulence, Pancreatic Enzymes Increased, Vomiting
	Uncommon	Pancreatitis Acute
Hepatobiliary Disorders	Common	Hepatic Enzyme Increased
	Uncommon	Acute Hepatitis
Skin and Subcutaneous Tissue Disorders	Very Common	Rash
	Common	Angioedema, Pruritus, Urticaria
	Uncommon	Stevens-johnson Syndrome,
Musculoskeletal and Connective Tissue Disorders	Common	Myalgia
	Uncommon	Osteonecrosis
Reproductive System and Breast Disorders	Uncommon	Gynaecomastia
General Disorders and Administration Site Conditions	Common	Asthenia, Fatigue

Frequency categories are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

[a] The ADR Lipodystrophy was attributed to the SOC Metabolism and Nutrition Disorders whereas the grouped term Lipodystrophy belongs to the SOC Skin and Subcutaneous Tissue Disorders.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TCLOAE03

5.2.3. General Safety of DRV/rtv in HIV-1 Infected Subjects

The general safety profile of DRV in HIV-1 patients during the clinical development program in clinical studies and during postmarketing is presented in Table 12. For a complete representation of the anticipated safety profile of the FDC, Table 12 is proposed to be added to the product labeling of the DRV/COBI FDC.

Table 12: Adverse Reactions to DRV/rtv in HIV-1 Patients in Clinical Studies and Postmarketing

System Organ Class	Frequency Category	Adverse Reactions
Infections and Infestations	Uncommon	Herpes simplex
Blood and Lymphatic System Disorders	Uncommon	Thrombocytopenia, Neutropenia, Anaemia, Leukopenia
	Rare	Increased Eosinophil Count
Immune System disorders	Uncommon	Immune Reconstitution Syndrome[a], (Drug) Hypersensitivity
Endocrine Disorders	Uncommon	Hypothyroidism, Increased Blood Thyroid Stimulating Hormone
Metabolism and Nutrition Disorders	Common	Lipodystrophy (Including Lipohypertrophy, Lipodystrophy, Lipoatrophy), Diabetes Mellitus, Hypertriglyceridaemia, Hypercholesterolaemia, Hyperlipidaemia
	Uncommon	Gout, Anorexia, Decreased Appetite, Decreased Weight, Increased Weight, Hyperglycaemia, Insulin Resistance, Decreased High Density Lipoprotein, Increased Appetite, Polydipsia, Increased Blood Lactate Dehydrogenase
Psychiatric Disorders	Common	Insomnia
	Uncommon	Depression, Disorientation, Anxiety, Sleep Disorder, Abnormal Dreams, Nightmare, Decreased Libido,
	Rare	Confusional State, Altered Mood, Restlessness
Nervous System Disorders	Common	Headache, Peripheral Neuropathy, Dizziness
	Uncommon	Lethargy, Paraesthesia, Hypoaesthesia, Dysgeusia, Disturbance in Attention, Memory Impairment, Somnolence,
	Rare	Syncope, Convulsion, Ageusia, Sleep Phase Rhythm Disturbance
Eye Disorders	Uncommon	Conjunctival Hyperaemia, Dry Eye
	Rare	Visual Disturbance
Ear and Labyrinth Disorders	Uncommon	Vertigo
Cardiac Disorders	Uncommon	Myocardial Infarction, Angina Pectoris, Prolonged Electrocardiogram QT, Tachycardia,
	Rare	Acute Myocardial Infarction, Sinus Bradycardia, Palpitations
Vascular Disorders	Uncommon	Hypertension, Flushing
Respiratory, Thoracic and Mediastinal Disorders	Uncommon	Dyspnoea, Cough, Epistaxis, Throat Irritation
	Rare	Rhinorrhoea
Gastrointestinal Disorders	Very common	Diarrhoea
	Common	Vomiting, Nausea, Abdominal Pain, Increased Blood Amylase, Dyspepsia, Abdominal Distension, Flatulence
	Uncommon	Pancreatitis, Gastritis, Gastrooesophageal Reflux Disease, Aphthous Stomatitis, Retching, Dry Mouth, Abdominal Discomfort, Constipation, Increased Lipase, Eructation, Oral Dysaesthesia,
	Rare	Stomatitis, Haematemesis, Cheilitis, Dry Lip, Coated Tongue

Table 12: Adverse Reactions to DRV/rtv in HIV-1 Patients in Clinical Studies and Postmarketing

System Organ Class	Frequency Category	Adverse Reaction
Hepatobiliary Disorders	Common	Increased Alanine Aminotransferase,
	Uncommon	Hepatitis, Cytolytic Hepatitis, Hepatic Steatosis, Hepatomegaly, Increased Transaminase, Increased Aspartate Aminotransferase, Increased Blood Bilirubin, Increased Blood Alkaline Phosphatase, Increased Gamma-glutamyltransferase
Skin and Subcutaneous Tissue Disorders	Common	Rash (Including Macular, Maculopapular, Papular, Erythematous and Pruritic Rash), Pruritus
	Uncommon	Angioedema, Generalised Rash, Allergic Dermatitis, Urticaria, Eczema, Erythema, Hyperhidrosis, Night Sweats, Alopecia, Acne, Dry Skin, Nail Pigmentation
	Rare	Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens-Johnson Syndrome, Erythema Multiforme, Dermatitis, Seborrhoeic Dermatitis, Skin Lesion, Xeroderma
	Not Known	Toxic Epidermal Necrolysis, Acute Generalized Exanthematous Pustulosis
Musculoskeletal and Connective Tissue Disorders	Uncommon	Myalgia, Osteonecrosis, Muscle Spasms, Muscular Weakness, Arthralgia, Pain in Extremity, Osteoporosis, Increased Blood Creatine Phosphokinase
	Rare	Musculoskeletal Stiffness, Arthritis, Joint Stiffness
Renal and Urinary Disorders	Uncommon	Acute Renal Failure, Renal Failure, Nephrolithiasis, Increased Blood Creatinine, Proteinuria, Bilirubinuria, Dysuria, Nocturia, Pollakiuria
	Rare	Decreased Creatinine Renal Clearance
Reproductive System and Breast Disorders	Uncommon	Erectile Dysfunction, Gynaecomastia
General Disorders and Administration Site Conditions	Common	Asthenia, Fatigue
	Uncommon	Pyrexia, Chest Pain, Peripheral Oedema, Malaise, Feeling hot, Irritability, Pain
	Rare	Chills, Abnormal Feeling, Xerosis

Within each frequency category, adverse reactions are presented in order of decreasing seriousness.
Frequency categories are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) and not known (frequency cannot be estimated from the available data).

[a] 'Immune reconstitution syndrome' is replaced by 'Immune reconstitution inflammatory syndrome' in version 15.1 of the Medical Dictionary for Regulatory Activities (MedDRA) terminology. This terminology will therefore be adapted in the PREZISTA SmPC.

Source: PREZISTA SmPC.[30]

5.3. Safety Profile of COBI

The safety profile of COBI was established by Gilead and the supporting data were submitted as part of the original COBI application (refer to the COBI SmPC).[35]

5.3.1. Relevant Safety Studies With COBI in Healthy Subjects

Cobicistat has been shown to be well tolerated at daily doses up to 400 mg when administered as a single agent in healthy subjects.

In a thorough QT/QTc study GS-US-216-0107, at COBI doses of 250 mg and 400 mg providing exposures (AUC over the dosing interval) approximately 2- or 4-fold above the recommended therapeutic dose, an expected dose-related increase in PR interval (+9.6 msec) was observed, not considered to be clinically significant (refer to Module 5.3.4.1/GS-US-216-0107-CSR). Results on QTc were below the threshold for regulatory concern.

Echocardiograms performed in study GS-US-216-0116 at baseline and at steady-state COBI exposures indicated no clinically significant change in left ventricular function (Module 5.3.4.1/ GS-US-216-0116-CSR).

Cobicistat has been shown to decrease the estimated glomerular filtration rate (eGFR) calculated by Cockcroft-Gault method ($eGFR_{CG}$) due to inhibition of tubular secretion of creatinine. The effect of COBI on serum creatinine was investigated in Phase 1 study GS-US-216-0121 (Module 5.3.3.3/GS-US-216-0121-CSR) in healthy subjects with normal renal function (eGFR ≥80 mL/min, N=18) and mild to moderate renal impairment (eGFR 50 to 79 mL/min, N=12). A statistically significant change in $eGFR_{CG}$ from baseline was observed within 7 days of treatment with COBI 150 mg among subjects with normal renal function (mean±SD change from baseline -9.9±13.1 mL/min) and mild to moderate renal impairment (mean±SD change from baseline -11.9±7.0 mL/min). These decreases in $eGFR_{CG}$ were reversible after COBI was discontinued. The actual glomerular filtration rate (actual GFR), as determined by the clearance of probe drug iohexol, was not altered from baseline following treatment of COBI among subjects with normal renal function and mild to moderate renal impairment. Similar observations on $eGFR_{CG}$ and $eGFR_{MDRD}$ were made in study GS-US-216-0124 (Module 5.3.3.3/GS-US-216-0124-CSR) investigating the pharmacokinetics of COBI in non-HIV-1 infected subjects with severe renal impairment (estimated creatinine clearance below 30 mL/min). On Day 7 of coadministration the $eGFR_{CG}$ was 10.5% lower vs. baseline among subjects with severe renal impairment and 8.4% lower among controls. The decreases in eGFR attributed to inhibition of proximal tubular secretion of creatinine by COBI mainly occur via inhibition of multidrug and toxin extrusion protein 1 (MATE1) (refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/ Section 3.2.5). An increase in serum creatinine due to COBI's inhibitory effect generally does not exceed 0.4 mg/dL from baseline.[33] Study GS-US-236-0130 examined the effect over a period of 30 days of 5 treatments (COBI, TDF, COBI+TDF, EVG/COBI/FTC/TDF and placebo) on renal function in healthy adult subjects.[8] The expected effect on eGFR for COBI-containing regimens was observed. The on-treatment actual GFR (iohexol plasma clearance) data showed small decreases from baseline versus placebo for COBI alone and for COBI+TDF at Day 15. 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).

Two studies (GS-US-216-0119 and GS-US-216-0115) with DRV and COBI in healthy subjects were conducted by Gilead as part of the COBI development program and showed that treatment with DRV/COBI coadministered as single agents (either given 600/150 mg twice daily or 800/150 mg once daily) was not associated with increased adverse safety findings versus rtv-boosted DRV. Study GS-US-216-0119 was a Phase 1 study in a total of 48 subjects and evaluated the PK and safety of twice-daily administration of COBI alone, and twice-daily

administration of COBI-boosted and rtv-boosted DRV, or COBI-boosted and rtv-boosted TPV (refer to GS-US-216-0119-CSR).[7] Study GS-US-216-0115 was a Phase 1 study evaluating the PK and safety of the once-daily administration of DRV/rtv 800/100 mg or DRV/COBI 800/150 mg coadministered as single agents in 33 healthy subjects (refer to Module 5.3.1.2/ GS-US-216-0115-CSR). In each study, each treatment was administered with food for 10 days.

5.3.2. Safety of COBI in HIV-1 Infected Subjects

Gilead has characterized the safety profile of COBI in HIV-1 infected subjects during its COBI development programs.[35,33] 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 5.4.2 and 5.7.3.

5.4. Safety Profile of DRV/COBI 800/150 mg Once Daily

5.4.1. Safety of DRV/COBI 800/150 mg Once Daily in Healthy Subjects

This section provides an overview of the safety data collected in Phase 1 studies conducted by the Applicant with the DRV/COBI FDC in healthy subjects, ie, studies TMC114IFD1001 (36 subjects) and TMC114IFD1003 (133 subjects). For detailed information on the design and safety analyses of these 2 studies, refer to the Summary of Clinical Safety in Module 2.7.4 and the CSRs in Module 5.3.1.1/TMC114IFD1001-CSR, Module 5.3.1.1/TMC114IFD1001-CSR-Err and Module 5.3.1.2/TMC114IFD1003-CSR, respectively.

5.4.1.1. Critical Aspects of the Safety Analysis

Safety data with DRV/COBI FDC in healthy subjects in Phase 1 studies are available in a limited number of subjects and for a short duration of exposure, as shown in Table 9. A summary of the study designs is provided in Section 2.

5.4.1.2. Adverse Events

Safety of DRV/COBI in studies in healthy volunteers conducted by Gilead (GS-US-216-0115, refer to Module 5.3.1.2/GS-US-216-0115-CSR, and GS-US-216-0119[7]) did not identify any safety concern.

The two new phase 1 studies conducted by the Applicant as part of the FDC clinical development plan, confirmed the positive safety profile of DRV/COBI FDC in healthy subjects. After 10 days of treatment with the DRV/COBI FDC either as formulation G003 or G004 (study TMC114IFD1001), the most frequently reported AEs by preferred term were headache (72.2%), fatigue (61.1%), diarrhea (30.6%), nausea (27.8%), skin irritation (27.8%), and pruritus (25.0%). No clinically relevant differences between treatments in incidence of AEs were observed. Most AEs were grade 1 or grade 2 in severity. No grade 4 AEs were reported. Grade 3 AEs were only reported for 3 subjects (8.3%): fatigue (DRV/rtv) and maculo-papular rash (DRV/COBI FDC tablets G003 and G004). Adverse events considered at least possibly related to study medication were reported for 66.7% of subjects. 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). Five subjects (13.9%) discontinued treatment prematurely due to an AE, all grade 2 or 3 in severity and all considered related to the study medication; 2 subjects during DRV/rtv treatment (both rash), 2 subjects during intake of DRV/COBI FDC G003 (rash and maculo-papular rash), and 1 subject during intake of DRV/COBI FDC G004 (maculo-papular rash).

After single dose administration of DRV/COBI either as FDC or as single agents, (study TMC114IFD1003), the most frequently reported AEs by preferred term (in at least 5% of subjects) were headache (40 subjects, 30.1%), muscle spasms (12 subjects, 9.0%), and diarrhea (11 subjects, 8.3%). No clinically relevant differences between treatments in incidence of AEs were observed. Most AEs were grade 1 or grade 2 in severity. No grade 3 or 4 AEs were reported. In this study, 20.3% of subjects had AEs that were considered at least possibly related to DRV, 19.5% of subjects had AEs that were considered at least possibly related to COBI. The most frequent AEs considered as at least possibly related to DRV and COBI were headache (8.3%), diarrhea (7.5%), nausea (3.8%). One subject (0.8%) experienced rash during this study. The rash occurred both under DRV/COBI single agent treatment (grade 1) and DRV/COBI FDC treatment (grade 2) and was assessed as at least possibly related at the 2 occasions. No subject permanently stopped or temporarily interrupted the study medication due to an AE.

