25 September 2014
EMA/669488/2014 Corr. 1
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Rezolsta

International non-proprietary name: darunavir / cobicistat

Procedure No. EMEA/H/C/002819/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Administrative information

Name of the medicinal product:	Rezolsta
Applicant:	Janssen-Cilag International N.V. Turnhoutseweg 30 B-2340 Beerse BELGIUM
Active substance:	COBICISTAT / DARUNAVIR ETHANOLATE
International Nonproprietary Name/Common Name:	DARUNAVIR / COBICISTAT
Pharmaco-therapeutic group (ATC Code):	(J05)
Therapeutic indication:	Indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years or older. Genotypic testing should guide the use of REZOLSTA (see sections 4.2, 4.3, 4.4 and 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	800 mg / 150 mg
Route(s) of administration:	Oral use
Packaging:	Bottle (HDPE)
Package size(s):	30 tablets

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List of abbreviations

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

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 2 October 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Rezolsta, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 November 2012.

The applicant applied for the following indication:

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is:

as new fixed combination medicinal product.

composed of administrative information, quality, non-clinical and clinical data with a letter from Gilead allowing reference to relevant quality, non-clinical and/or clinical data.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0036/2013 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

Not applicable

Scientific Advice

The applicant received Scientific Advice from the Netherlands on 13 October 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: Canada

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Janssen-Cilag S.p.A.

Via C. JanssenBorgo San Michele
Latina
04100
Borgo San Michele
ITALY

1.3. Steps taken for the assessment of the product

- The application was received by the EMA on 2 October 2013.
- The procedure started on 23 October 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2014 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 31 December 2013 (Annex 2).
- During the CHMP meeting on 3-6 February 2014. PRAC adopted RMP Advice and assessment overview on 6 February 2014 (Annex 3).
- During the meeting on 20 February 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 February 2014 (Annex 4).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 June 2014 (Annex 5).
- During the CHMP meeting on 9-12 June 2014 PRAC adopted RMP Advice and assessment overview on 13 June 2014 (Annex 6).
- During the CHMP meeting on 26 June 2014, the CHMP agreed on a list of outstanding issues to be addressed by the applicant (Annex 7).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 August 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 5 September 2014 (Annex 8).
- During the meeting on 22 -25 September 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Rezolsta.

2. Scientific discussion

2.1. Introduction

Problem statement

Protease inhibitors (such as Darunavir) have been part of antiretroviral regimens for more than a decade with adequate virologic suppression and high barrier to resistance. They are combined with a pharmacokinetic enhancer, ritonavir (rtv 100 mg), to increase plasma exposure. No fixed dose combination (FDC) of a protease inhibitor and its pharmacoenhancer is available, which would increase simplicity and reduce medication errors. A new pharmaco-enhancer Cobicistat (COBI) has been developed and is to be combined with CYP3A dependent antiretroviral agents; elvitegravir (an integrase inhibitor), atazanavir and darunavir (both protease inhibitors).

The current application concerns a 'substitution indication' of a fixed dose combination of DRV 800 mg and COBI 150 mg. Both components have been registered. Darunavir (DRV; "PREZISTA") 800 mg once daily (qd) has been registered with another pharmaco-enhancer, ritonavir 100 mg, for the indication: '*PREZISTA, co-administered with low dose ritonavir is indicated in combination with other antiretroviral medicinal products for the treatment of patients with human immunodeficiency virus (HIV-1) infection.*

PREZISTA 400mg and 800 mg tablets may be used to provide suitable dose regimens for the treatment of HIV-1 infection in adult and paediatric patients from the age of 12 years and at least 40 kg body weight who are:

- *antiretroviral therapy (ART)-naïve (see section 4.2).*
- *ART-experienced with no darunavir resistance associated mutations (DRV-RAMs) and who have plasma HIV-1 RNA < 100,000 copies/ml and CD4+ cell count ≥ 100 cells x 106/l. In deciding to initiate treatment with PREZISTA in such ART-experienced patients, genotypic testing should guide the use of PREZISTA (see sections 4.2, 4.3, 4.4 and 5.1).*

COBI 150 mg (TYBOST) has been registered as a pharmaco-enhancer of DRV in 2013. With the current application the applicant submits data on a FDC of the two components and applies for the same indication for this FDC, DRV/COBI 800/150 mg qd as mentioned above for DRV/RTV 800/100 mg qd.

About the product

The FDC of Rezolsta (DRV/COBI) 800/150 mg qd consists of two registered components: the antiretroviral agent DRV and a pharmaco-enhancer COBI. The single agents DRV and COBI have already been authorised for combined use at the same dose levels as in the FDC.

DRV (previously designated as TMC114), is an HIV-1 protease inhibitor and is currently indicated for the treatment of HIV-1 infection in adults and in paediatric 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 authorisation in the European Union 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 in 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.

COBI, Cobicistat, (TYBOST, formerly known as GS-9350) is a new chemical entity developed by Gilead for use as a PK enhancer to increase systemic exposure of co-administered medicinal products metabolized by CYP3A enzymes, including the HIV-1InSTI elvitegravir (EVG) in a fixed dose combination Stribild. On 24 May 2013 this single tablet regimen (STR) EVG/COBI/FTC/TDF (STRIBILD) was granted marketing authorization by the European Commission 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.

In addition, COBI is registered in the European Union on 25 July 2013 as a separate component to be combined with the HIV protease inhibitors atazanavir and darunavir. The current indication is: Cobicistat (TYBOST) is indicated as a pharmacokinetic enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults.

COBI is a structural analogue of rtv and a potent, mechanism-based inhibitor of CYP3A. Cobicistat itself has no detectable antiviral activity against HIV-1 in vitro and does not directly contribute to the efficacy of an ARV regimen.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 800 mg of darunavir (as ethanolate) and 150 mg of cobicistat as active substances.

Other ingredients are:

Tablet core: hypromellose, colloidal silicon dioxide, silicified microcrystalline cellulose, crospovidone, and magnesium stearate

Tablet film-coat: polyvinyl alcohol, macrogol, titanium dioxide, talc, iron oxide red, iron oxide black

The product is available in high density polyethylene (HDPE) bottle, fitted with polypropylene (PP) child resistant closure with induction seal.