None of the laboratory, electrocardiogram (ECG) or vital signs abnormalities were reported as AEs in either study.

For further details on the safety results of the studies TMC114IFD1001 and TMC114IFD1003, refer to Module 2.7.4/Section 2.3.2.1 and Section 2.3.2.2, and the CSRs in Module 5.3.1.1/ TMC114IFD1001-CSR and Module 5.3.1.2/TMC114IFD1003-CSR.

Overall, the results of the safety analyses of these 2 Phase 1 studies demonstrate that the single or repeated (10 days) administration of DRV/COBI 800/150 mg as FDC in healthy adult subjects under fed and fasted conditions was generally safe and well tolerated. No safety signals were detected during treatment with DRV/COBI 800/150 mg in adult healthy subjects.

5.4.2. Safety of DRV/COBI FDC 800/150 mg Once Daily in HIV-1 Infected Subjects

This section provides an overview of the safety data collected in the Week-24 primary safety analysis of study GS-US-216-0130 in 313 HIV-1 infected subjects. For detailed information on the safety analyses for study GS-US-216-0130, refer to the Summary of Clinical Safety in Module 2.7.4 and the CSR in Module 5.3.5.2/GS-US-216-0130-W24-CSR.

5.4.2.1. Critical Aspects of the Safety Analysis

The study population included in study GS-US-216-0130 reflects the targeted adult population in the intended indication of the FDC, and is the same as in the approved adult indication of the DRV/rtv 800/100 mg once daily regimen.

The primary analysis of study GS-US-216-0130 was conducted when the last subject completed the Week-24 visit or dropped out earlier. The safety and tolerability of the regimen through 48 weeks of treatment are evaluated as a secondary objective of this study. After 48 weeks of treatment, subjects were given the option to participate in an open-label 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 termination of COBI development for any reason. The number of subjects treated in the study (313 subjects in total) allows detecting AEs of reasonable frequency (in the range of 1 to 5%) during a 6-month treatment. The Week-24 analyses obtained from this dataset are considered adequate to support the DRV/COBI FDC application as the long-term safety profile of DRV through 192 weeks is established and the safety profile of COBI in HIV-1 infected subjects through 48 weeks has been well characterized during the clinical development program of COBI.

For completeness, the safety data are tabulated for the total subject group as well as for the 2 subgroups by previous ARV treatment experience. However, the review of the safety data of study GS-US-216-0130 in this Clinical Overview is focused on the total subject group because of the small sample size of the subgroup of treatment-experienced subjects, and because the safety profile of DRV/rtv 800/100 mg once daily is generally similar in treatment-experienced and treatment-naïve subjects, as shown in DRV/rtv registrational studies.

5.4.2.2. Study Population and Extent of Exposure

Of the 313 subjects who received at least 1 dose of both study medications DRV and COBI in study GS-US-216-0130, 295 were treatment-naïve and 18 were treatment-experienced (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/Section 8.1).

Demographic data, baseline disease characteristics and extent of exposure of the subjects treated in study GS-US-216-0130 are summarized in Section 4.2.1.

The median duration of exposure to study medication through the cut-off date for the Week-24 analysis was 31.4 weeks (range 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.

Adherence to DRV and COBI as measured by pill count is discussed in Section 4.2.2.

5.4.2.3. Overall Incidence of Adverse Events

Treatment with DRV/COBI 800/150 mg once daily coadministered as single agents was generally well tolerated in the 313 HIV-1 infected adult subjects. The majority of the AEs were mild to moderate.

In the Week-24 analysis, 5.8% of subjects experienced at least 1 grade 3 (5.1%) or grade 4 (0.6%) 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 considered study drug-related by the investigator: 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 of any severity. 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 reported AEs were consistent with those expected in the subject population and the known safety profiles of the study medications.[35,30]

For a tabular presentation, overall and by subgroups (treatment-experienced subjects and treatment-naïve subjects), refer to Module 2.7.4/Table 16 and Table 17.

5.4.2.4. Mortality, Serious Adverse Events and Other Significant Adverse Events

There were no deaths in the Week-24 analysis of study GS-US-216-0130.

Fifteen subjects (4.8%) experienced one or more SAEs, including 3 subjects (1.0%) who each had one SAE considered as drug-related by the investigator (immune reconstitution syndrome, rash, and maculo-papular rash).

Treatment was permanently discontinued in 15 subjects (4.8%) because of 1 or more AEs. The most common AEs that led to discontinuation were rash (preferred term) and maculo-papular rash, both of which were experienced by 3 subjects (1.0%). Nausea and hypersensitivity each resulted in discontinuation of 2 subjects (0.6%). All but 2 AEs that led to discontinuation were considered by the investigators to be study drug-related. No subjects discontinued the study drugs due to a renal AE.

Table 13 presents AEs considered related to DRV/COBI by the investigator, occurring in at least 2 subjects. Overall, 39.3% of subjects experienced at least 1 AE that was DRV/COBI related. Diarrhea (14.7%) and nausea (14.4%) were the most frequently reported AEs (in more than 5% of subjects) considered to be related to DRV/COBI. Related rash, including maculo-papular rash and macular rash, was reported by 6.1% of subjects.

All AEs considered related to DRV/COBI and that occurred in at least 2 subjects (Table 13), are considered ADRs to DRV/COBI (Table 17) except dry mouth, dizziness, dysgeusia, peripheral neuropathy, malaise, insomnia and dermatitis. There was insufficient data to consider these AEs as ADRs (for a summary of the assessment, refer to Appendix 2). The AE frequent bowel movement is considered as an ADR but was grouped under the grouped term diarrhea.

Table 13: 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 2.7.4/Table 18.

5.4.2.5. Critical Evaluation of Safety Parameters of Special Interest to DRV/COBI

Eleven clinical entities of special interest (AEs of interest), each consisting of grouped preferred terms were used to further evaluate the safety profile of DRV/COBI. Criteria for generating such entities 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 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.

This section provides a review of the AEs of interest collected in study GS-US-216-0130. Table 14 provides a summary of these AEs of interest. This table did not include the entities 'Cardiac conduction abnormalities' and 'Fat redistribution' as no AEs from these entities were reported throughout the study.

Overall, 23.6% of subjects experienced at least 1 AE of interest. Adverse events of interest to DRV/COBI 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%).

None of the AEs of interest were grade 4 and few were grade 3 (rash, grouped term, reported in 2 [0.6%] subjects, hepatotoxicity in 2 [0.6%] subjects and immune reconstitution syndrome in 1 [0.3%] subject). Most AEs of interest were grade 1, 9.3% of subjects experienced a grade 2 AE of interest. A few cases AEs were serious (rash, grouped term, reported in 2 [0.6%] subjects, and immune reconstitution syndrome in 1 [0.3%] subject). Seven subjects (2.2%) discontinued treatment for an AE of interest, all rash-related.

Table 14: 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 2.7.4/Table 20.

5.4.2.6. Laboratory Safety Parameters

There were no clinically relevant changes from baseline through Week 24 in mean values for hematology parameters or clinical chemistry parameters, for 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 for 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 consisted of changes in creatine kinase (5.8%) and ALT (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.

All laboratory-related AEs were grade 1, not serious, and did not lead to treatment discontinuation. The most frequently reported laboratory-related AEs were hypercholesterolemia and hypertriglyceridemia, experienced by 4 subjects (1.3%) each.

Renal Laboratory Parameters

In study GS-US-216-0130, there were no anomalies suggestive of renal proximal tubular dysfunction. The renal laboratory assessments showed changes consistent with the known COBI inhibitory effects on renal tubular creatinine secretion without affecting the glomerular filtration (see Section 5.3.1).

No abnormalities in proximal tubular dysfunction markers (hypophosphatemia, proteinuria, normoglycemic glucosuria) were reported in the Week-24 analysis (urinalyses were done by dipstick test, 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).

An increase from baseline in serum creatinine was noted from Week 2 onwards (mean change 0.09 mg/dL), the increase remained stable till Week 24 (mean change 0.12 mg/dL). The mean change from baseline of the $eGFR_{CG}$ was –9.6 mL/min at Week 2, and –11.5 mL/min at Week 24. A similar decrease was noted in eGFR using the modification of diet in renal disease method, but no change was observed when using the eGFR assessed by cystatin C clearance, which is independent of creatinine (refer to Module 5.3.5.2/GS-US-216-0130-W24-CSR/ Table 5.3.14).

For details on renal laboratory parameters results, refer to Module 2.7.4/Section 3.3.7.1.

5.4.2.7. Other Safety Parameters

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 obtained in the Week-24 analysis of study GS-US-216-0130.

5.4.2.8. Pharmacokinetic/Pharmacodynamic Relationships

Consistent with the findings from the registrational DRV/rtv studies TMC114-C211 and TMC114-C229, in study GS-US-216-0130 with DRV/COBI, no apparent PK/PD relationships were observed between DRV AUC_{24h} and the occurrence of rash, diarrhea, nausea, or vomiting, or between DRV AUC_{24h} and the worst toxicity grade in alkaline phosphatase, ALT, AST, amylase, lipase, glucose, total cholesterol, LDL, HDL, or triglycerides. For further details on exposure-response relationships, refer to the Summary of Clinical Pharmacology Studies, Module 2.7.2/Section 3.4.1.2.

5.4.2.9. Adverse Drug Reaction Analysis

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 Module 2.7.4/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 system organ class are provided in Module 2.7.4/Appendix 3. For laboratory abnormalities considered as ADRs, the Division of AIDS (DAIDS) grading scale was used for severity grading (refer to Module 2.7.4/Section 1.3).

Overall, 62.6% of subjects experienced at least 1 ADR in the Week-24 analysis of the study. Individual ADRs with an incidence >10% were diarrhea (25.2%), nausea (21.4%), and rash (grouped term, 16.0%) (Table 15).

The majority of the ADRs were mild in severity. Adverse drug reactions with severity at least grade 2 were reported in 19.8% of subjects. The most frequently reported ADRs with grade 2 or more (incidence ≥5%) were rash (grouped term, 5.8%) and diarrhea (5.1%). The incidence of severe ADRs (grade 3 or 4) was 2.9%. The most frequent (≥1%) ADR of grade 3 or 4 severity was drug hypersensitivity (Table 15).

Four subjects (1.3%) experienced 1 serious ADR, ie, drug hypersensitivity, immune reconstitution syndrome, rash (preferred term) and maculopapular rash. Twelve subjects (3.8%) 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.

Table 15: 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[a]	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[a]	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[a]	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[a]	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 Module 2.7.4/Appendix 3.
Source: Module 2.7.4/Table 24.

Graded abnormalities in selected laboratory parameters, considered to be ADRs, are AST, ALT, alkaline phosphatase, total cholesterol, LDL cholesterol, triglycerides, glucose, amylase, lipase, creatinine (Table 16). 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 creatinine was observed in 17.7% of subjects, the increase was grade 1 in 14.5% of subjects and grade 2 in 3.2% of subjects (Table 16 and Module 2.7.4/Table 25). These percentages differ from grades described in Section 5.4.2.6, due to the use of a different severity rating scale (refer to Module 2.7.4/Section 1.3 for details on grading scales). There were no grade 3 or grade 4 abnormalities in creatinine.

Table 16: Laboratory-related Adverse Drug Reactions, Grade 2 to 4 – 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 2	17 (5.8)	0	17 (5.5)
Grade 3	5 (1.7)	1 (5.6)	6 (1.9)
Pancreatic Lipase (U/L)			
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 2	9 (3.1)	1 (5.6)	10 (3.2)
Lipids and Glucose			
Cholesterol (mg/dL)			
Grade 2	19 (6.9)	2 (11.8)	21 (7.2)
Grade 3	3 (1.1)	0	3 (1.0)
Glucose (mg/dL)			
Grade 2	9 (3.3)	2 (11.8)	11 (3.8)
LDL Cholesterol (mg/dL)			
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 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 2	3 (1.0)	-	3 (1.0)
AST (U/L)			
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 2.7.4/Table 25.

Table 17 presents DRV/COBI ADRs listed by system organ class and frequency category and is proposed to be added to the SmPC of the DRV/COBI FDC. The most frequent ADRs reported are diarrhea, nausea, and rash (grouped term), this is consistent with the most frequent AEs considered related to study medication by the investigator (Table 13).

Table 17: DRV/COBI Adverse Drug Reactions - GS-US-216-0130 Week-24 Analysis

ADR System Organ Class	Frequency category	Adverse Drug Reactions
Immune System Disorders	Common	(Drug) Hypersensitivity
	Uncommon	Immune Reconstitution Inflammatory Syndrome[a]
Metabolism and Nutrition Disorders	Common	Anorexia, Hypercholesterolaemia, Hypertriglyceridaemia
	Uncommon	Diabetes Mellitus
Psychiatric Disorders	Common	Abnormal Dreams
Nervous System Disorders	Common	Headache
Gastrointestinal Disorders	Very common	Diarrhoea, Nausea
	Common	Abdominal Distension, Abdominal Pain, Dyspepsia, Flatulence, Vomiting
	Uncommon	Pancreatitis Acute
Skin and Subcutaneous Tissue Disorders	Very Common	Rash
	Common	Angioedema, Pruritus, Urticaria
Musculoskeletal and Connective Tissue Disorders	Common	Myalgia
General Disorders and Administration Site Conditions	Common	Fatigue
	Uncommon	Asthenia
Hepatobiliary Disorders	Common	Hepatic Enzyme Increased
Investigations	Common	Increased Blood Creatinine

Frequency categories are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

[a] ' Immune reconstitution syndrome' is replaced by 'Immune reconstitution inflammatory syndrome' in version 15.1 of the MedDRA terminology. This terminology will therefore be used in the DRV/COBI FDC SmPC.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TCLOAE02.

5.4.2.10. Safety in Special Populations

No subgroup analyses in special populations were done in the safety analysis of study GS-US-216-0130.

The safety of the DRV/COBI FDC has not been established in pediatric patients aged from 3 to <18 years. The DRV/COBI FDC should not be used in children below 3 years of age in view of toxicity observed in juvenile rats dosed with DRV (see Section 5.1).

As limited information is available on the use of DRV/COBI in older patients (65 years of age and older), caution should be exercised in the administration of DRV/COBI in older patients, reflecting the greater frequency of decreased hepatic function and of concomitant disease or other therapy.