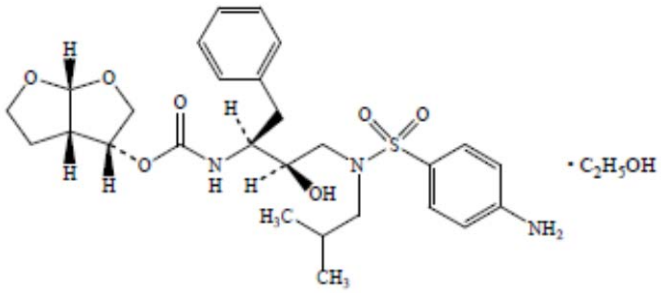
2.2.2. Active Substance

Darunavir ethanolate

General information

The information for darunavir reflects the currently approved active substance information for Prezista tablets (EU/1/06/380/001-008) of the same applicant.

The chemical name of Darunavir ethanolate is [(1S,2R)-3-[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl) propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester monoethanolate and has the following structure:



Darunavir ethanolate is a white to off-white powder, very slightly soluble in aqueous solutions. This solubility increases with decreasing pH, but remains very slightly soluble in the pH region between 1 and 12.

Darunavir ethanolate exhibits stereoisomerism due to the presence of five chiral centres. Enantiomeric purity is controlled routinely. The active moiety is presented in the solid state as a pseudo-polymorph. Other solvates are also possible, but are not relevant as ethanol is the solvent used during the final manufacturing step in the chemical synthesis. An extensive polymorphism study was performed. Darunavir ethanolate was isolated either as a solvate crystalline material or as non-solvated amorphous material. A non-solvated crystalline form was not obtained.

Manufacture, characterisation and process controls

Darunavir ethanolate is synthesized in 4 main steps using commercially available well defined starting materials with acceptable specifications. The manufacturing process is the same as described for Prezista tablets.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

Specifications, analytical procedures and validation data are in accordance with those currently authorised in Prezista MAA. Darunavir specification includes tests for identification (IR, HPLC), physical description, assay (HPLC), chromatographic purity (HPLC), ethanol (GC), residual solvent (GC), residue on ignition (Ph Eur), water content (KF), heavy metals (Ph Eur) and particle size (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of 9 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of 9 commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data of darunavir from the proposed manufacturers stored in the intended commercial package for 36 months at 5 °C (3 commercial scale batches), at 25 ºC / 60% RH and for up to 36 months (3 commercial scale batches), at 30 °C / 65% RH for up 36 months (3 commercial scale batches) and for up 60 months (7 commercial scale batches), and at 40 ºC / 75% RH for up 6 months (9 commercial scale batches) according to the ICH guidelines were provided.

The parameters tested were the same as for release except identification and were stability indicating.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

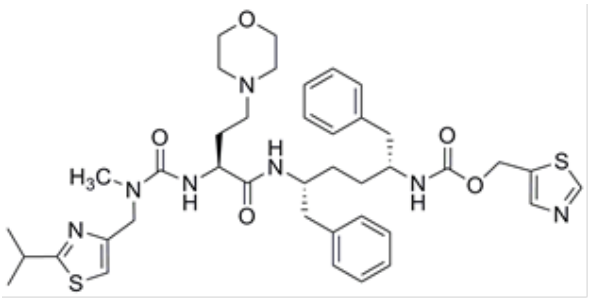
Cobicistat

General information

The information for cobicistat reflects the currently approved active substance information for Tybost film –coated tablets (EU/1/13/872/001-2) of Gilead Sciences International Ltd.

Cobicistat on silicon dioxide is defined as the active substance. It is isolated by adsorption of cobicistat onto silicon dioxide to provide a stable solid form, which facilitates handling and is suitable for further finished product processing.

The chemical name of cobicistat is 1,3-Thiazol-5-ylmethyl [(2R,5R)-5-{[(2S)-2-[(methyl{[2-(propan-2-yl)-1,3-thiazol-4-yl]methyl}carbamoyl)amino]-4-(morpholin-4-yl)butanoyl]amino}-1,6-diphenylhexan-2-yl]carbamate (refer to cobicistat molecule) and has the following structure:



Cobicistat on silicon dioxide is a white to pale yellow powder and is hygroscopic as determined by dynamic vapor sorption at room temperature. The intrinsic aqueous solubility of cobicistat free base is 75 µg/mL and is significantly enhanced under acidic conditions

Cobicistat exhibits stereoisomerism due to the presence of three chiral centres. It is produced as a single isomer. The stereochemical configurations at these chiral centers are controlled through the synthetic process and use of starting materials having suitably high chiral purities Enantiomeric purity is controlled routinely. Cobicistat active substance is amorphous.

Manufacture, characterisation and process controls

Cobicistat is synthesized in 4 main steps using commercially available well defined starting materials with acceptable specifications. The manufacturing process is the same as described in Tybost film-coated tablets MAA.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

Specifications, analytical procedures and validation data are in accordance with those currently authorised for Tybost. Cobicistat specification includes tests for appearance, identification of silicon dioxide, identification of cobicistat (UV, HPLC, IR), water content (Ph Eur), assay (HPLC), impurity content (HPLC), chiral purity , residual solvents , and heavy metals.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data of 20 representative batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on 3 commercial scale bathes of cobicistat from the proposed manufacturers stored in the intended commercial package for 36 months at 5 °C, at 25 ºC / 60% RH and for up to 36 months and at 30 °C / 75% RH for up 12 months (1 commercial scale batches) and for up 12 months according to the ICH guidelines were provided.

A photostability study was conducted on one batch in accordance with ICH Q1B Guideline, Photostability Testing of New Drug Substances and ProductsStress test studies were also conducted following the ICH Q1A(R2) Guideline, Stability Testing of New Drug Substances and Products. The analytical methods used were the same as for release except identification and were stability indicating.

The parameters tested were appearance, assay, impurity content, chiral impurities and water content.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

This fixed dose combination was developed based on prior formulation experience with darunavir in Prezista, the inclusion of cobicistat, and the need to minimize tablet size while combining two active substances in one fixed dose combination film coated tablet was also studied during the pharmaceutical development.

Daruvavir is currently authorised as active substance of Prezista and the excipients used for the fixed dose combination product were identical in terms of manufacturing and quality as the authorised active substance. The issue of the use of the ethanolate and the potential to change during manufacture or on storage was addressed with the Prezista formulations. The applicant showed that whilst the hydrate form is also possible, it has the same bioavailability as the ethanolate form. During stability studies ethanol content was monitored as a means of estimating potential conversion of the

ethanolate to hydrate and no significant changes were observed. Stereoisomeric purity of darunavir was also monitored during manufacture and on storage and no evidence of inter-conversion was found.

Cobicistat is currently authorised The issue of the use of the cobicistat adsorbed onto an inert silicon dioxide carrier was addressed and accepted for the authorised formulations of cobicistat. The amorphicity of the cobicistat was confirmed using x-ray diffraction during stability studies. No changes were observed in the finished product over the shelf-life. Stereoisomeric purity of cobicistat was also monitored during manufacture and on storage and no evidence of inter-conversion was found.

Darunavir is a very slightly soluble in aqueous solutions across the pH range of 1 to 12, and is administered at a high dose (800-mg) in the finished product. The combination of low aqueous solubility and high dose requires the use of surfactant in the medium to enhance solubility. In contrast, the cobicistat solubility varies from soluble to practically insoluble depending on the pH, and cobicistat is administered at a lower dose (150 mg) in the finished product. The variable solubility range and lower dose for cobicistat enables sink conditions to be met without the use of surfactant.

The finished product is formulated with commonly used pharmaceutical excipients typically employed in solid dosage forms that are manufactured via a granulation process. The excipients are described in detailed monographs in the Ph Eur and are generally recognized as safe. The stability of the active substances and their compatibility with the excipients was demonstrated in stability studies during development and is confirmed by the primary stability data included in this dossier.

Several formulations were explored to optimize the inclusion of cobicistat, the filler used, and core tablet weight. Based on the findings from these experiments, two formulations differing in filler composition and core tablet weight were evaluated in a comparative bioavailability study. A bioavailability study compared the formulations to coadministration of single agent darunavir tablets (provided as two, 400 mg darunavir tablets) and cobicistat 150 mg tablets. Darunavir Cmax and AUC24h values were comparable between both formulations. Given the similarity in relative bioavailability results for both formulations, the formulation chosen for further development was the one which closely align with Prezista formulation and used the simplest finished product composition.

The dissolution methods for the active substances were adequately developed and showed sufficient discriminative power. The use of surfactant for darunavir dissolution is justified based on the solubility of the substance.

The development of the manufacturing process was based, in part, on the knowledge gained during the development and manufacturing of the authorised Prezista. The fixed dose composition is manufactured by fluid bed granulation of darunavir with a binder (hypromellose), which is then blended with cobicistat and other excipients (silicified microcrystalline cellulose and povidone), followed by milling and blending with magnesium stearate. The final blend is compressed and tablets are film coated with non-functional coating.

Designs of Experiments (DoE) studies were performed after primary stability batch production to establish the operating ranges for each process step. Material input variability was also examined to evaluate the impact of material variations that would be expected during routine production. The Quality target product profile (QTPP), critical quality attributes (CQA's), critical process parameters (called critical control points) of the steps milling and blending, sieving and final blending, compression and film-coating was also provided. However, no formal risk assessment was performed to link material attributes and process parameters to finished product CQA's. No design space is claimed.

White, high density polyethylene (HDPE) bottles with child-resistant polypropylene (PP) closure with induction seal liner were selected as the container closure system based on the ability to adequately

protect the finished product throughout its shelf life. The HDPE bottle is a standard and widely used pharmaceutical container. The induction seal liner has been incorporated into the packaging design for seal integrity and as a tamper evident feature. The compatibility of the primary packaging materials of the container closure system with the finished product is demonstrated by the stability data.

Manufacture of the product and process controls

The manufacturing process consists of 8 main steps: preparation of binder solution, fluid bed granulation and drying, milling and blending, sieving and final blending, compression, preparation of the film-coating suspension, film coating and packaging. The process is considered to be a standard manufacturing process.

A validation protocol was provided. The process validation activities for the tablets will be performed at the commercial manufacturing site for three batches at the commercial scale. The process validation batches were manufactured within the operating ranges according to the instructions listed in the manufacturing batch record. As well as performing the in-process tests, additional sampling procedures and in-process testing limits were performed during process validation. This was considered satisfactory.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification darunavir (HPLC, NIR), identification cobicistat (HPLC, DAD), assay (HPLC), chromatographic purity related to darunavir (HPLC), chromatographic purity related to cobicistat (HPLC), uniformity of dosage unit (Ph Eur), dissolution, and microbiological purity (Ph Eur).

Batch analysis results are provided for of five batches used for clinical bioavailability, bioequivalence, development, and/or stability studies confirms the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data of 3 commercial scale batches of finished product stored under long term conditions for 18 months at 25 ºC / 60% RH, for up 18 months under intermediate conditions at 30 °C/75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, purity, dissolution, ethanol content, water content, stereo-isomeric purity of darunavir and cobicistat (one batch of tablets), water activity, microbial purity and amorphicity of cobicistat. The stability test methods are the same as the release test methods. The analytical procedures used are stability indicating.

Two batches were included in an in-use stability study. The bottles were stored at 25 °C/60% RH and 30 °C/75% RH. Initially 15 tablets were removed from the bottles. Then the bottles are opened 5 days/week, 1 time/day without removal of a tablet during a period of 6 weeks. The remaining tablets are tested for appearance, assay, chromatographic purity, dissolution, ethanol, water, stereo-isomeric purity, amorphicity (of cobicistat) and microbiological purity. All results are within specification with only a small decrease of ethanol content and increase of water during the study. The

in-use stability was performed at the beginning and will also be performed at 18 months and at 24 months (the end of shelf-life). Bottles are regularly opened to simulate the daily use of the medication by the patient and to support the in-use shelf-life.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Darunavir

Darunavir is a protease inhibitor. The inhibitory constant (Ki) for darunavir was <0.09 nM, which is comparable to lopinavir and lower than for other protease inhibitors. Darunavir binds tightly to HIV-1 protease to form highly stable complex with both wild type (Kd 4.5 x 10^{-12} M) and mutant proteases.

In vitro antiviral activity was investigated in T-cell lines (MT4 and MT2 cells) infected with HIV-1, HIV-2, and SIV and in HIV-1 infected human peripheral blood mononuclear cells (PBMCs) and human monocytes/macrophages. In T-cell lines, EC50 of darunavir was 2.29 – 6.26 nM against HIV-1, 4.70 – 8.49 nM against HIV-2 and 9.28 nM against SIV. The EC50 values in HIV-1 infected human PBMCs and monocytes/macrophages were comparable to those observed in the T-cell lines. EC50 of darunavir increased by a median factor of 5.4 in the presence of 50% human serum.

The 50% cytotoxic concentration (CC50) was found to be greater than 100 µM. With a median EC50 of 3.8 nM using the MTT assay in MT4 cells, a selectivity index (SI=CC50/EC50) >26000 was determined.