The DRV/COBI FDC has not been investigated in patients with hepatic impairment. Separate studies of DRV/rtv and COBI single agent suggest no dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment (Section 3.1.8.5). However, due to an increase in unbound DRV plasma concentrations (Section 3.1.8.5), the DRV/COBI FDC should be used with caution in these patients. There are no data regarding the use of DRV or COBI in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of DRV and/or COBI exposure and a worsening

of its safety profile. Therefore, the DRV/COBI FDC must not be used in patients with severe hepatic impairment (Child-Pugh Class C).[35,30]

Limited information is available on the use of DRV/COBI in patients coinfected with hepatitis B or C. Among 1,968 treatment-experienced patients receiving DRV/rtv 600/100 mg twice daily, 236 patients were coinfected with hepatitis B or C. Coinfected patients were more likely to have baseline and treatment emergent hepatic transaminase elevations than those without chronic viral hepatitis.[30]

The DRV/COBI FDC has not been investigated in patients with renal impairment. Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine (see Section 5.3.1). An increase in serum creatinine due to COBI's inhibitory effect generally does not exceed 0.4 mg/dL from baseline.[35] This effect on serum creatinine, leading to a decrease in the estimated creatine clearance, should be taken into consideration when the DRV/COBI FDC is administered to patients in whom the estimated creatinine clearance is used to guide aspects of their clinical management, including adjusting doses of coadministered medicinal products. Cobicistat has not been studied in HIV-1 infected patients with baseline creatinine clearance below 70 mL/min. The DRV/COBI FDC should not be initiated in patients with creatinine clearance less than 70 ml/min if one or more co-administered agent requires dose adjustment based on creatinine clearance (e.g. FTC, lamivudine, TDF or adefovir dipivoxil) (see also Section 3.1.8.4).[35]

There are currently inadequate data to determine whether co-administration of TDF and COBI is associated with a greater risk of renal adverse reactions compared with regimens that include TDF without COBI.

Supportive safety results in suppressed HIV-1 infected subjects with mild to moderate renal impairment, switching from a DRV/rtv-containing regimen to a DRV/COBI-containing regimen in ongoing study GS-US-236-0118 are presented in Section 5.7.3.

5.5. Week-24 Safety Profile of DRV/COBI 800/150 mg Once Daily Versus DRV/rtv 800/100 mg Once Daily

In order to put the safety profile of DRV/COBI 800/150 mg once daily into perspective, the results of the Week-24 ADR analysis of study GS-US-216-0130 were reviewed with the Week-24 ADR analyses of the DRV/rtv 800/100 mg once daily treatment arms from the 2 historical studies TMC114-C211 and TMC114-C229. Comparisons between these studies are to be interpreted with caution given the inherent limitations associated with the use of historical data as control.

In general, the incidence of individual ADRs (any grade) in the Week-24 analyses of study GS-US-216-0130 and of the historical studies was similar. Higher frequencies of gastrointestinal-related ADRs (nausea, vomiting and flatulence) were observed in study GS-US-216-0130 but were mainly driven by grade 1 events and therefore of limited clinical concern (refer to Module 2.7.4/Appendix 4). The incidence of the ADR rash (any severity grade) was higher in study GS-US-216-0130 (16.0%), than in studies TMC114‑C211 (8.2%) and

TMC114-C229 (5.8%). The higher incidence of rash, along with a higher proportion of rash events leading to discontinuation in GS-US-216-0130 was due to grade 1 and grade 2 events. There were no noticeable differences in the incidence of grade 3 rashes and there were no cases of grade 4 rash (refer to Module 2.7.4/Table 28). 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. Rash was mostly mild to moderate, often occurring within the first 4 weeks of treatment and resolving with continued dosing. The incidence of all other ADRs was similar in study GS-US-216-0130 and in the historical studies (refer to Module 2.7.4/Section 3.3.11).

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) and are considered attributable to the known inhibitory effects of COBI on renal tubular creatinine secretion (Module 2.7.4/Table 29).

Four ADRs of at least grade 2 occurring in the historical studies were not reported in study GS-US-216-0130: acute pancreatitis, acute hepatitis, Stevens-Johnson syndrome and asthenia. These ADRs are expected to also occur with DRV when boosted with COBI, which justifies the addition of the relevant safety data from DRV/rtv experience to the SmPC of the DRV/COBI FDC 800/150 mg (see also Section 5.2).

5.6. Long-term Safety

Preliminary data available from the Week-48 safety and tolerability analysis of study GS-US-216-0130 (see Section 5.7.1), with DRV/COBI as single agents, are consistent with the findings of the Week-24 analyses and confirm the favorable safety profile of DRV/COBI in HIV-1 infected subjects.

The positive long-term safety profile of DRV 800 mg once daily when boosted with rtv 100 mg has been established through the Week-192 safety data from study TMC114-C211 and the Week-48 safety data from study TMC114-C229 (see Section 5.2).

5.7. Safety in Ongoing Studies and Programs

This section presents an overview of:

- the available Week-48 safety data of the ongoing study GS-US-216-0130 (Section 5.7.1).
- 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 of [redacted] (Section 5.7.2).
- 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 5.7.3).

5.7.1. 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]). For further details on the results of this interim Week-48 analysis, refer to Module 2.7.4/Section 3.4.1.

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 was 351.5 patient-years in the Week-48 analysis and 180.6 patient-years in the Week-24 analysis.

5.7.1.1. 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 (refer to Module 2.7.4/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 by the investigator 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.

There were no new grade 4 AEs in the Week-48 analysis (refer to Module 2.7.4/Table 31). None of the new grade 3 AEs reported were considered related to the study medication (refer to Module 2.7.4/Table 30).

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 (refer to Module 2.7.4/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.

5.7.1.2. 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 and 0.10 mg/dL at Week 48 (refer to Module 2.7.4/Figure 1 and 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.

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 1 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. Four of these subjects had last recorded creatinine value <0.4mg/dL. Except for one subject (CRF ID 1236-4051), none of the 7 subjects presented laboratory abnormalities suggestive of renal proximal tubulopathy or signs of subclinical kidney disease. One subject (CRF ID 1236-4051) discontinued the study medication due to a renal AE: renal tubular disorder (verbatim: proximal tubulopathy, started Week 36, grade 1, not serious and assessed by the investigator as not related to the study medication).

5.7.1.3. Adverse Drug Reactions

The Week-48 ADR profile of DRV/COBI 800/150 mg once daily was evaluated based on the list of ADRs as identified from the Week-24 analysis. No new safety signals were identified in the Week-48 analysis. The overall ADR profile of DRV/COBI 800/150 mg once daily at Week 48 is consistent with the Week-24 profile. 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. For details, refer to Module 2.7.4/Section 3.4.1.3.

Table 18 presents DRV/COBI ADRs by system organ class and frequency category, experienced by subjects in the Week-48 analysis of study GS-US-216-0130. The Week-48 findings are generally in line with those of the Week-24 analysis. Pancreatic enzyme increased and hyperlypidemia were the only additional ADRs observed in the Week-48 review compared to the Week-24 analysis. Frequencies were increased in the Week-48 analysis as compared to the Week-24 analysis for the ADRs diabetes mellitus (from uncommon to common) and headache (from common to very common).

Table 18: DRV/COBI Adverse Drug Reactions - GS-US-216-0130 Week-48 Analysis

ADR System Organ Class	Frequency category	Adverse Drug Reactions
Immune System Disorders	Common	(Drug) Hypersensitivity
	Uncommon	Immune Reconstitution Inflammatory Syndrome[a]
Metabolism and Nutrition Disorders	Common	Anorexia, Diabetes Mellitus, Hypercholesterolaemia, Hypertriglyceridaemia
	Uncommon	Hyperlipidaemia
Psychiatric Disorders	Common	Abnormal Dreams
Nervous System Disorders	Very Common	Headache
Gastrointestinal Disorders	Very Common	Diarrhoea, Nausea
	Common	Abdominal Distension, Abdominal Pain, Dyspepsia, Flatulence, Vomiting
	Uncommon	Pancreatic Enzymes Increased, Pancreatitis Acute
Hepatobiliary Disorders	Common	Hepatic Enzyme Increased
Skin and Subcutaneous Tissue Disorders	Very Common	Rash
	Common	Angioedema, Pruritus, Urticaria
Musculoskeletal and Connective tissue Disorders	Common	Myalgia
General Disorders and Administration site Conditions	Common	Fatigue
	Uncommon	Asthenia
Investigations	Common	Increased Blood Creatinine

Frequency categories are defined as follows: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000).

[a] 'Immune reconstitution syndrome' is replaced by 'Immune reconstitution inflammatory syndrome' in version 15.1 of the MedDRA terminology. This terminology will therefore be used in the DRV/COBI FDC SmPC.

Source: Module 5.3.5.2/GS-US-216-0130-Anal-W48-SAF-AE/TCLOAE01.

5.7.2. Serious Adverse Events Related to DRV/COBI Reported After the Cut-off for This Overview

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 Clinical Overview (reported after the cut-off date of [redacted] for the Week-24 primary analysis in GS-US-216-0130) did not identify any safety concerns (refer to Module 2.7.4/Section 3.4.1).

5.7.3. Safety Results in Ongoing Study GS-US-236-0118

A study (GS-US-236-0118)[6] is ongoing in HIV-1 infected subjects with mild to moderate renal impairment (eGFR between 50 and 89 mL/min, inclusive). 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.

5.8. Postmarketing Experience

The most recent periodic safety update report for DRV, covering the period 24 December 2011 to 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 Company Core Data Sheet and Risk Management Plan are recommended. The cumulative postmarketing exposure till December 2012, based on the grams of DRV distributed worldwide is estimated 6,[redacted],[redacted]person-months or 5[redacted],[redacted] person-years.

At the time of finalization of this Clinical Overview, no postmarketing data are available for COBI.

6. GUIDANCE FOR CLINICAL USE

This section provides further insight into the optimal clinical use of the DRV/COBI FDC. The recommendations listed below are based on the data collected during the FDC development and principles well-defined for the use of ART.

Therapy should be initiated by a healthcare provider experienced in the management of HIV infection.

The recommended DRV/COBI FDC dose regimen is 1 tablet taken orally, once daily with food. Patients should be instructed to take DRV/COBI FDC within 30 minutes after completion of a meal. The type of food does not affect the exposure to DRV. The DRV/COBI FDC should not be taken twice daily.

To ensure administration of the entire dose of the DRV/COBI FDC, the FDC tablet should be swallowed whole.

If a dose of DRV/COBI FDC is missed within 12 hours of the time it is usually taken, patients should be instructed to take the prescribed dose of DRV/COBI FDC with food as soon as possible. If this is noticed later than 12 hours of the time it is usually taken, the missed dose should not be taken and the patient should resume the usual dosing schedule. Doses should not be doubled. This guidance is based on the 11 hour half-life of DRV in the presence of COBI and the recommended dosing interval of approximately 24 hours.

Treatment guidelines strongly recommend resistance testing prior to initiating therapy or switching therapy when there is incomplete virologic suppression. In deciding to initiate treatment with the DRV/COBI FDC in ART-experienced adults with no DRV-RAMs, who have

plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100x10^6 cells/L, genotypic testing should guide the use of DRV/COBI FDC. In all other ART-experienced patients or if HIV-1 genotype testing is not available, the use of DRV/COBI FDC is not appropriate and DRV/rtv twice daily should be used.[30] Combinations with optimized background regimens other than ≥2 NRTIs have not been studied in this population. Limited data is available in patients with HIV-1 clades other than B.

As for all other ARV drugs, the DRV/COBI FDC should be combined with other active ARV drugs to maximize the virologic response and to reduce the risk of the development of resistance, as per HIV treatment guidelines. Careful consideration should be given to the treatment history of the individual patient, and the selection of agents to use in the background regimen. Regular assessment of virological response is advised. In the setting of lack or loss of virological response, resistance testing should be performed.

Darunavir/COBI should not be used in combination with another ARV that requires PK enhancement (eg, EVG and other HIV PIs), since dosing recommendations for such combination have not been established. The DRV/COBI FDC should not be used concurrently with products or regimens containing rtv or COBI. The FDC should not be used in combination with the individual components of the FDC (DRV or COBI).

After therapy with the DRV/COBI FDC has been initiated, patients should not alter the dosage or discontinue therapy without instruction of their healthcare provider.

Cobicistat, in contrast to rtv, is not an enzyme inducer, and switching PK enhancer from rtv to COBI may result in increased exposure to concomitantly administered drugs whose metabolism has been induced by rtv. Therefore, caution is needed during the first 2 weeks after switch from rtv to COBI, particularly if doses of any concomitantly administered medicinal products have been titrated or adjusted during use of rtv as a PK enhancer.

Patients should be advised that current ARV therapy does not cure HIV and that appropriate precautions should continue to be employed to prevent sexual transmission of HIV-1.

When initiating a new ARV regimen, informing the patient of the nature and likelihood of potential side effects is likely to improve adherence, and improve patient satisfaction with the regimen. It is important that side effects are controlled as early as possible and that the patients are supported not to withdraw from the therapy due to side effects that can be managed.

As medication adherence is critical to successful ARV therapy, regular adherence monitoring and counseling is important.

7. BENEFITS AND RISKS ASSESSMENT

The DRV/COBI FDC benefit-risk profile for the treatment of HIV-1 infection in treatment-naïve adults and treatment-experienced adults with no DRV RAMs with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count ≥100x10^6 cells/L is based on the benefit-risk profile of the combined use of DRV and COBI and on the additional benefits provided by having DRV and COBI coformulated in a single FDC tablet.

7.1. Risks of COBI-boosted DRV

The clinical safety profile of the DRV/COBI FDC is based on the established clinical safety profiles of the 2 individual agents.

Cobicistat has been shown to decrease estimated creatinine clearance due to inhibition of tubular secretion of creatinine and to induce a non clinically significant increase in the ECG PR interval (see Section 5.3.1). These findings may also apply to the DRV/COBI FDC and will be addressed in the FDC SmPC.

The safety profile of DRV 800 mg once daily when boosted with rtv is established in TMC114-C211 up to 192 weeks and in TMC114-C229 up to 48 weeks (see Section 5.2), and through postmarketing experience (see Section 5.8). Darunavir/rtv was generally safe and well tolerated in HIV-1 infected subjects. The DRV ADRs identified through this extensive experience apply to the DRV/COBI FDC and will be listed in the FDC SmPC.

The Week-24 safety profile of DRV/COBI 800/150 mg once daily coadministered as single agents is further characterized in study GS-US-216-0130, in 313 HIV-1 infected adult subjects with a median exposure of 31.4 weeks. The ADR profile of DRV/COBI 800/150 mg once daily is consistent with the ADR profile of the single agents DRV and COBI, though with a higher incidence of mild to moderate rash (16.0% with DRV/COBI versus 8.2% and 5.8 % with DRV/rtv in the 2 historical studies). Darunavir systemic exposure was not correlated with any safety parameters when DRV was boosted with COBI. In the Week-48 safety and tolerability analysis of study GS-US-216-0130, 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.

The drug-drug interaction potential of the DRV/COBI FDC is based on that of the single agents. As COBI has less overall effects on drug metabolizing enzymes and transporters compared to rtv, different drug-drug interactions could be expected with DRV/COBI as compared to DRV coadministered with rtv.

Safety, efficacy and PK of DRV/COBI in pediatric patients <18 years of age have not been established.

Risks considered relevant to the FDC were derived from the DRV/rtv and COBI Risk Management Plans. In general, in case of a common or overlapping risk/missing information, the most conservative approach was adopted. Overall, important risks and missing information with DRV/COBI as listed below will be addressed in the product labeling and/or monitored through routine and additional pharmacovigilance activities (refer to the DRV/COBI FDC Risk Management Plan located in Module 1.8.2):

- **Important identified risks:** Severe skin reactions, Hepatotoxicity, Hyperglycaemia, Lipid abnormalities, Pancreatitis, Fat redistribution, Immune reconstitution inflammatory syndrome, Development of drug resistance, Drug-drug interactions.
- **Important potential risks:** Coronary artery events, Cardiac conduction abnormalities, Convulsions.
- **Important missing information:** long-term safety of COBI-boosted DRV in HIV-1 infected adults, safety data in children 3 to <18 years of age, in older people (65 years and above), in pregnant and breastfeeding women, in patients with renal impairment, and in patients with severe hepatic impairment (Child-Pugh score C).

7.2. Benefit of COBI-boosted DRV – Antiviral Activity

The efficacy profile of COBI-boosted DRV in HIV-1 infected adult subjects is driven by DRV, as COBI is devoid of antiviral activity.

As COBI 150 mg is an adequate PK enhancer (see Section 1.2), the antiviral activity profile of COBI-boosted DRV can be reasonably extrapolated from the registrational efficacy data of rtv-boosted DRV 800 mg once daily. How this is supported by the results of the clinical development program, is discussed separately for treatment-naïve subjects and for treatment-experienced subjects in the sections below.

7.2.1. Treatment-naïve HIV-1 Infected Subjects

In study GS-US-216-0130, COBI-boosted DRV 800 mg once daily with a background regimen of 2 fully active NRTIs was efficacious at suppressing HIV-1 RNA <50 copies/mL through 24 weeks in 83.7% (95% CI 79.0% to 87.8%) of the 295 treatment-naïve subjects per FDA-defined snapshot analysis and 78.6% (95% CI 73.5% to 83.2%) per TLOVR algorithm. No subjects developed resistance to DRV or to their concomitant NRTI regimen. These results are consistent with the Week-24 results of study TMC114-C211 where 81.6% of subjects on rtv-boosted DRV achieved virologic response per FDA-defined snapshot analysis (79.6% per TLOVR algorithm).

The observed level of COBI exposure was high enough to provide robust PK enhancement. The population PK-based DRV exposures in GS-US-216-0130 were consistent with the DRV PK determined in HIV-1 infected subjects following DRV/rtv administration in TMC114-C211, indicating adequate PK enhancement of DRV by COBI. These results further support that the Phase 1 findings of a lower C_{tau} with DRV/COBI compared to DRV/rtv can be considered as not clinically relevant.

Therefore, treatment with DRV/COBI FDC 800/150 mg once daily in combination with other ARVs is expected to provide substantial and durable efficacy benefits in ART-naïve subjects, offering a high genetic barrier to resistance, and preserving future treatment options.

7.2.2. Treatment-experienced HIV-1 Infected Subjects

Results from study GS-US-216-0130 in the subgroup of treatment-experienced subjects are not contributive as the small sample size (n=18) did not allow to draw any firm conclusions on virologic response or PK/PD relationships.

The virologic response rate was 61.1% (95% CI 35.7% to 82.7%) in the Week-24 FDA snapshot analysis, numerically lower than in study TMC114-C229 (70.1%; N=294). In the TLOVR analysis, 44.4% (95% CI 21.5% to 69.2%) of treatment-experienced subjects reached and maintained confirmed HIV-1 RNA !50 copies/mL through Week 24. One subject with poor pill bottle returns, indicative of poor adherence, developed DRV genotypic (a single DRV RAM I84I/V) but not phenotypic resistance. No subjects developed resistance to their concomitant NRTI regimen.

While a larger treatment-experienced dataset would have been optimal, the evidence of the primary pharmacodynamic properties of COBI as a PK enhancer supports the expectation of an efficacy profile of DRV/COBI comparable to that observed with DRV/rtv 800/100 mg once daily in treatment-experienced patients with no DRV RAMs with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L.

Therefore, the Applicant considers that the existing comprehensive programs on the single agents and the newly generated data support the use of the DRV/COBI FDC 800/150 mg once daily for the treatment of HIV-1 infection in treatment-experienced adults with no DRV RAMs with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L and can be expected to provide substantial and durable efficacy benefits in these subjects.

7.3. Benefit of DRV/COBI FDC - Treatment Convenience

The additional benefit of the DRV/COBI FDC rests on providing patients the convenience of taking one single tablet instead of 2 separate pills, once daily, on top of their background regimen, and consequently on simplifying the DRV-containing ARV regimen. Literature reports show that simplification of ART through the use of FDCs increases convenience for the patient, potentially resulting in improved adherence, and hence in a reduction of risk of virologic failure. This not only has benefits at the level of the individual patient, but also potentially for the health care system.[22]

Adherence to a drug regimen is an absolute requirement for the successful treatment of chronic diseases, in particular HIV, as it may contribute to reducing the incidence of resistance. Improved adherence can be achieved by simplification of the medication regimen. This can include simplification of posology schedule (eg, from twice daily to once daily dosing, removal of restrictions on timing, food or comedications) and the use of FDCs (pill burden reduction). The current HIV treatment guidelines recognize the importance of treatment simplification: coformulations and simplified dosing schedules are all recognized as strategies which may increase patient treatment adherence.[2,34,36]

Fixed dose combinations have been associated with improved adherence compared to their separate components in well-conducted meta-analyses and clinical studies. A meta-analysis

conducted in a large cohort of ~20,000 chronic disease patients, with HIV having the greatest weight in the analysis, concluded that an FDC provides a strong armamentarium in chronic disease management with the risk of non-adherence to a medication regimen being reduced by 24% to 26% with FDCs.[1] Moreover, an additional spillover adherence effect of an FDC-based ART on the remaining regimen components (ie, the effect of combining 2 pills in a regimen on the adherence of the remaining non-combined pills) has been described. In one study, the use of an FDC appeared to substantially improve adherence to a third component in the regimen compared to HIV-infected patients who received a nonfixed regimen, and thus increases the likelihood of achieving 95% adherence to the entire ART regimen.[19]

The Department of Health and Human Services guideline recommends using FDCs to aid adherence and stipulates that adherence to an ART has been correlated strongly with HIV viral suppression, reduced rates of resistance, an increase in survival, and improved quality of life.[36]

7.4. Benefit-Risks Conclusions

The evidence included in this Clinical Overview supports the positive benefit-risk profile for the use of DRV/COBI FDC 800/150 mg once daily, in combination with other ARV drugs and with food, for the treatment of HIV-1 infection in treatment-naïve adults and treatment-experienced adults with no DRV RAMs with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L, as described in the proposed indication of the SmPC in Module 1.

The DRV/COBI FDC represents an efficacious and safe simplification of a once daily DRV-containing ARV regimen that provides improved patient convenience, which should lead to enhanced adherence, less medication errors and improved outcome in these patients.

REFERENCES

All literature references are considered supportive but have been included for the convenience of the reviewer.

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APPENDICES

Appendix 1: Regulatory and Scientific Rationale of Module 5 Approach

The legal basis for this darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) marketing authorization application (MAA) in the European Union is Article 10b of Directive 2001/83/EC. To support this Article 10b application, a full dossier is submitted. Hence, all data on the FDC have to be submitted, as per Annex I, Part I of the Directive. Notice to Applicants, Volume 2A, Procedures for marketing authorization, Chapter 1 Marketing Authorisation, allows that studies on the single individual substances are included in the application for a fixed-combination, especially to justify the absence of certain specific data on the combination and to ensure a full "stand-alone" dossier.

During the EMA [redacted] Meeting of [redacted], the EMA recommended that for such application, at least data from the single individual substances considered 'pivotal' (eg, supporting the information of the SmPC) for the assessment of the FDC are included in the MAA. As due to the particularities of each application, the extent of the data on single substances used to support the FDC may vary, the Applicant further discussed the dossier content and data presentation with the [redacted] and [redacted] (meeting minutes are included in Module 1.2.5.14).

The DRV/COBI FDC 800/150-mg tablet is to be administered once daily and is dosed according to the same once-daily dosage regimen as the single agents. The tablet is intended to be used in the same adult population for which DRV/low-dose ritonavir (rtv) 800/100 mg once daily (coadministered as single agents) is registered, ie, antiretroviral therapy (ART)-naïve adults and ART-experienced adults with no DRV resistance associated mutations (RAMs) and who have plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L. The intended indication for the FDC of DRV/COBI 800/150 mg does not represent a new combination regimen but 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.

A complementary bridging clinical program in line with EMEA/CHMP/EWP/633/02 Rev2 and EMEA/CHMP/EWP/240/95 Rev1, aimed at generating pharmacokinetic data that support the development of a FDC formulation and bridge the comprehensive datasets of the individual agents to the FDC formulation. This program consists of 3 studies: a Phase 1 study investigating the relative oral bioavailability of 2 FDC formulations of DRV/COBI 800/150 mg (G003 and G004) to that of DRV/rtv 800/100 mg coadministered as single agents (TMC114IFD1001) completed by the Applicant, a Phase 1 study conducted by the Applicant (TMC114IFD1003) to assess the bioequivalence of the selected FDC formulation (G006) compared to DRV and COBI coadministered as single agents under fasted and fed conditions, and an ongoing Phase 3b, open-label, single-arm study (GS-US-216-0130) conducted by Gilead in collaboration with the Applicant. Study GS-US-216-0130 generates additional safety data on treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in combination with 2 NRTIs, and also further provides supportive evidence of the efficacy and pharmacokinetic profile of DRV/COBI in the targeted population.

No drug-drug interaction studies have been conducted with DRV/COBI (FDC or coadministered as single agents). The drug-drug interaction potential of DRV/COBI is based on the interactions observed with the single agents. Extrapolations are based on the known in vitro and in vivo pharmacological profile of the single agents DRV and COBI and the medications involved. A summary of the data from the single individual substances most relevant to this combination is provided in the Summary of Clinical Pharmacology Studies. Interaction potential and recommendations for concomitant use is presented in Section 4.5 of the SmPC.

As the FDC combines 2 products at the same once daily dosage regimen as the selected dose for the single agents, no dose selection study was performed (EMEA/CHMP/EWP/240/95 Rev. 1).

The efficacy profile of COBI-boosted DRV in HIV-1 infected adult subjects is driven by DRV, as COBI has no detectable antiviral activity against HIV-1. As COBI 150 mg is an adequate PK enhancer, the antiviral activity profile of COBI-boosted DRV can be reasonably extrapolated from the registrational efficacy data of rtv boosted DRV 800 mg once daily (TMC114-C211 and TMC114-C229). These studies formed the basis of approval of the DRV/rtv 800/100 mg once daily regimen. These data are summarized in this application.

Moreover, the intended indication for the FDC concerns a substitution indication of DRV/COBI registered coadministration and the EMEA/CHMP/EWP/240/95 Rev. 1 guideline does not require a comparative trial with the FDC formulation and comparative pharmacokinetic data are generally considered sufficient.

The resistance profile of DRV/COBI FDC is driven by DRV as COBI does not have antiviral activity and therefore does not select any HIV resistance mutations. The clinical resistance profile of DRV/rtv 800/100 mg once daily has been established in the study TMC114-C211 (ART-naïve subjects) and in study TMC114-C229 (ART-experienced subjects without DRV RAMs). The results of the Week-24 resistance analysis of the GS-US-216-0130 provide supporting evidence.

The absence of synergistic toxicity based on the assessment of the preclinical data and the Phase 1 PK bridging results and the established long-term safety profile of DRV when boosted with rtv, support the extrapolation of the rtv-boosted DRV safety profile to the FDC tablet. Further support for the DRV/COBI safety profile is provided by the Phase 3b, single-arm study (GS-US-216-0130) and study GS-US-236-0118 performed by Gilead as part of the EVG/COBI program in HIV-1 infected adults with mild to moderate renal impairment.

The PK bridging approach in support of this FDC MAA for DRV/COB was discussed with the Medicines Evaluation Board (MEB, The Netherlands, [redacted], WAG 4392/case 227585, minutes MEB SA meeting in Module 1.2.5.14) and with the FDA ([redacted] 113,198/Reference ID 3046745) for the development of the FDC product.

Based on the above regulatory and scientific rationale, FDC data has not been submitted in several indents of Module 5 but has been replaced by relevant data from the existing development programs of the individual compounds DRV (in combination with rtv) and COBI.

A full list of all clinical studies conducted with the single individual substances that are considered relevant to support the marketing authorization application for the DRV/COBI FDC is provided in the table below. The study identifier and study title are provided, as well as the initial MAA in which the reports reside (FDC for studies conducted as part of the bridging clinical program, DRV or COBI for studies already submitted as part of the single agent MAAs). This overview further indicates which studies are included in the FDC MAA as they are considered “pivotal” (key) for the benefit-risk assessment of the FDC, and which studies are considered “supportive”. A justification for the absence of any data not presented in Module 5 of the FDC MAA has also been included in this table.