In vitro selection experiments with wild type HIV-1 isolates in the presence of increasing concentrations of darunavir revealed mutations at codons 37, 41, 55, 70, 71, 74, 77 and 85. From 7 in vitro selection experiments starting with wild type HIV-1 strains, 3 resulted in emerging viruses with a fold change >4. Selection experiments with protease inhibitor-resistant HIV-1 revealed 22 mutations, of which 11 not yet reported to be associated with resistance to proteases (L11I, I15V, G16E, L23I, S37N, L63P, V82I, T91A, T91S, Q92R, and L76V). A minimum of eight of the darunavir in vitro selection mutations were required in the HIV-1 protease to render a virus resistant to darunavir (fold change >10), from which at least 2 were already present in the baseline virus. Eighteen of 20 protease inhibitor-resistant recombinant viruses were susceptible to darunavir (fold change ≤4). Among 3309 recombinant HIV-1 isolates with decreased susceptibility to at least one protease inhibitor, EC50 values were ≤10 nM for 78% of the isolates and >100 nM for 3% of the isolates. Eighty percent of the isolates exhibited a darunavir fold change of ≤4 and 10% of >10.

Darunavir did not significantly inhibit human angiotensin converting enzyme, caspase 3, caspase 7, cathepsin C, cathepsin D, cathepsin E, factor VIIa, factor Xa, matrix metalloproteinase-2, matrix metalloproteinase-9, metalloproteinase neutral endopeptidase, thrombin, and renin.

In vitro, hERG current was not inhibited (up to 10 µM, which is similar to 10-fold the human free maximum plasma level) and the cardiac action potential (sheep isolated cardiac Purkinje fibres) remained unaffected after 10 µM darunavir. In conscious telemetered beagle dogs, darunavir did not affect cardio-haemodynamic and ECG parameters at C_{max} slightly higher and AUC values slightly lower than clinical exposure. At oral dose up to 2000 mg/kg in rats, darunavir did not show any effect on gastrointestinal transit time, neurobehavioral and motor activity, or respiration. Cmax was comparable to human exposure and AUC values were lower.

Combinations with current antiretrovirals were studied in an anti-HIV-1/IIIB MT4 cell-based assay. The data indicate additivity with all nucleoside/nucleotide reverse transcriptase inhibitors, all tested non-nucleoside reverse transcriptase inhibitors. A modest synergistic effect with amprenavir, nelfinavir and ritonavir was observed whereas additive effects were described for the combination with atazanavir, indinavir, lopinavir, saquinavir, and tipranavir and with the fusion inhibitor enfuvirtide.

Cobicistat

Cobicistat is a structurally modified analogue of the protease inhibitor ritonavir, which is devoid of anti-retroviral activity. Cobicistat has been shown to inhibit the activity of human CYP3A enzymes (IC50 values 0.03 to 0.15 µM). Cobicistat or its metabolites M21, M26 and M31 did not have an inhibitory effect on HIV-1 protease at concentrations up to 30 µM. No antiviral activity was observed of cobicistat against two HIV-2 isolates.

CC50 of cobicistat in MT2 lymphoblastoid T-cells and in HepG2 hepatoma cells was 89 µM and 44 µM respectively.

Cobicistat showed significant binding to the benzothiazepine sensitive L-type calcium channel, hERG potassium channel and sodium channel, at a concentration of 10 µM, which is 105-fold higher than the proposed clinical Cmax (free).

No effects were observed on the central nervous system in the rat at Cmax approximately 4.2-fold higher than that observed clinically. At higher doses (≥150 mg/kg), salivation along with decreased arousal, locomotor activity, motor activity and a decrease in body temperature were noted. No effects were observed on the respiratory system in the rat at doses up to 500 mg/kg.

Cobicistat inhibited the hERG potassium current and the hCav1.2 L-type calcium channel, but was a weak inhibitor of the hNav1.5 sodium channel (with IC50 values of 1.8-1.9 µM, 6 µM and 86.5 µM, respectively). In the rabbit Purkinje fibre assay, cobicistat caused a significant shortening of action

potential duration at ≥ 1 µM (0.78 µg/mL, approximately 10-fold the clinical unbound exposure). In isolated rabbit heart, shortening of the monophasic action potential duration was also observed as well as an increase in coronary perfusion pressure and a decrease in ventricular function at concentrations ≥ 1-1.5 µM and decrease in the QT interval and increase in the PR and RR interval at ≥3 µM. In vivo, no significant effect on QT interval was observed in the dog, following single oral doses of up to 45 mg/kg. Increases in PR interval were noted at ≥15 mg/kg where the plasma levels were reported to be 3.2 to 4.9 fold higher than that observed clinically.

The potential for drug-drug interactions with cobicistat and clinically approved or investigational antiretroviral drugs was evaluated. The selected drugs were tenofovir, emtricitabine, abacavir, lamivudine, zidovudine, efavirenz, nevirapine, raltegravir, elvitegravir, atazanavir and darunavir. Overall, no significant changes were observed in the activity of any of the tested antiretroviral drugs in the presence of 5 µM cobicistat.

Given that the use of atazanavir is associated with PR prolongation in man, that cobicistat also appears to increase PR interval (in vitro and in vivo), and that in man, cobicistat is to be used in combination with atazanavir (as part of an anti-retroviral treatment regimen), the effects of cobicistat (0.45 to 1.5 µM)/atazanavir (1.5 µM) were evaluated in the rabbit isolated heart. The effects on heart rate and PR interval appeared to be more pronounced when atazanavir (1.5 µM) and cobicistat (1.5 µM) were administered in combination; however, the observed differences were not considered to be clinically significant. It is noted that during this study, cobicistat alone had no effect on the QT interval or monophasic action potential duration at up to 1.5 µM.

Combination darunavir and cobicistat

No studies were performed with the combination of darunavir and cobicistat. This was considered acceptable by the CHMP.

2.3.3. Pharmacokinetics

Darunavir

In animals, darunavir absorption was rapid following oral administration in all species (T_{max} 0.5 – 6 hours). The absolute oral bioavailability was 37% to 58% in adult rats and 60 to 122% in dogs. In rats and dogs, the plasma clearance and the volume of distribution were moderate to high. Plasma kinetics of darunavir were less than dose proportional in all investigated species, especially at high dose levels. In adult rodents including pregnant rats, repeated oral dosing resulted in a decrease in systemic exposure, mainly due to induction of CYP3A iso-enzymes, which are extensively involved in the metabolism of darunavir. In dogs, no decrease in exposure or enzymatic induction was observed after repeated administration.

Darunavir exposure (plasma, brain, and liver concentration) was much higher in juvenile rats (aged 12 or 26 days) probably due to incomplete maturation of the blood-brain barrier and liver enzymes involved in the elimination of darunavir. It was nonetheless lower on day 26 than on day 12, presumably reflecting the development of drug metabolising enzymes and the blood-brain barrier.

The plasma protein binding was moderate to high in all tested species and was concentration dependent. At 0.5 µg/ml, plasma protein binding ranged from 63 % in rabbits to 95 % in rats. In human the plasma protein binding was relative constant (~ 94%) up to a concentration of 4.7 µg/ml, whereas about 75% was bound at 18.8 µg/ml. The blood to plasma concentration ratios ranged from 0.64 to 1.11 across all species at 0.5 µg/mL, indicating some distribution of darunavir to blood cells, especially in the rabbit and dog in which the plasma protein binding was lower than in the other species After oral administration of 14C-darunavir in rats, the tissue distribution of 14C-darunavir was

extensive and rapid. The highest concentrations of radioactivity were measured in the liver and adrenal gland. No undue retention or accumulation was observed, except in melanin-rich tissues such as the pigmented parts of the eye. However, from these tissues a gradual decrease of the radioactivity levels could be demonstrated, showing the reversibility of this binding. Darunavir crossed the placenta in pregnant rats, with levels of radioactivity found in foetuses being about 20% of that in maternal blood.

The metabolism of darunavir following single oral administration was extensive and qualitatively similar in all species, including humans. In vitro and in vivo studies in rats, dogs and humans identified three major Phase I metabolic reactions: carbamate hydrolysis, aliphatic hydroxylation at the isobutyl moiety and aromatic hydroxylation at the aniline moiety. In dogs and humans, the major Phase I metabolic pathway was the carbamate hydrolysis whereas in rats, hydroxylation in a different part of the molecule was more important. Phase II glucuronidation was a minor pathway in rats, dogs and humans. No unique human metabolites were identified. In human liver, CYP3A was almost exclusively involved in the metabolism of darunavir. Darunavir inhibited CYP3A in human liver microsomes with an inhibitory constant (Ki) value of 0.40 µM (0.22 µg/mL). In mice and rats, darunavir treatment induced hepatic microsomal CYP3A4. UDP-GT activity was additionally induced in rats. In dogs, no induction effects were observed.

Following a single dose in rats, most radioactivity was excreted within 24 h and was almost complete in 96 h. In all examined species, the predominant route of excretion for 14C-darunavir was via the feces (94% in rats, 86% in dogs and 82% in humans). Urinary excretion was about 4% of the administered dose in rats and dogs but was higher (12.2%) in humans. Unchanged darunavir was mainly excreted in feces and amounted to up to 12.3% in rats, 26% in dogs and 6.8% in humans. In plasma, unchanged compound accounted for the largest fraction of the radioactivity in the 3 species. In rats, darunavir was excreted in milk with milk to plasma AUC ratios up to 2.3 in dams.

Six anti-HIV compounds were investigated for inhibitory effects in human liver microsomes. The results showed that saquinavir and amprenavir are predicted to be minor to moderate inhibitors of darunavir metabolism in vivo, whereas delavirdine, ritonavir, indinavir and nelfinavir are likely to be strong inhibitors.

Darunavir inhibits P-gp and may therefore inhibit transepithelial permeation of P-gp substrates.

Cobicistat

Clearance values were high relative to hepatic blood flow and volumes of distribution were similar to those for total body water. After oral dosing, bioavailability was low or low/moderate (33%, 11% and 7% in rat, dog and monkey resp.), likely due to high first-pass elimination. After repeated oral dosing, there were species differences in autoinduction during these studies, with hepatic microsomal fractions from treated mice and rats showing higher levels of CYP3A, but with no increases in treated dogs.

Binding of cobicistat in plasma was moderately high. Fraction unbound values were similar in nonclinical species (mean values 4.75%-6.54%) to humans (6.3%). Cobicistat does not distribute well into the cellular fraction of blood from mouse, rat, dog, or human.

After oral administration of 14C-cobicistat to albino and pigmented rats, radioactivity was rapidly and widely distributed to most tissues. Generally, the radioactivity was preferentially distributed into glandular tissues and organs of elimination. The tissues showing the highest concentrations of radioactivity, excluding the gastro intestinal tract, included liver, adrenal, kidney, and pituitary. The tissues with the lowest C_{max} values were eye, spinal cord, and brain, bone, and secondary sex organs. In rats, cobicistat was shown to be associated with melanin. Dosimetry analysis confirmed that concentrations were declining and that this association was reversible.

The primary metabolic pathways for cobicistat are methine oxidation of the isopropyl moiety (M31, GS-9612), cleavage adjacent to the methylurea (M26, GS-341842), cleavage of the carbamate (M21, GS-9454), and cleavage and deethylation of the morpholine (M39). Combinations of these routes and other routes of oxidative metabolism were also detected. Oxidation is primarily catalyzed by CYP3A, which can generate all metabolites, with a minor role for CYP2D6 (which contributes to the generation of M31). Cobicistat is a potent inhibitor of human CYP3A with inactivation kinetics similar to those of ritonavir. Inhibition of CYP3A is relatively specific as cobicistat did not inhibit human CYP1A2, CYP2C9, or CYP2C19, is a very weak inhibitor of CYP2C8 (IC_{50} 30.1 µM), a weak inhibitor of CYP2D6 (IC_{50} 9.2 µM), and a modest inhibitor of CYP2B6 (IC_{50} 2.8 µM). Cobicistat is a weak inhibitor of human hepatic microsomal UGT1A1 activity (IC_{50} 16.3 µM).

After oral administration of 14C-cobicistat to mice, rats, and dogs, recovery of radioactivity was high with the majority being found in feces. Recovery was largely complete by 48 hours post-dose. After oral administration of 14C-cobicistat to bile duct cannulated animals, an average of 69.3% and 63.9% of dosed radioactivity was recovered in bile in rats and dogs, respectively. Cobicistat was present in milk samples 2 hours post dose on lactation day 10 with milk to plasma ratios ranging from 1.3 to 1.9.

With respect to hepatic uptake transporters, cobicistat is a moderate inhibitor of OATP1B1 and OATP1B3. Cobicistat is a weak inhibitor of intestinal efflux transporters; however, high concentrations of cobicistat in the intestinal lumen, which are achievable briefly during absorption, may inhibit MDR1 (P-gp) and BCRP. Cobicistat inhibits the renal efflux transporter, novel organic cation transporter 1. Cobicistat is also an in vitro inhibitor of the renal transporters, OCT2 and MATE1.

Combination darunavir and cobicistat

No non-clinical studies were performed with the combination of darunavir and cobicistat. This was considered acceptable by the CHMP.

2.3.4. Toxicology

Studies were performed with oral administration.