Module 5: Clinical Study Reports				
Submission Component and location within FDC MAA	**Compound**	**Key / Supportive**	**Single agent MAA (if not re-submitted in FDC MAA)**	**Location in single agent MAA (if not re-submitted in FDC MAA)**
5.3 Clinical Study Reports				
5.3.1 Reports of Biopharmaceutic Studies				
5.3.1.1 Bioavailability (BA) Study Reports				
TMC114IFD1001 - A Phase I study to evaluate, under fed and steady-state conditions, the pharmacokinetics and relative bioavailability of two fixed dose combination formulations (G003 and G004) of darunavir/cobicistat 800/150 mg versus darunavir/ritonavir 800/100 mg coadministered as single agents.	FDC	Key		
TMC114-C143 - The effect of food on the bioavailability of TMC114 coadministered with a low dose of ritonavir.	darunavir	Key		
GS-US-236-0105 - A Single and Multiple Dose-Escalation First-in-Human Study Evaluating the Safety, Tolerability, and Pharmacokinetics of GS-8374 Administered in Combination with the Pharmacoenhancer GS-9350**.**	cobicistat	Key		
TMC114-C102 - The effect of food on the bioavailibility of an oral solution of TMC114.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.1
TMC114-C114 - The absolute bioavailability of TMC114,formulated as a tablet, administered alone and in the presence of low dose ritonavir, in healthy subjects compared to intravenous administration, alone and in the presence of low dose ritonavir.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.1
TMC114-C118 - The relative bioavailability of a single intake TMC114, after 2-days b.i.d. low dosing of ritonavir, with the experimental formulation TF036 under fed and fasted conditions as compared to the Vit ETPGS/ PEG400 oral solution under fed and fasted conditions**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.1
5.3.1.2 Comparative BA and bioequivalence (BE) Study Reports and related information				
TMC114IFD1003 - A single-dose, open-label, 3-panel, randomized, pivotal crossover study to assess the bioequivalence of darunavir when co-administrated with cobicistat as either a fixed dose combination tablet (G006) or as single agents under fed and fasted conditions in healthy subjects**.**	FDC	Key		
GS-US-216-0115 - A Phase 1 Multiple Dose Study to Evaluate the Relative Bioavailability and Pharmacokinetics of Darunavir Coadministered with the Pharmacoenhancer GS-9350 versus Ritonavir.	cobicistat	Key		
TMC114-C103 - The systemic exposure of TMC114 in experimental formulations in fed and fasted conditions as compared to TMC114 Vit E-TPGS/PEG400 oral solution under fasted conditions**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C116 - A Phase I, open-label, randomized, crossover study to compare the rate and extent of absorption of TMC114 following a single administration of the clinical trial and commercial tablet formulation in the presence of low-dose ritonavir (Pivotal Bioequivalence Trial).	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2

Submission Component and location within FDC MAA	Compound	Key / Supportive	Single agent MAA (if not re-submitted in FDC MAA)	Location in single agent MAA (if not re-submitted in FDC MAA)
TMC114-C117 - The relative bioavailability of a single intake TMC114, boosted with a low dose of ritonavir with the experimental solid formulations TF042, TF043 and TF044 as compared to the Vit E-TPGS/PEG400 oral solution	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C136 - The relative bioavailability of a single intake of TMC114, boosted with a low dose of ritonavir with the experimental solid formulations TF051 and TF052 under fasted conditions as compared to the Vit ETPGS/ PEG400 oral solution under fasted conditions**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C144 - The relative bioavailability of a single intake of TMC114, formulated as the test tablets F011, F012, and F013, as compared to the reference table F001, all coadministered with a low dose of ritonavir.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C148 - The relative bioavailability of a single intake of TMC114, boosted with a low dose of ritonavir, and formulated as the experimental tablets TF036A, TF036B and TF036C, as compared to the experimental tablet TF036**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C154 - To determine the relative bioavailability of TMC114 of batches of F002 tablets with different particle size distributions.blet TF036**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C156 - The relative bioavailability of TMC114, formulated as F002 tablets using different batches of drug substance**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C162 - A Phase I, open label, randomized, 2-panel, 2-way crossover pivotal bioequivalence trial between the commercial tablet formulation (F016) and the 'improved' tablet formulation (F032) of darunavir (DRV), in the presence of low-dose ritonavir under fasted and fed conditions [new]	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C166-CRPP - Exploratory bioavailability (BA) trial of single-dose darunavir coadministered with low-dose ritonavir in healthy subjects, as follow-up to trial TMC114-C116	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C167 - A Phase I, open label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of an improved tablet formulation of TMC114 (F026) to that of Phase III/commercial tablet formulation (F016) in the presence of low-dose ritonavir and under fasted conditions.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C168-CRPP - A Phase I, open-label, randomized, crossover trial in healthy subjects to assess the bioavailability of darunavir formulated as the commercial tablet or as the clinical trial tablets, without coadministration of ritonavir and under fed conditions**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C169 - A Phase I, open-label, randomized, crossover trial in healthy subjects to compare the oral bioavailability of a suspension formulation of darunavir (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.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
TMC114-C176 - A Phase I, open-label, randomized, 2-panel, 2-way crossover pivotal bioequivalence trial between the commercially available 400-mg tablet formulation (F030) and the 800-mg tablet formulation of darunavir (G002), in the presence of low-dose ritonavir under fasted and fed conditions.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2

Submission Component and location within FDC MAA	Compound	Key / Supportive	Single agent MAA (if not re-submitted in FDC MAA)	Location in single agent MAA (if not re-submitted in FDC MAA)
TMC114-C182 - A Phase I, open label, randomized, single dose crossover study in healthy subjects to compare the oral bioavailability of darunavir 800 mg to that of the commercial 400 mg tablet under fed and fasted conditions and in the presence of low-dose ritonavir**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.2
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.				
5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies				
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.	darunavir	Key		
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.	darunavir	Key		
TMC114-BA10243 - Partial validation of a method for the determination of TMC114 and ritonavir in human K2-EDTA plasma samples.	darunavir	Key		
TMC114-TiDP3-BA1389 - Validation of a method for the determination of TMC114 and ritonavir in human plasma samples.	darunavir	Key		
QPS 60-0949 - Validation of a Method for the Determination of GS-9137 and GS-9350 in K2EDTA Human Plasma by LC-MS/MS.	cobicistat	Key		
20137v2 - Covance Laboratories, Inc. Final Validation Report, Addendum No. 1: Validation of a Method for the Determination of GS-9350 in Human Plasma using HPLC with MS/MS Detection**.**	cobicistat	Key		
20238v1 - Tibotec Pharmaceuticals Ltd. Validation Report – Validation (partial) of an LC-MS/MS Method for the Determination of JNJ25875382 (TMC114, R319064) and JNJ-16382028 (R115891) in Human Heparin Plasma.	cobicistat	Key		
20219v1 - Covance Laboratories, Inc. Final Validation Report: Abbreviated Validation of a Method for the Determination of GS-9350 and GS-9612 in Human Plasma by HPLC with MS/MS Detection**.**	cobicistat	Key		
TMC114-ABL1982-AVR - Validation of the determination of TMC114 in human plasma using LC-MS/MS.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
TMC114-ABL3021-AVR - Validation of the combined determination of TMC114 and Ritonavir in human plasma using LC-MS/MS**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
TMC114-ABL3173-AVR - The validation of the free TMC114 in human plasma by centrifugal filtration with a 10.000 MW filter**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
TMC114-ABL5150-AVR - The cross-validation of the determination of TMC114 and Ritonavir in human plasma using an API-4000 LC-MS/MS system**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4

Submission Component and location within FDC MAA	Compound	Key / Supportive	Single agent MAA (if not re-submitted in FDC MAA)	Location in single agent MAA (if not re-submitted in FDC MAA)
TMC114-ABL1983-AVR - Validation of the determination of TMC114 in human urine using LC-MS/MS.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
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.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
TMC114-PBR040553-AVR - Validation of a method for the determination of TMC114 and Ritonavir in human heparin plasma samples**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
TMC114-BA819 - Validation of an LC-MS/MS method for the determination of TMC114 (R319064)/R115891/R366619 in human heparin plasma	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.1.4
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				
TMC114-C109 - An open-label, single dose, mass balance study with 14C-labelled TMC114 with and without a low dose of ritonavir**.**	darunavir	Key		
GS-US-216-0111 - A Phase 1 Study to Evaluate the Pharmacokinetics, Metabolism and Excretion of GS-9350 (Mass Balance Study).	cobicistat	Key		
GS-US-216-0113 - A Phase 1 Study to Evaluate the Pharmacokinetics, Safety and Tolerability of GS-9350 in Healthy Volunteers**.**	cobicistat	Key		
TMC114-C101 - Safety, tolerability and pharmacokinetics of increasing single oral doses of TMC114 in healthy adult subjects**.**	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.3.1
TMC114-C104 - Randomized, placebo-controlled, double-blind, multiple dose escalation trial to examine the safety, tolerability and pharmacokinetics of oral twice or three times daily TMC114 doses in healthy subjects.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.3.1

Submission Component and location within FDC MAA	Compound	Key / Supportive	Single agent MAA (if not re-submitted in FDC MAA)	Location in single agent MAA (if not re-submitted in FDC MAA)
TMC114-C137 - The pharmacokinetics, safety and tolerability of TMC114, formulated as tablet TF036 and boosted with a low dose of ritonavir, for various multiple dose regimens.	darunavir	Supportive	PREZISTA EMEA/H/C/000707	M5.3.3.1
GS-US-236-0101 - A Phase 1 Multiple Dose Study to Evaluate Relative Bioavailability of Elvitegravir, Emtricitabine, and Tenofovir DF plus Pharmacoenhancer GS-9350 Fixed-Dose Combination Tablet vs. the Individual Components Ritonavir Boosted Elvitegravir, Em	cobicistat	Supportive	TYBOST MAA	M5.3.3.1
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				
TMC114-C134 - Pharmacokinetic and safety assessment of multiple dose TMC114 in combination with low-dose ritonavir in subjects with impaired hepatic function.	darunavir	Key		
GS-US-216-0121 - A Randomized, Blinded, Placebo-Controlled Phase 1 study Evaluating the Effect of GS-9350 and Ritonavir on Renal Function as Assessed by Markers of Glomerular Filtration Rate**.**	cobicistat	Key		
GS-US-216-0124 - A Phase 1, Open-Label, Parallel-Design, Multiple Dose Study to Evaluate the Pharmacokinetics of Cobicistat-Boosted Elvitegravir in Subjects with Severe Renal Impairment**.**	cobicistat	Key		
GS-US-183-0133 - A Phase 1, Open-Label, Parallel-Group, Multiple Dose Study to Evaluate the Pharmacokinetics of Cobicistat-Boosted Elvitegravir in Subjects with Normal and Impaired Hepatic Function.	cobicistat	Key		
5.3.3.4 Extrinsic Factor PK Study Reports				
TMC114-C107 - The pharmacokinetic interaction between rifabutin and TMC114, coadministered with low-dose ritonavir, in healthy subjects**.**	darunavir	Key		
TMC114-C111 - The pharmacokinetic interaction between TMC114, boosted with low doses of ritonavir, and efavirenz in healthy subjects**.**	darunavir	Key		
TMC114-C119 - The pharmacokinetic interaction between TMC114/rtv and nevirapine in HIV-1 infected patients.	darunavir	Key		
TMC114-C120 - The effect of TMC114, boosted with low doses of ritonavir, on pravastatin pharmacokinetics in healthy subjects**.**	darunavir	Key		
TMC114-C121 - The pharmacokinetic interaction between paroxetine or sertraline and TMC114, coadministered with low-dose ritonavir, in healthy subjects**.**	darunavir	Key		
TMC114-C122 - The effect of ranitidine and of omeprazole on the pharmacokinetics of TMC114, coadministered with a low dose of ritonavir, in healthy subjects.	darunavir	Key		

Appendix 2: Individual Case Assessment of Related AEs not Considered DRV/COBI ADR

AE	Cases Summary[a]	Relevant Information Subject Level	Rationale Assessment	Final Assessment Decision
Dry Mouth	3 (1.0%) cases, 2 Grade 1, 1 Grade 2 3 related cases (by the investigator) 0 serious AEs 1 AE leading to drug discontinuation time to onset range: 5-65 days	**2825-4196:** Start DRV/COBI: 2012-01-16 / Start AE: 2012-02-15, resolved (10d) (G1) and 2012-03-20, resolved 1 month after drug withdrawal (G2, not related) / Concurrent AEs: during the 2d episode, many other AEs in the oral cavity, all assessed as not related (oropharyngeal pain, palatal disorder, parasesthesia oral, sensitivity of teeth), except for 1 (dysgeusia). **0364-4150**: Start DRV/COBI: 2011-12-22 / Start AE: 2011-12-26, ongoing (G1) / Concurrent AEs: diarrhea, nausea, insomnia / Concomittant medication: eszopiclone / Active med history: depression. **0571-4174**: Start DRV/COBI: 2012-01-05 / Start AE: 2012-01-16, resolved (29d) (G1)/ Concurrent AEs: diarrhea, nausea; depression 3 months later.	Too few cases and information to make a meaningful assessment. Cases confounded by med history and/or concurrent med conditions (oral cavity roblems, gastrointestinal tract upset, psychiatric conditions) and the disease itself (xerostomia is common in HIV-infected subjects).	No ADR
Malaise	3 (1.0%) cases, 3 Grade 1 2 related cases (by the investigator) 0 serious AEs 0 AEs leading to drug discontinuation time to onset range: 1-2 days	**0121-4142:** Start DRV/COBI: 2011-12-20 / Start AE: 2011-12-20, ongoing (G1) / Concurrent AEs: dizziness, flatulence, nausea. **6046-4091**: Start DRV/COBI: 2011-12-01 / Start AE: 2011-12-02, ongoing (G1) / Concurrent AEs: abnormal dreams, dizziness. **2157-4050**: Start DRV/COBI: 2011-11-14 / Start AE: 2011-11-15, resolved (3d) (G1, not related) / Active med history: anxiety, lack of energy, difficulty faling asleep.	Malaise is a very aspecific term and could be closely related to the other concomitant complaints.	No ADR
Dizziness	9 (2.9%) cases, 8 Grade 1, 1 Grade 2 3 related cases (by the investigator) 0 serious AEs 0 AEs leading to drug discontinuation time to onset range: 1-56 days	**0121-4142**: Start DRV/COBI: 2011-12-20 / Start AE: 2011-12-20, resolved (2d) (G1)/ Concurrent AEs: flatulence, malaise, nausea. **1961-4136**: Start DRV/COBI: 2011-12-20 / Start AE: 2011-12-20, resolved (30d) (G1). **6046-4091**: Start DRV/COBI: 2011-12-01 / Start AE: 2011-12-02, resolved (17d) (G1) / Concurrent AEs: abnormal dreams, malaise. **1536-4127**: Start DRV/COBI: 2011-12-15/ Start AE: 2011-12-22, resolved (1d) (G1, not related) / Concurrent AEs: hyperhidrosis, nausea. **1537-4284**: Start DRV/COBI: 2012-02-21 / Start AE: 2012-04-16, resolved (3d) (G1, not related) /Concurrent AEs: sinusitis / Active med history: depression.	No clinical pattern in these cases. Of the 9 cases, most (6) were assessed by the investigator as not related. The related cases do not differ in information from the not related cases. Most cases were Grade 1 and none led to drug discontinuation. Variable time to onset and duration.	No ADR