Darunavir

Due to a more rapid clearance in animals, the maximum achieved exposure to darunavir in animal studies was low compared to the human therapeutic level, and adding ritonavir could not much further enhance it. Likely, this difference was caused by the fact that ritonavir is a much stronger inhibitor of CYP3A4 in humans than in animals.

In single dose toxicity studies, darunavir was well tolerated in mice at oral doses up to 100 mg/kg. Treatment related mortality and macroscopic findings (distended or fluid-filled gastro-intestinal tracts) occurred at oral doses ≥ 280 mg/kg. In rats, no treatment-related mortality or toxicologically relevant observations were observed at oral doses up to approximately 500 mg/kg. Also higher doses were investigated, but systemic exposure did not increase significantly beyond that observed at 500 mg/kg. In dogs, the maximum tolerated dose was 75 mg/kg, with vomiting being the limiting adverse effect.

Repeated dose studies in mice were performed for 2 weeks and 3 months. No NOAELs were established, but changes were minimal. Rat studies were performed up to 6 months, with darunavir alone or in combination with ritonavir. Darunavir alone induced an increase in the red blood cell (RBC) turnover, indicated by a limited decrease in RBC counts, increases in reticulocytes and bilirubin and extramedullary hematopoiesis in the spleen. Also observed were prolonged APTT, without evidence of bleeding, increases in platelets, and liver and thyroid changes which were associated with liver

enzyme induction and an enhanced metabolism of thyroid hormones. Effects of the combination of darunavir and ritonavir in rats were similar to the effects seen with each compound alone, with evidence of a small increase in effect on RBC parameters, liver and thyroid. In the liver, increases in liver transaminase activities, centrilobular hypertrophy accompanied by multinucleated hepatocytes and some single cell necrosis were observed. The transaminase increases were associated with ritonavir rather than darunavir. In addition, histopathological changes (increased incidence/severity of islet fibrosis/siderocytes in males) were observed in the pancreas. In dog studies with darunavir (up to 12 months duration), limited effects were observed in the liver (hepatocellular pigment and vacuolation and a limited increase in alkaline phosphatase, up to 45%). Dogs did not tolerate the combination of darunavir and ritonavir (vomiting, reduced body weight) and this combination was only investigated up to 2 weeks.

Darunavir was not genotoxic in the Ames test, in the in vitro chromosomal aberration test in human lymphocytes and in an in vivo mouse micronucleus test.

Darunavir was evaluated for carcinogenic potential by oral gavage administration to mice and rats up to 24-months. Daily doses up to 1000 mg/kg were administered to mice and doses up to 500 mg/kg were administered to rats. A dose-related increase in the incidences of hepatocellular adenomas and carcinomas was observed in males and females of both species. Thyroid follicular cell adenomas were noted in male rats. Administration of darunavir did not cause a statistically significant increase in the incidence of any other benign or malignant neoplasm in mice or rats. The observed liver and thyroid tumours were associated with liver enzyme induction and are considered not relevant to humans.

There was no effect of darunavir on fertility or early embryonic development in rats. Embryo-foetal development studies were performed in rats, rabbits and mice. In mice, embryo-foetal development was also investigated in combination with ritonavir, to increase exposure to darunavir. Darunavir was not embryotoxic or teratogenic in rats, rabbits or mice. The exposure was low and did not exceed the human therapeutic exposure. In the pre- and postnatal development study in rats, darunavir caused a reduction in pup body weight gain, especially during lactation but also post-weaning. A slight delay was observed in the opening of the eyes and ears. Juvenile toxicity studies in rats with age ranging from 5 days up to sexual maturity at 50 days showed that exposure in juvenile rats younger than 23 days of age was higher than in adult rats. Toxicity seemed also higher at age lower than 23 days. In animals aged 23-50 days, toxicity was not higher than in adult animals. In studies where dosing commenced at less than 23 days of age (equivalent to less than 2 years of age in humans), a NOAEL was not established. Mortality was observed at most dose levels (from 20 mg/kg/day up to 1000 mg/kg/day) and in some cases convulsions and other apparent central nervous system effects preceded these deaths. High plasma, liver and brain exposure values were observed, which were both dose- and age-dependent and considerably greater than those observed in adult rats. These findings were attributed to the ontogeny of CYP liver enzymes involved in the metabolism of darunavir and the immaturity of the blood brain barrier.

Local tolerance studies showed no skin irritation or eye irritation. Darunavir showed no potential for sensitization in the local lymph node assay in mice.

No immunotoxicity was observed in a T-cell dependent antibody response test in rats after administration of darunavir at exposures which were similar to or just below human exposures (highest dose 500 mg/kg). Also in combination with ritonavir (100/50 mg/kg) no immunotoxicity was observed (exposure of darunavir below human exposure).

Cobicistat

The single-dose toxicity of cobicistat was low; the maximum tolerated dose (MTD) was 100 mg/kg in mice (moribund euthanasia occurred at 300 mg/kg), and the NOAEL was 500 mg/kg in rats.

Repeated dose studies in mice were performed up to 13 weeks. Increased liver weight, hepatocellular hypertrophy and vacuolation were observed and considered due to enzyme induction. Rat studies were performed up to 6 months. Reversible changes were observed in liver and thyroid which were associated with microsomal enzyme induction. Hematological changes (not exceeding 10% versus controls) included slightly lower mean values for erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, and mean corpuscular hemoglobin, and slightly higher mean platelet counts. Serum chemistry changes observed after 13 and/or 26 weeks of dosing included slightly higher mean gamma glutamyltransferase, cholesterol, total protein, albumin, globulin, and calcium. Slight urinary changes were not associated with remarkable clinical chemistry changes or with histopathological changes in the kidney. Dog studies were performed up to 39 weeks. Changes in the thymus and adrenal gland in dogs observed in high dose animals after 13-weeks of dosing were absent after 39-weeks of dosing, and were considered stress related. In dogs administered 20 mg/kg/day for 39-weeks, clinical signs (salivation, emesis, fecal changes), decreases in body weight and food consumption, and minimal, adaptive changes in the liver (increased weights, hypertrophy) were noted. After 39-weeks of dosing at 10 mg/kg/day, effects were limited to minimal hepatocellular hypertrophy in males, and slightly increased liver weights in females. Clinical pathology changes in the 4-week study included slight non-significant changes in bilirubine and ALP and approximately 2-fold increase in ALT. In the 39-week study, slight increase in platelet count and slight decreases in total protein and albumin were observed and 2-fold increase in ALP; these changes were reversible following cessation of dosing. Slight urinary changes were not associated with remarkable clinical chemistry changes or with histopathological changes in the kidney.

Cobicistat was not genotoxic in the Ames test, in a mouse lymphoma assay and in an in vivo rat micronucleus assay.

In the 104-week carcinogenicity study in mice with cobicistat, no drug-related increase in tumor incidence was observed. In rats, increases in follicular cell adenomas and/or carcinomas in the thyroid gland were observed in the 104-week carcinogenicity study as well as a follicular cell carcinoma in the thyroid of one high dose male in the 26-week rat study. These findings are considered due to hepatic microsomal enzyme induction, which is considered rodent-specific and not relevant for humans.

No adverse effects were observed in a rat fertility study with cobicistat; at the no observed effect level (NOEL) for reproductive parameters, the exposure was approximately 2.3-fold higher than human therapeutic exposures. No teratogenic effects were observed in rat and rabbit developmental toxicity studies. In rats, increases in post-implantation loss, skeletal variations and decreased fetal weights were associated with significant maternal toxicity. At the NOEL/NOAELs in the rat and rabbit studies exposures were approximately 1.9 and 4.7 fold higher, respectively, than human therapeutic exposures. In the pre/postnatal study, the maternal NOAEL for general toxicity was 30 mg/kg/day, and the NOAEL for reproduction in the dams and viability and growth of the offspring was 75 mg/kg/day, the highest dose tested (exposures on lethal dose [LD] 10 were 1.3-fold human therapeutic exposures). In the juvenile toxicity phase of the pre/postnatal study in rats with cobicistat, the NOAEL for toxicity of cobicistat is 75 mg/kg/day for juvenile rats where exposures were 2.7-fold higher (for males and females) than therapeutic adult human exposures at the therapeutic dose.

Cobicistat was mildly irritating to skin and a non-severe irritant to eyes. Cobicistat showed no potential for sensitization in the local lymph node assay in mice.

In a 28-day T-cell dependent antibody response study in rats, a decreased anti-KLH IgG titer was observed in females at ≥ 50 mg/kg/day.). Decreased anti-KLH IgG responses in males did not reach statistical significance at 150 mg/kg/day. No cobicistat-related changes in the anti KLH IgM response in males and females were noted.

Combination darunavir and cobicistat

No non-clinical studies were performed with the combination of darunavir and cobicistat. This was considered acceptable by the CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

Darunavir is not expected to pose a risk to the environment. However, the available data do not allow to conclude on the potential risk of cobicistat to the environment. The applicant is requested to provide information on the water solubility of cobicistat, determined with a GLP-compliant study according to OECD 105 and to provide a new bioconcentration study meeting the OECD 305 (2012) guideline, using test concentrations below the limit of solubility in water. A study in sediment-dwelling organisms according to OECD 218 is being performed and expected in Q2 2015.

The applicant will provide calculation on the missing DT50 values for sediment as resulted in the provided water sediment studies (OECD 308) or use the recalculated values (see table below), as the results of the provided water sediment studies (study TMC114-NC335 and TMC114-NC319) for Darunavir only include DT_{50} values for the whole systems. No half-lives for water and sediment were calculated and no statistical information was provided. Therefore the quality of the stated DT_{50} values could not be verified. Recalculated DT_{50} values with statistical analysis (FocusDegKin v2) are as follows:

Aerobe systems	**DT_{50} [d] at 20°C**	**SFO, Error Level Chi^2 test**	**DT_{50} [d] at 12 C**	**Conclusion for**
Water TR*	8.1	18.2	15.2	
Sediment TR	75.3	3.4	141.5	P
Whole System TR	26.4	9.0	49.6	
Water WR**	27.0	5.4	50.7	P
Sediment WR	142.3	13.6	267.4	vP
Total System WR	45.6	9.0	85.7	
Anaerobe systems				
Water TR	24.6	8.8	46.2	P
Sediment TR	stable		>1000	vP
Whole System TR	104.9	n.d.	197.1	vP
Water WR	17.7	6.0	33.3	
Sediment WR	243.9	3.0	458.3	vP
Total System WR	74	n.d.	139	P

*Taunton River, USA

**Weweantic River, USA

Darunavir ethanolate exceeds the persistence trigger in the water sediment compartments indicating Darunavir as very persistent in the environment.

The applicant will also discuss the study results of the activated sludge inhibition test (OECD 209), as Darunavir ethanolate shows up to100 mg/l test concentrations only slightly effects to microorganism (max. 11.5%). At a test concentration of 1000 mg/l increased unexplained oxygen consumption was observed. Furthermore the laboratory prepared the test substance as stock solution (2g/l) although

the water solubility was limited (163 mg/l). Therefore a NOEC equal to the maximum water solubility is recommended.

2.3.6. Discussion on non-clinical aspects

Because cobicistat has no pharmacological action, pharmacodynamics interactions between darunavir and cobicistat are not expected.

Darunavir did not affect hERG current and sheep Purkinje fibre action potential duration in vitro and did not affect ECG parameters in dogs. Systemic exposure in dogs was however not higher than clinical exposure and in humans. Cobicistat inhibited hERG current with IC50 values more than 15 times clinical unbound Cmax. In vivo, cobicistat induced increases in PR but not in QT interval. Overall, no cardiovascular interactions are expected at clinical exposures. Also other pharmacological interactions between darunavir and cobicistat are not expected.

Darunavir inhibits P-gp and cobicistat may inhibit P-gp at high concentrations in the intestinal lumen. Interactions of the combination of darunavir and cobicistat with substrates of P-gp are therefore possible. This is however also possible for the combination of darunavir and ritonavir and the interaction is mentioned in section 4.5 of the SmPC. Otherwise, no relevant pharmacokinetic interactions are expected between darunavir and cobicistat, apart from the intended interaction regarding CYP3A inhibition.

The combination of darunavir and cobicistat may be expected to cause decreases in red blood cell parameters, since both compounds induced (limited) haematological effects. This can however be monitored clinically and has been included in the RMP.

Effects on the liver induced by both compounds are mainly considered due to adaptive changes caused by enzyme induction. These changes can be considered not clinically relevant. Increases in transaminase activities and single cell necrosis as observed in the liver in the rat study treated with the combination darunavir + ritonavir correlated with ritonavir and not with darunavir. No histopathological changes due to toxicity and no relevant transaminase activity increases were caused by darunavir. Cobicistat induced approximately 2-fold increases in ALT and ALP in dogs, but caused no histopathological changes in the liver due to toxicity. Overall, it does not seem likely that a significantly increased risk for liver toxicity exists for the combination of darunavir and cobicistat and non-clinical studies with the combination are not considered necessary. Also regarding genotoxicity, carcinogenicity and reproductive toxicity, no studies with the combination are necessary because both compounds have been sufficiently characterised and there are no special causes for concern.