AE	Cases Summary[a]	Relevant Information Subject Level	Rationale Assessment	Final Assessment Decision
		1543-4287: Start DRV/COBI: 2012-02-21/ Start AE: 2012-02-21, resolved (2d) (G1, not related)/ Concurrent AEs: abdominal discomfort, chest pain, fatigue, nausea, upper respiratory tract infection. **2157-4025:** Start DRV/COBI: 2011-11-03 / Start AE: 2011-11-30, resolved (1d) (G1, not related) / Concurrent AEs: headache. **2475-4005**: Start DRV/COBI: 2011-10-27 / Start AE: 2011-10-28, ongoing (G2, not related)/ Concurrent AEs: anxiety, chest pain, hypoaesthesia. **5545-4128**: Start DRV/COBI: 2011-12-15 / Start AE: 2011-12-29, resolved (13d) (G1, not related) / Concurrent AEs: dyspepsia.		
Dysgeusia	2 (0.6%) cases, 1 Grade 1, 1 Grade 2, 2 related cases (by the investigator) 0 serious AEs 1 AE leading to drug discontinuation time to onset range: 3-74 days	**2825-4196**: Start DRV/COBI: 2012-01-16 / Start AE: 2012-03-29, resolved 1 month after drug withdrawal (G2) / Concurrent AEs: dry mouth, palatal disorder, oral paresthesia, sensitivity of teeth. **1598-4003**: Start DRV/COBI: 2011-10-26 / Start AE: 2011-10-28, resolved (14d) (G1) / Concurrent AEs: diarrhea, fatigue / Active med history: anxiety, depression.	Too few cases and information to make a meaningful assessment, and events confounded by med history and/or concurrent med conditions; one of the two events resolved while drug was continued.	No ADR
Peripheral neuropathy	3 (1.0%) cases, 1 Grade 1, 1 Grade 2, 1 Grade 3 2 related cases (by the investigator) 0 serious AEs 1 AE leading to drug discontinuation time to onset range: 18-35 days	**1541-4147**: Start DRV/COBI: 2011-12-21, drug stopped / Start AE: 2012-02 (exact day of onset unknown), ongoing (G3) / Concurrent AEs: immune reconstitution syndrome (G3) / Active med history: herpes simplex 2 / AE treated with Aciclovir and Valaciclovir. **1609-4059**: Start DRV/COBI: 2011-11-16/ Start AE: 2011-12-03, ongoing (G2), history of Vitamin B intake. **5490-4252**: Start DRV/COBI: 2012-02-14 / Start AE: 2012-03-19, ongoing (G1, not related) / History of syphillis, active med history of anxiety, depression, herpes simplex virus types 1 and 2, non-insulin dependent diabetes mellitus, cramping in bilateral hands and feet.	Very short time to onset and too few cases and insufficient information (eg, symptoms, localisation, electromyography results) to make a meaningful assessment. Cases possibly confounded by underlying condition (eg, zoster, diabetes).	No ADR
Insomnia	7 (2.2%) cases, 7 Grade 1 3 related cases (by the investigator) 0 serious AEs 0 AEs leading to drug discontinuation time to onset range: 5-216 days	**0364-4150**: Start DRV/COBI: 2011-12-22 / Start AE: 2011-12-26, ongoing (G1) / Concurrent AEs: diarrhea, dry mouth, nausea / Active med history: depression. **2728-4039**: Start DRV/COBI: 2011-11-08 / Start AE: 2012-02-15, ongoing (G1). **2728-4072**: Start DRV/COBI: 2011-11-22 / Start AE: 2011-12-01, ongoing (G1) / Active med history: generalized anxiety disorder, depression, insomnia.	Variable time to onset and duration. Of the 7 cases, 4 were assessed by the investigator as not related and 6 had underlying psychiatric conditions. All cases were grade 1 and none led to drug discontinuation.	No ADR

AE	Cases Summary[a]	Relevant Information Subject Level	Rationale Assessment	Final Assessment Decision
		0589-4316: Start DRV/COBI: 2012-03-02 until 2012-03-26 / Start AE: 2012-03-09, ongoing (G1, not related) / Active med history: anxiety, depression, post-traumatic stress disorder. **1942-4203**: Start DRV/COBI: 2012-01-18 to 2012-02-10 / Start AE: 2012-01-28, resolved (8d), (G1, not related) / Concurrent AEs: abdominal pain, biliary dyskinesia, gastritis / Active med history: bipolar illness, depression. **2157-4083**: Start DRV/COBI: 2011-11-29 / Start AE: 2012-07-01, ongoing, (G1, not related) / History of insomnia. **2157-4159**: Start DRV/COBI: 2011-12-28 / Start AE: 2012-03-28, ongoing, (G1, not related) / History of insomnia, active med history of anxiety, depression		
Dermatitis	6 (1.9%) cases, 3 Grade 1, 3 Grade 2 2 related cases (by the investigator) 0 serious AEs 0 AEs leading to drug discontinuation time to onset range: 10-111 days	**1537-4185**: Start DRV/COBI: 2012-01-10 / Start AE (rash): 2012-01-20, resolved (4d), (G1). **2157-4130**: Start DRV/COBI: 2011-12-16 to 2012-03-06 / Start AE: 2011-12-25, resolved (7d), (G2) / Concurrent AEs: 2.5 months later rash (G3) reported as dermatitis allergic, and rash maculo-papular and rash vesicular leading to drug discontinuation. **0661-4200**: Start DRV/COBI: 2012-01-20 / Start AE: 2012-04-11, ongoing, (G1, not related) / Concurrent AEs: rash, ongoing, (G1, not related). **1780-4179**: Start DRV/COBI: 2012-01-08 / Start AE (anal dermatitis): 2012-01-26, resolved (18d), (G2, not related). **2157-4048**: Start DRV/COBI: 2011-11-11 to 2011-12-07 / Start AE: 2011-11-20, resolved (10d), (G2, not related) / Concurrent AEs: pyrexia (ALT, AST within normal range) / Active med history: generalized dry skin. **2157-4145**: Start DRV/COBI: 2011-12-20/ Start AE: 2012-04-08, resolved (6d), (G1, not related).	Among the 6 cases, 4 are suggestive of rash (including the 2 related cases). The remaining two cases cover separate conditions that do not qualify as ADRs (anal dermatitis and a not related dermatitis with a time to onset of 111 days). Rash is a listed ADR for DRV/COBI.	No ADR

G=Grade, d=day(s); med=medical
a Grade=worst grade.

Janssen Research & Development

Clinical Overview Addendum

Physiologically-based Pharmacokinetic Modeling of Interactions of CYP3A4 Inhibitors with Cobicistat

DRV/COBI (darunavir/cobicistat)

Status:	Approved
Date:	2 April 2015
Prepared by:	Janssen Infectious Diseases - Diagnostics BVBA
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ARVs	antiretrovirals
ATV	atazanavir
AUC	area under the plasma concentration-time curve
AUC_{tau}	area under the curve across the dosing interval
CL/F	the apparent oral clearance after administration of the drug
C_{max}	maximum plasma concentration
CLss/F	apparent oral clearance at steady state
C_{tau}	plasma concentration at the end of the dosing interval
COBI	cobicistat
CYP	cytochrome P450 enzyme(s)
DRV	darunavir
EVG	elvitegravir (Vitekta®)
GSI	Gilead Sciences, Inc.
HIV	human immunodeficiency virus
MRT	mean residence time
n	number of subjects
PAM	post-authorization measure
PBPK	physiologically-based pharmacokinetic
P-gp	p-glycoprotein
PI	protease inhibitors
pKa	ionisation constant
QTc	QT interval duration corrected for heart rate
RMP	Risk Management Plan
rtv	low-dose ritonavir
SmPC	Summary of Product Characteristics
T½ λz	estimate of the terminal elimination half-life of the drug in serum/plasma, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λz)
Vss	apparent steady state volume of distribution
Vz/F	apparent volume of distribution during the terminal phase

1. PRODUCT DEVELOPMENT RATIONALE

1.1. Introduction and Background

Cobicistat (COBI; developed by Gilead Sciences, Inc. [GSI]) is a potent mechanism-based cytochrome P450 (CYP) 3A inhibitor, similar to ritonavir (rtv), 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 such as atazanavir (ATV; developed by Bristol Myers), darunavir (DRV; developed by Janssen), and elvitegravir (EVG; developed by GSI). COBI is also a CYP3A substrate.

In the European Union, Tybost® (COBI 150-mg tablets) is indicated as a pharmacokinetic enhancer of the HIV-1 protease inhibitors (PI) ATV and DRV, and was approved on 19 September 2013. In the approved fixed dose combination of Stribild® (developed by GSI), COBI 150 mg is also used to enhance the activity of the HIV-1 integrase strand transfer inhibitor EVG. The fixed dose combination tablet containing DRV 800 mg and COBI 150 mg for oral once daily use, trade name REZOLSTA®, was approved on 19 November 2014.

This submission fulfils a post authorisation measure (PAM) for REZOLSTA and an additional pharmacovigilance activity (Category 3) agreed in the REZOLSTA Risk Management Plan (RMP). This submission follows a similar PAM for Tybost 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 (DDI) with COBI.

This clinical overview presents a discussion 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).

1.2. Overview of Data Included in This Submission

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.

Report AD-216-2113 evaluated 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)

Studies listed in Table 1 and Table 2 were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and applicable governmental regulatory requirements.

Note that the analyses performed in this document were performed subsequent to, and independently of, the formal clinical study reports. Results and conclusions described here are not intended to supplant or supersede those original reports and may show some small numeric differences in parameter values due to differences in the methodologies employed.

The PBPK model for COBI was developed with GastroPlus 8.5. Since the aim was to understand potential interactions involving COBI as a victim of CYP3A inhibition, the focus was on steady-state pharmacokinetics of COBI at a dose of 150 mg once daily. The GastroPlus manual recommends using a pKa-based model calibrated with measured solubility data. Data are available for pKa values and pH-dependent solubility for COBI.

An independent Good Clinical Practice-compliant analysis of COBI population pharmacokinetics is also included in this submission (Module 5.3.3.5/COBI population PK report). The population pharmacokinetic analysis focused on data obtained from COBI dosed 150 mg once daily, mostly with other agents, and is referenced throughout this overview and in Report AD-216-2113.

2. OVERVIEW OF BIOPHARMACEUTICS

No new information is submitted.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

3.1. Human Absorption and Disposition of Cobicistat in Vitro and in Vivo

Relevant information on the absorption and distribution of COBI can be found in Module 5.3.2.2/AD-216-2113 Sections 4.3.1 and 4.3.2.

Biotransformation of COBI is by oxidation by CYP enzymes, with no evidence for metabolism by direct conjugation or hydrolysis. In humans the primary catalyst of COBI oxidation is CYP3A with CYP2D6 playing a minor role in generating M31 (Module 4.2.2.4/AD-216-2106). COBI is not a substrate for human CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19 (Module 4.2.2.4/AD-216-2025 and /AD-216-2108). Similar results were obtained with the structurally-related HIV PI, rtv (Module 4.2.2.4/AD-216-2025).

The prominent role of CYP3A in COBI metabolism is consistent with clinical data in which the pharmacokinetics of COBI were affected by CYP3A inducers. Treatment with the potent CYP3A inducer, tipranavir, reduced the median COBI half-life by 61%, from 5.76 to 2.24 hours (Module 5.3.4.1/GS-US-216-0119-CSR). Treatment with the moderate CYP3A inducer, rifabutin, had less effect on the median half-life of COBI (reduced 25% from 3.33 to 2.49 hours, when co-dosed with EVG), but the median plasma concentration at the end of the dosing interval (C_{tau}) of COBI was reduced from 22.8 to 6.5 ng/mL (Module 5.3.3.4/GS-US-216-0123-CSR). The pharmacokinetics of rtv are also affected by potent CYP3A inducers, such as rifampicin.[1] In contrast, the pharmacokinetics of rtv are not affected significantly by the potent CYP2D6 inhibitor fluoxetine, with the mean area under the plasma concentration-time curve (AUC) increased by only 19% (from 128.1 ± 34.1 to 152.3 ± 33.0 µg•hr/mL) and the harmonic mean half-life increased by only 6% (from 4.78 to 5.07 hours).[2] Similar results are expected with COBI when coadministered with rifampicin or fluoxetine since rtv is structurally related to COBI and is metabolized in a similar manner. These data are consistent with a major role for CYP3A and a minor role for CYP2D6 in elimination.

Renal excretion is a minor route of elimination of COBI in humans with an average of 8.06% of radioactivity recovered in urine following oral administration of [^{14}C]COBI (150 mg) to healthy male volunteers (Module 5.3.3.1/GS-US-216-0111-CSR). Radioprofiling revealed that the majority of the urinary radioactivity was unchanged COBI. The quantitative role for direct biliary excretion in COBI elimination is difficult to estimate; however, subjects with moderate hepatic impairment showed little change in COBI clearance compared to the normal matched control group (mean apparent oral clearance after administration of the drug [CL/F] 17,204.6 mL/hr in impaired subjects and 16,717.0 mL/hr in controls) suggesting that biliary excretion was not an important route of elimination (Module 5.3.3.3/GS-US-183-0133-CSR).

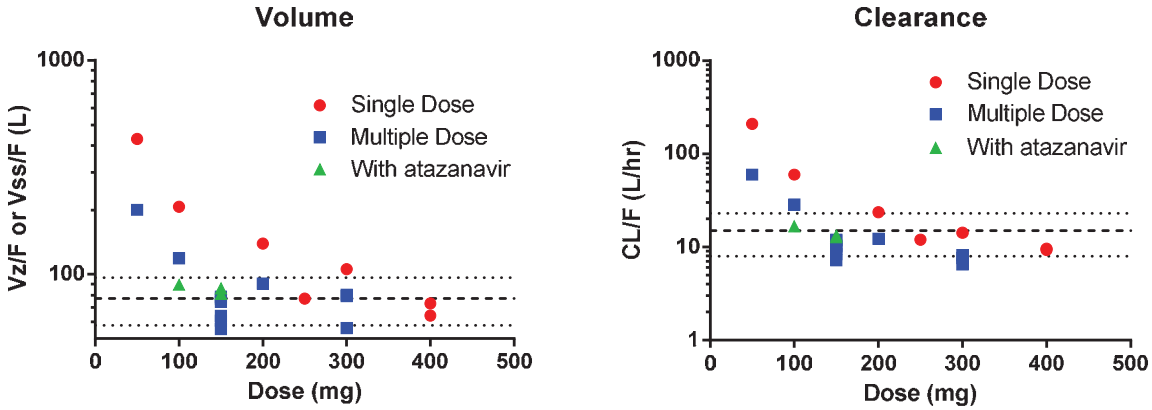
3.2. Pharmacokinetic Drug Interaction Properties of Cobicistat

The effects of COBI on drug metabolism enzymes and transporters have been assessed and a summary is presented in Module 5.3.2.2/AD-216-2113/Section 4.4. A full description of the drug interaction profile of COBI 150 mg has been previously submitted and is adequately reflected in the Tybost Summary of Product Characteristics (SmPC).

3.3. Single and Multiple-Dose Clinical Pharmacokinetics of Cobicistat

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 (Table 1). 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 (Figure 1). With the single doses of COBI, apparent clearance reaches a minimum, and mean residence time (MRT) reaches a maximum, at doses ≥200 mg (Table 3) whereas with multiples doses these were reached at dose ≥150 mg once daily with only modest changes at higher dose (Table 4).

Figure 1: Dose-dependence of Mean Non-compartmental Pharmacokinetic Parameters of Cobicistat Following Single or Multiple Oral Doses



Dashed lines are the population pharmacokinetic typical values derived using data from subjects dosed with 150 mg cobicistat once daily (volume 77 L and clearance 15 L/hr). Dotted lines represent population interindividual variability (25% for volume and 53% for clearance) determined by population pharmacokinetic analysis.

Source: Module 5.3.2.2/AD-216-2113/Figure 6.

Table 3: Mean Non-compartmental Pharmacokinetic Parameters for Cobicistat Following a Single Oral Dose

Dose mg	Study (Group)	n	T½ λz hr	C_{max} ng/mL	AUC ng•hr/mL	Vz/F L	CL/F L/hr	MRT hr
50	0101 (1)	12	1.4	52.1	238.8	429.0	209.8	4.2
100	0101 (2)	11	2.4	290.4	1675.7	206.5	59.7	6.0
200	0101 (3)	12	4.1	1118.7	8491.6	139.1	23.6	8.0
250	0107 (A)	48	4.5	2168.6	20845.1	77.0	12.0	8.9
300	0113 (1)	12	5.2	2264.6	21195.5	105.7	14.2	9.1
400	0107 (B)	48	5.5	3823.3	43134.9	72.9	9.3	10.1
400	0113 (2)	12	4.6	3930.3	41544.1	64.1	9.6	9.7

Source: Module 5.3.3.1/GS-US-216-0113-CSR, Module 5.3.4.1/GS-US-216-0101-CSR and /GS-US-216-0107-CSR.

Table 4: Mean Non-compartmental Pharmacokinetic Parameters for Cobicistat Following Multiple Oral Doses

Dose mg	Study (Group)	n	T½ λz hr	C_{max} ng/mL	AUC ng•hr/mL	Vz/F L	CLss/F L/hr	MRT hr
50	0101 (1)	12	2.3	159.2	840.7	200.1	59.6	5.7
100	0101 (2)	11	2.9	562.0	3524.6	118.7	28.5	6.5
150	0112 (1)	9	4.6	1764.8	19042.8	55.4	8.4	9.9
150	0112 (2)	22	4.4	1863.0	16606.7	60.6	9.5	9.3
150	0112 (3)	17	4.4	1731.4	15640.3	63.8	10.1	9.3
150	0116 (A)	35	4.5	1634.4	12990.5	78.5	12.0	8.8
150	0116 (B)	36	4.5	3410.7	13143.2	77.0	11.8	8.5
150	0121 (1)	12	4.9	3674.2	15038.8	74.2	10.4	8.5
150	0121 (4)[a]	18	7.7	1565.8	24042.9	79.4	7.2	12.2
200	0101 (3)	12	5.1	1550.3	17048.8	90.5	12.3	9.2
150 twice daily	0119 (1)	11	6.0	2894.9	32557.9	56.0	6.5	10.3
300	0113 (d4)	12	6.7	1596.1	40423.7	79.1	8.2	11.2
300	0113 (d7)	12	7.4	1885.0	45179.1	80.3	7.6	12.0

[a] Mild/moderate renally impaired subjects

Source: Module 5.3.3.1/GS-US-216-0113-CSR, Module 5.3.3.3/GS-US-216-0121-CSR, Module 5.3.3.4/GS-US-216-0112-CSR, and Module 5.3.4.1/GS-US-216-0101-CSR, /GS-US-216-0116-CSR, and /GS-US-216-0119-CSR.

As described in Module 5.3.2.2/AD-216-2113/Section 4.7, addition of 300 mg ATV to 100 mg COBI reduced the COBI apparent volume of distribution during the terminal phase (Vz/F) and apparent oral clearance at steady state (CLss/F). 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 (Figure 1).

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. Analyses on Excretion of Cobicistat

The clearance of COBI and probe drugs eliminated by known mechanisms was compared in order to explore the potential routes of elimination for COBI (Module 5.3.2.2/AD-216-2113/Section 4.9). 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: the CYP3A probe substrate, midazolam, was dosed alone, or with COBI on the final day 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: COBI 150 mg once daily clearance at steady state shows a weaker, but significant, correlation with the clearance of desipramine, a CYP2D6 substrate (Module 5.3.3.4/GS-US-216-0112-CSR). Additionally, the plasma exposures of the oxidative metabolite E3, which is generated by CYP3A4 and/or CYP2D6, was <1% of circulating parent exposures (AUC_{tau}), was minimal in urine (0.7% of total radioactivity), and only accounted for 14% of the total radioactive dose administered. This result suggests that CYP2D6, in the setting of maximally inhibited CYP3A4 metabolism (the only non CYP2D6 route of metabolism), is not a major metabolizing enzyme for COBI (Module 5.3.3.1/GS-US-216-0111-CSR).

- CYP2B6 and P-glycoprotein (P-gp): 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).

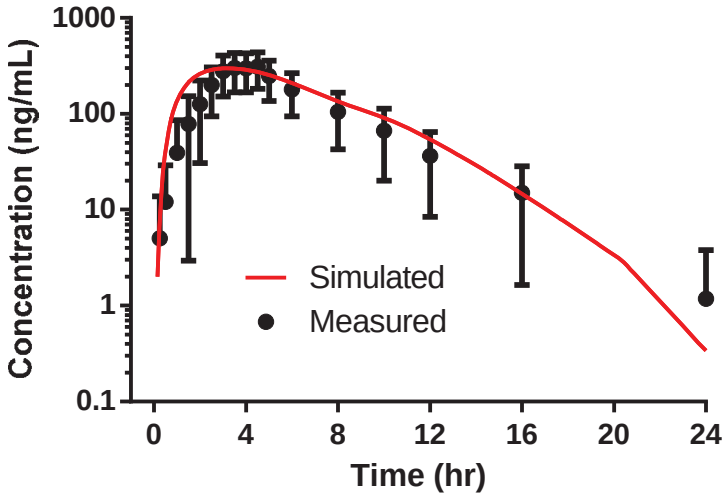
3.5. Development of a Physiologically-based Pharmacokinetic Model for Cobicistat

A PBPK model 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.

The PBPK model was developed in four stages:

- First, a compartment model with fixed clearance (hepatic and renal) was developed to check performance of the solubility/gut physiology model. From the population pharmacokinetic analysis (Module 5.3.3.5/COBI population PK report), and from results outlined in Module 5.3.2.2/AD-216-2113/Section 4.8, it was found that a one-compartment model was sufficient to describe the data. 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 (Figure 2) (GastroPlus Record 0101-100-SD). GastroPlus predicted approximately 40% of the bioavailable dose would be absorbed through the caecum and colon.

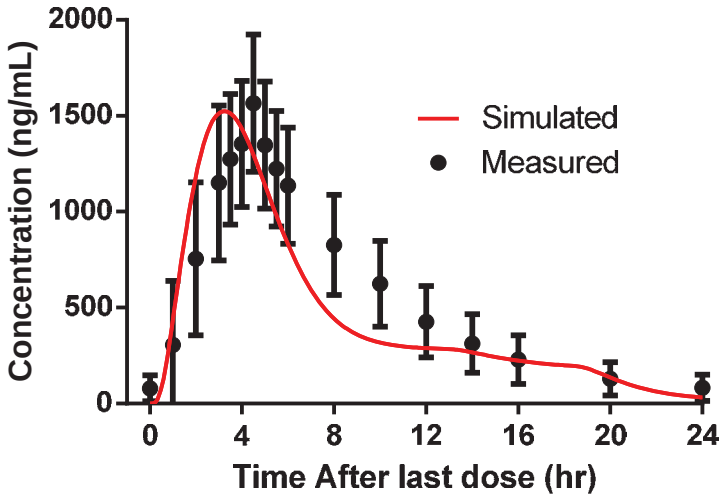
Figure 2: Single Dose 100 mg Cobicistat Pharmacokinetics (Mean ± SD, n=12) Compared to GastroPlus Compartmental Model with Fixed Clearance



Source: Module 5.3.2.2/AD-216-2113/Figure 17.

- 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. Calibration of the model was based on parameter scanning to approximately match the simulated data to the pharmacokinetic profile in Figure 2, and using in vitro data of the metabolism of COBI by recombinant CYP2D6 and CYP3A4 (Module 5.3.2.2/AD-216-2113/Section 7.3). 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.
- 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 (Vss) 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 this case, the physiology was switched to a fed state to match the study practice. Without further modification, the model predicted exposure that was too low, likely due to high clearance due to insufficient CYP3A inactivation. Therefore, 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 a multiple dosing, with still a predominant contribution from CYP3A of 76% in COBI elimination. A representative concentration-time profile is in Figure 3 (r^2=0.84) (GastroPlus Record 0116-150-SS).

Figure 3: Predicted and Measured (Mean ± SD, n=35) Cobicistat Plasma Concentrations on Day 10 of Dosing 150 mg Once Daily



Source: Module 5.3.2.2/AD-216-2113/Figure 18.

Further details on the development of the PBPK model can be found in Module 5.3.2.2/AD-216-2113/Section 4.10.5.

In summary, a 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. This major role for CYP3A is consistent with the clinical data.

4. OVERVIEW OF EFFICACY

No new information is submitted.

5. OVERVIEW OF SAFETY

No new information is submitted.

6. BENEFITS AND RISKS CONCLUSIONS

This clinical overview describes a discussion of data collected from multiple clinical 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).

CYP metabolism is the major mode of elimination of COBI with renal excretion accounting for approximately 10% of total clearance at steady state and biliary excretion likely a minor route of elimination.

A comparison of the clearance of COBI and probe drugs eliminated by known mechanisms confirmed that CYP3A is the major enzyme involved in the elimination of COBI with no

evidence for involvement of CYP2B6 and moderate association with CYP2D6 activity. The prominent role of CYP3A was consistent with clinical data in which the pharmacokinetics of COBI were affected by CYP3A inducers.

COBI exhibited dose non-linear and time-dependent pharmacokinetics with a plateau in increased bioavailability and decreased clearance reached at a dose of 150 mg. This pharmacokinetic profile was similar when COBI 150 mg was administered with ATV 300 mg, a potent inhibitor of CYP3A, demonstrating that COBI 150 mg maximally inhibits CYP3A activity even when coadministered with another potent CYP3A inhibitor.

A PBPK model suggested that CYP2D6 played a relatively limited role in COBI clearance with CYP3A playing a major role, even when CYP3A was largely inhibited.

Overall, this new review of clinical data (sensitivity of COBI clearance to induction of CYP3A, correlation between COBI clearance and that of CYP3A and CYP2D6 probe substrates, and the effect of a potent CYP3A inhibitor on COBI clearance) and the development of a PBPK model provide confirmation of the routes for COBI elimination and its interaction with potent inhibitors of CYP3A, consistent with previous in vitro and in vivo analyses.

The conclusions from this report do not change the known safety profile of COBI. No update to the RMP for REZOLSTA is warranted given that these data do not change the positive benefit-risk balance for this product when used as part of ARVs combination therapy in the treatment of HIV-1 infected adults and do not lead to the addition or deletion of a safety concern in the RMP for REZOLSTA.

Concomitant administration with a CYP3A inhibitor did not result in clinically significant changes in COBI pharmacokinetics and no dose adjustment is required. COBI pharmacokinetic data are adequately described in the REZOLSTA SmPC. No updates to prescribing information are therefore proposed.

No additional studies are considered needed to further characterize the enzymes/proteins involved in the elimination of COBI.

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Janssen Research & Development

Clinical Overview 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: 28 September 2015
Prepared by: Janssen Infectious Diseases - Diagnostics BVBA
EDMS number: EDMS-ERI-111366616, 1.0

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

abbreviation	description of abbreviated term
AE	adverse event
aGFR	actual glomerular filtration rate
ARV	antiretroviral
ATV	atazanavir
$CL_{iohexol}$	iohexol clearance
COBI	cobicistat
CSR	clinical study report
DRV	darunavir
eGFR	estimated glomerular filtration rate
$eGFR_{CG}$	stimated glomerular filtration rate (eGFR) by the Cockcroft-Gault method
EVG	elvitegravir
FDC	fixed dose combination
FTC	emtricitabine
GCP	Good Clinical Practice
GGT	gamma glutamyltransferase
HIV(-1)	human immunodeficiency virus (type 1)
ICH	International Conference on Harmonization
INSTI	integrase strand-transfer inhibitor
M=E	missing=excluded
NRTI	nucleoside reverse transcriptase inhibitor
PAM	post-authorization measure
PI	protease inhibitor
PRT	proximal renal tubulopathy
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
TFV	tenofovir

1. PRODUCT DEVELOPMENT RATIONALE

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).

Study GS-US-236-0118 was a Phase 3 study in human immunodeficiency virus type 1 (HIV-1) infected antiretroviral (ARV) treatment-naïve and ARV treatment-experienced subjects with mild to moderate renal impairment. The primary objective was to evaluate the effect of COBI-containing regimens, specifically Stribild® (STB, elvitegravir [EVG]/COBI/emtricitabine [FTC]/tenofovir disoproxil fumarate [TDF]) or a regimen including a protease inhibitor (PI) with or without TDF, on renal parameters in HIV-1 infected subjects with mild-to-moderate renal impairment. 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): STB (150 mg of EVG, 150 mg of COBI, 200 mg of FTC, and 300 mg of 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 PI/COBI cohort).

In Study GS-US-236-0118, subjects had screening estimated glomerular filtration rate (eGFR) by the Cockcroft-Gault method ($eGFR_{CG}$) between 50 and <90 mL/min (in contrast with screening $eGFR_{CG}$ ≥70 mL/min in pivotal Phase 3 studies of STB or COBI, GS-US-236-0102, GS-US-236-0103, and GS-US-216-0114). The primary endpoints were changes from baseline in eGFR assessed using creatinine- and cystatin C-based methods, and changes in actual GFR (aGFR) assessed using iohexol clearance ($CL_{iohexol}$). The primary endpoint results were presented in the interim Week 48 CSR submitted previously. The final study results including secondary objectives and safety data through 96 weeks of treatment are included in this submission.

The study also assessed efficacy, and included a substudy to assess the pharmacokinetics of COBI, FTC, tenofovir (TFV), EVG, ATV, and DRV at baseline and following once-daily, multiple-dose administration of STB, COBI-boosted ATV (ATV/COBI)+2 NRTIs, or DRV/COBI+2 NRTIs. These results were presented in the interim Week 48 CSR submitted previously.

All studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocols.

2. OVERVIEW OF BIOPHARMACEUTICS

No new information is submitted.

3. OVERVIEW OF CLINICAL PHARMACOLOGY

Updated clinical virology data from Study GS-US-236-0118 are presented in Module 2.7.2/ Section 4; no resistance was reported in the study.

No new pharmacology data are provided.

4. OVERVIEW OF EFFICACY

Study GS-US-236-0118 was primarily a safety study; however, efficacy was assessed as a secondary objective. Efficacy findings are presented in Module 5.3.5.2/GS-US-236-0118 Final CSR and summarized below.

Analysis of the primary efficacy endpoint (HIV-1 ribonucleic acid [RNA] <50 copies/mL at Week 24, snapshot analysis) was performed and presented in the Week 48 CSR submitted previously, and demonstrated that STB had potent antiviral efficacy in ARV treatment-naïve subjects with mild-to-moderate renal impairment, as evidenced by the high rate of virologic success at Weeks 24 and 48.

A high rate of virologic success was also seen at Week 96 for subjects who received STB for the Week 96 full analysis set: 88.9%, 24 of 27 subjects (HIV-1 RNA <50 copies/mL, snapshot analysis). The percentages of subjects with HIV-1 RNA <50 copies/mL at Week 96 was 96.4% (27 of 28 subjects; full analysis set; missing=excluded [M=E]). HIV-1 RNA levels decreased following initiation of study drug; the mean (standard deviation [SD]) baseline HIV-1 RNA level was 4.76 (0.652) $\log_{10}$ copies/mL and the mean (SD) change from baseline at Week 96 was –3.44 (0.725) $\log_{10}$ copies/mL for the full analysis set. Immunologic improvement was evidenced by increases in CD4+ cell counts following initiation of study drug; the mean (SD) baseline CD4+ cell count was 356 (174.2) cells/μL and the mean (SD) increase from baseline at Week 96 was 301 (192.5) cells/μL (full analysis set).

As reported in the Week 48 CSR submitted previously, virologic suppression was maintained over 48 weeks of treatment in ARV treatment-experienced subjects with mild-to-moderate renal impairment who switched pharmacokinetic enhancer to COBI from low-dose ritonavir (rtv). Virologic suppression was also maintained at Week 96 in the COBI boosted PI (PI/COBI) cohort based on the Week 96 full analysis set: 90.7% of subjects (49 of 54 subjects) had virologic success (HIV-1 RNA <50 copies/mL, snapshot analysis). The percentages of subjects with HIV-1 RNA <50 copies/mL at Week 96 was 96.4% (53 of 55 subjects; full analysis set; M=E). Immunologic control was maintained; the mean (SD) baseline CD4+ cell count was 627 (263.2) cells/μL for the full analysis set, and there were no clinically relevant changes from baseline in CD4+ cell counts.

5. OVERVIEW OF SAFETY

This submission provides safety data from the final analysis of Study GS-US-236-0118, which evaluated COBI-containing ARV regimens, including STB, in subjects with mild to moderate renal impairment. Safety findings are presented in Module 2.7.4 and summarized below.

5.1. Summary of Clinical Study Safety Experience

5.1.1. Extent of Exposure

In Study GS-US-236-0118, the median duration of exposure to study drug was 98.0 weeks (first quartile, third quartile [Q1, Q3]: 95.1, 119.0 weeks) for the STB cohort and 120.1 weeks (Q1, Q3: 64.4, 132.3 weeks) for the PI/COBI cohort (Module 2.7.4/Section 1.2). The majority of the subjects received study drug for &96 weeks (72.7%, 24 subjects in the STB cohort; 67.1%, 49 subjects in the PI/COBI cohort).

5.1.2. Subject Demographics

In the STB cohort of Study GS-US-236-0118 (n=33), most subjects were male (81.8%), with a mean age of 50 years (range, 22 to 72 years) (Module 2.7.4/Section 1.3). Subjects were predominantly white (42.4%) or black (39.4%). 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/%L; 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 (n=73), most subjects were male (82.2%), with a mean age of 54 years (range, 29 to 73 years). Subjects were predominantly white (76.7%) or black (19.2%). All subjects had HIV-1 RNA #50 copies/mL at baseline. The mean (SD) CD4+ cell count was 627 (263.2) cells/%L. 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%).

5.1.3. Adverse Events

In Study GS-US-236-0118, COBI-containing regimens, specifically STB or a regimen including a PI with or without TDF, were generally well tolerated in HIV-1 infected subjects with mild-to-moderate renal impairment (Table 1). The safety profiles in both the STB and PI/COBI cohorts were consistent with the known safety profiles of the respective regimen components.

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 (anemia; increased blood creatine phosphokinase). Any adverse event (AE) was reported for all subjects (33 subjects), most frequently diarrhea (36.4%, 12 subjects); insomnia (21.2%,

7 subjects); and nausea, nasopharyngitis, and headache (each 18.2%, 6 subjects; Table 2). Adverse events considered related to study drug by the investigator were reported for 48.5% of subjects (16 subjects), most frequently 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). 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; AEs of anemia, decreased creatinine renal clearance, increased gamma-glutamyl transferase [GGT], and wrist fracture). Four subjects (12.1%) discontinued study drug due to an AE, including 3 subjects who discontinued due to renal AEs (see Sections 5.1.4 and 5.2.2; 1 also had increased blood creatine phosphokinase), and 1 subject who discontinued due to hepatitis C and Hodgkin disease that were not considered to be related to study drug by the investigator.

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), most frequently upper respiratory tract infection (20.5%, 15 subjects); nasopharyngitis (19.2%, 14 subjects), and bronchitis, diarrhea and headache (each 13.7%, 10 subjects; Table 2). Adverse events considered related to study drug by the investigator were reported for 27.4% of subjects (20 subjects), most frequently nausea and headache (each reported for 4 subjects); and diarrhea and abnormal dreams (each reported for 3 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 (see Sections 5.1.4 and 5.2.2). All AEs resulting in discontinuation of study drug were nonserious, and all except an event of abnormal glomerular filtration rate were considered related to study drug by the investigator.

Table 1: 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

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Source: Module 5.3.5.2/GS-US-236-0118 Final CSR/Section 11.1/Table 23

Table 2: 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]	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

5.1.4. Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

No treatment-emergent deaths were reported in Study GS-US-236-0118 (Module 2.7.4/ Section 2.1.2).

In the STB cohort of Study GS-US-236-0118, the incidence of SAEs was 18.2% (6 subjects; Module 2.7.4/Section 2.1.3). No SAEs were reported for >1 subject. Two SAEs were considered related to study drug by the investigator: anaemia and increased blood creatine phosphokinase. 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) (Module 2.7.4/Section 2.1.5.1.1.2).

No subject who discontinued study drug had renal AEs and laboratory findings consistent with PRT (Section 5.2.2).

In the PI/COBI cohort of Study GS-US-236-0118, the incidence of SAEs was 15.1% (11 subjects). No SAEs were reported for >1 subject. One SAE was considered related to study drug by the investigator: nephrolithiasis. 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). No subjects who discontinued study drug had renal AEs and laboratory findings consistent with PRT.

5.1.5. Clinical Laboratory Abnormalities

In the STB cohort of Study GS-US-236-0118, graded laboratory abnormalities were reported for all subjects (33 subjects; Module 2.7.4/Section 3.1). 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).

In the PI/COBI cohort of Study GS-US-236-0118, 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). The most frequently reported grade 3 or 4 abnormalities overall were hyperbilirubinemia (22 subjects), hematuria (7 subjects), and hyperglycemia (5 subjects).

5.2. Renal Safety Profile

Renal events and renal laboratory parameters were comprehensively evaluated because renal toxicity has been associated with TDF, 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 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.

5.2.1. Primary Renal Endpoints: Changes from Baseline in GFR

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), 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 3). 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).

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 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 3). The pattern of changes in other eGFR endpoints was consistent with that for $eGFR_{CG}$, both for creatinine- and cystatin C-based endpoints.

Table 3: 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

	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
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
$eGFR_{CKD\text{-}EPI,\ cysC,\ unadjusted}$ (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

5.2.2. Renal SAEs, Discontinuations due to Renal AEs, and Association of Renal Events with PRT

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 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, 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). Further details are provided in Module 2.7.4/Section 2.1.5.1.1.

No subjects were considered to have renal SAEs (Module 2.7.4/Section 2.1.5.1.1.2).

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 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). No subject had treatment-emergent laboratory findings consistent with PRT.

5.2.3. Other Renal Endpoints

Serum Creatinine

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), after which they generally stabilized and were nonprogressive through Week 96 (median change from baseline at Week 96 was 0.17 mg/dL; Module 2.7.4/ Section 3.2.1). 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.

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.

Serum Phosphorus and Urine Fractional Excretion of Phosphate

In the STB cohort in Study GS-US-236-0118, hypophosphatemia was reported for 3 of 33 subjects (9.1%; Module 2.7.4/Section 3.2.3); grade 1 for 2 subjects, and grade 2 for 1 subject. None was reported as an AE, or a confirmed abnormality. In the PI/COBI cohort, 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.

In both cohorts, small increases in median values for fractional excretion of phosphate ($FEPO_4$) were noted as early as Week 2, after which they generally stabilized and were nonprogressive through Week 96 (median changes from baseline at Week 96: STB 3.8%; PI/COBI 1.9%; Module 2.7.4/Section 3.2.6). 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.

Glycosuria

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 2.7.4/Section 3.2.4). Glycosuria was grade 2 in severity for 2 subjects and grade 3 in severity for 3 subjects. One subject had confirmed normoglycemic glycosuria (grade 2). 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.

Proteinuria

In the STB cohort in Study GS-US-236-0118, proteinuria &trace was present at baseline in 18 subjects (54.5%; Module 2.7.4/Section 3.2.5). Treatment-emergent graded proteinuria was reported as a laboratory abnormality for 19 subjects (57.6%). 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.

6. BENEFITS AND RISKS CONCLUSIONS

For REZOLSTA, subjects with decreased kidney function (renal impairment) has been identified as missing information. Cobicistat inhibits the tubular secretion of creatinine, which results in a modest decrease in creatinine based assessments of eGFR without affecting aGFR.

Study GS-US-236-0118 evaluated the effect of COBI containing regimens, specifically STB (EVG/COBI/ FTC/ TDF) or a regimen including a PI with or without TDF, on renal parameters

in HIV-1 infected subjects with mild to moderate renal impairment. Cobicistat inhibits the tubular secretion of creatinine, which results in a modest decrease in creatinine based assessments of eGFR without affecting aGFR.

Stribild should not be initiated in patients with creatinine clearance <70 mL/min. It is recommended that STB is not initiated in patients with creatinine clearance <90 mL/min unless, after review of the available treatment options, it is considered that STB is the preferred treatment for the individual patient. The threshold for initiation of STB is based upon the inclusion criteria from pivotal Phase 3 studies, GS-US-236-0102 and GS-US-236-0103, in which subjects were required to have screening eGFR by the Cockcroft-Gault method, $eGFR_{CG}$, ≥70 mL/min. This threshold took into account the anticipated effect of COBI on $eGFR_{CG}$ and consideration that dose adjustment required for TDF is not possible with the STR should $eGFR_{CG}$ decrease to <50 mL/min on treatment. Prior to Study GS-US-236-0118, no studies had been conducted in HIV-1 infected subjects initiating STB below the 70 mL/min threshold. In addition, no analyses of renal parameters over 144 weeks of treatment had been presented in relation to the creatinine clearance thresholds of <90 mL/min for initiation or <70 mL/min on-treatment.

In Study GS-US-236-0118, subjects had screening $eGFR_{CG}$ between 50 and <90 mL/min. The renal safety profiles of COBI-containing regimens in Study GS-US-236-0118, specifically STB or a regimen including a PI with or without TDF, were consistent with those from the pivotal Phase 3 studies. No subjects were considered to have renal SAEs. Six subjects discontinued STB or COBI due to renal-associated AEs; none had treatment-emergent laboratory findings consistent with PRT. All had baseline $eGFR_{CG}$ <70 mL/min.

Importantly, Study GS-US-236-0118 was designed to assess changes in eGFR and aGFR using a broader range of assessments than the pivotal studies, and confirmed that COBI does not alter actual renal function in HIV-1 infected subjects. In the STB cohort, decreases in creatinine-based estimates of GFR were nonprogressive with increased duration of treatment, while there was no notable effect on cystatin C-based estimates of GFR. In the PI/COBI cohort (ARV treatment experienced subjects who switched pharmacokinetic enhancer to COBI from rtv), there were no clinically relevant changes in median values for creatinine- or cystatin C- based estimates of GFR. These findings are consistent with previous data for COBI, and further demonstrate that COBI does not adversely impact actual GFR.

In addition to the GFR findings described above, there were no clinically relevant changes from baseline in median values for other renal endpoints (serum phosphorus; urine $FEPO_4$), and few subjects had clinically relevant changes in urine glucose or urine protein.

Overall, the clinical data from Study GS-US-236-0118 continue to support a favorable benefit-risk profile for the DRV/COBI FDC in patients with mild to moderate renal impairment and are consistent with data from previous studies. The Week 96 data do not warrant an update to the REZOLSTA prescribing information. Similarly, no update to the REZOLSTA RMP is warranted given that the Study GS-US-236-0118 final data do not change the positive benefit-risk balance of REZOLSTA.

The evidence included in this Clinical Overview Addendum supports the positive benefit-risk profile for the use of DRV/COBI FDC 800/150 mg once daily, in combination with other ARV drugs and with food, for the treatment of HIV-1 infection in treatment-naïve adults and treatment-experienced adults with no DRV RAMs with plasma HIV-1 RNA <100,000 copies/mL and CD4+ cell count $\geq 100 \times 10^6$ cells/L, as described in the proposed indication of the SmPC.

The DRV/COBI FDC represents an efficacious and safe simplification of a once daily DRV containing ARV regimen that provides improved patient convenience, which should lead to enhanced adherence, less medication errors and improved outcome in these patients.