2.3.7. Conclusion on the non-clinical aspects

There are no objections against the registration of the fixed dose combination of darunavir and cobicistat from a non-clinical point of view.

The applicant will submit additional study results related to the environmental risk assessment during 2015 (timelines specified below).

ERA

1. The CHMP requests the applicant to provide additional information on the water solubility of cobicistat, for example by performing an OECD 105 study. The applicant proposes to provide this by Q1 2015.
2. The applicant has started a study on the effects of cobicistat in sediment-dwelling organisms (OECD 218) The CHMP requests the study details upon availability. The applicant proposes to provide this by Q2 2015.

3. The CHMP requests the applicant to calculate the missing DT50 values for sediment as resulted in the provided water sediment studies (OECD 308) or to use the recalculated values for darunavir. The applicant proposes to provide this by Q1 2015.

4. The CHMP requests the applicant to discuss the study results of the activated sludge inhibition test (OECD 209) for darunavir. The applicant proposes to provide this by Q1 2015.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

The clinical program for DRV/COBI FDC is based on the development programs of the 2 single agents and PK bridging of DRV co-administered with COBI to DRV co-administered with low-dose ritonavir (rtv).

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

- Study GS-US-216-0115 compared DRV/rtv 800/100 mg co-administered as single agents with DRV/COBI 800/150 mg co-administered as single agents following repeated once daily dosing under fed conditions.
- Study TMC114IFD1001 compared two candidate DRV/COBI 800/150-mg FDC tablet formulations versus DRV/rtv 800/100 mg co-administered as single agents in healthy subjects following repeated once daily dosing under fed conditions.

Absorption

The *in vitro* transport characteristics of DRV and Cobi have not been investigated in the context of this current submission DRV and COBI as a fixed dose combination (FDC).

Bioavailability

Darunavir

The absolute bioavailability of DRV was investigated in support of the marketing authorization of DRV. When tablet formulations of DRV (F014 [400-mg] and F015 [200-mg] used for a 600 mg dose) were co-administered with rtv 100 mg under fed conditions, the absolute bioavailability of DRV was 82%, compared with 37% when DRV was given without rtv.

Cobicistat

The absolute bioavailability of COBI has not been investigated. The intrinsic aqueous solubility of COBI free base (0.075 mg/mL, pH ~ 7) is significantly enhanced under acidic conditions at pH 2 (70 mg/mL).

Monolayers of Caco-2 cells were used as an in-vitro model to investigate the bidirectional permeability and polarized transport characteristics of COBI. Similar to ritonavir (RTV), COBI was found to have high forward permeability through Caco-2 cells and showed no evidence for marked efflux.

The potential for COBI to be a substrate for MDR1 or BCRP was evaluated using MDCK II cells expressing these transporters. COBI was reported to be a substrate for these transporters based on increased efflux ratios in MDR1 and BCRP over-expressing cells. Consistent with MDR1 and BCRP-dependent transport, the COBI efflux ratios were decreased in the presence of the MDR1 inhibitor cyclosporin A (10 µM) and the BCRP inhibitor Ko134 (10 µM).

The absolute bioavailability of DRV when administered as the DRV/COBI FDC has not been studied.

Relative bioavailability studies (GS-US-216-0115, TMC114IFD1001, and TMC114IFD1003) have been conducted to compare the systemic exposure to DRV following the administration of various DRV/COBI 800/150-mg FDC tablet formulations, DRV/COBI 800/150 mg co-administered as single agents, and DRV/rtv 800/100 mg co-administered as single agents.

Study GS-US-216-0115

An open-label, randomized, 2-period crossover Phase 1 study in 33 healthy subjects to evaluate the Relative Bioavailability and Pharmacokinetics of Darunavir when co-administered with the Pharmacoenhancer GS-9350 (COBI) versus Ritonavir.

A summary of pharmacokinetic parameters [mean (%CV)] of DRV following multiple-dose administration with GS-9350 (150 mg once daily) or RTV (100 mg once daily) is presented below:

Table 1 PK Parameters of COBI Following Administration of DRV/COBI 800/150 mg Once Daily (Day 10) (Study GS-US-216-0115)

DRV Plasma PK Parameters	Treatment A DRV+GS-9350 (N=31)	Treatment B DRV+RTV (N=31)	Geometric Least-Squares Means Ratio (%) of Test/Reference (Treatment A/Treatment B) (90% CI)
C_{max} (ng/mL) Mean (%CV)	7737.1 (21.8)	7464.2 (20.3)	103.36 (100.34, 106.48)
AUC_{tau} (ng·h/mL) Mean (%CV)	81,084.2 (31.0)	79,987.0 (34.0)	101.78 (97.40, 106.36)
C_{tau} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)	69.43 (59.02, 81.68)
C_{0h} (ng/mL) Mean (%CV)	2395.5 (50.7)	2483.8 (34.3)	89.39 (80.36, 99.44)

C_{0h}, predose concentration following observed, multiple doses of study drug at steady-state; CI, confidence interval; CV, coefficient of variation; DRV, darunavir; PK, pharmacokinetic; RTV, ritonavir.
Treatment A: DRV (2 × 400 mg tablets) + GS-9350 (1 x 150 mg tablet); Treatment B: DRV (2 × 400 mg tablets) + RTV (1 × 100 mg capsule)
Note: Ratios were estimated as the geometric LSmeans ratio of Test vs. Reference.

Study TMC114IFD1001

This was a Phase 1, open-label, randomized, 3-period crossover study to investigate the oral bioavailability of DRV/COBI 800/150 mg administered as 2 different FDC tablet formulations compared with DRV/rtv 800/100 mg co-administered as single agents.

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

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

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

Cobicistat PK

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

Table 3 PK Parameters of COBI Following Administration of 2 Different FDC Tablet Formulations of DRV/COBI 800/150 mg (G003 and G004) (Day 10) (Study TMC114IFD1001)

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

$C_{ss,av}$=average plasma concentration at steady-state; N=maximum number of subjects with data; qd=once daily.

Darunavir PK

The PK characteristics of rtv following 10 days of co-administration with DRV are summarized in Table 4.

Table 4 PK Parameters of rtv Following Multiple-Dose Administration of DRV/rtv 800/100 mg (Day 10) (Study TMC114IFD1001)

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

$C_{ss,av}$=average plasma concentration at steady-state; N=maximum number of subjects with data; qd=once daily.

Bioequivalence

Study TMC114IFD1003

TMC114IFD1003 was an open-label, randomized, 3-panel, single-center, single-dose, crossover Phase 1 study to investigate the oral bioequivalence of DRV/COBI 800/150 mg administered as the G006 FDC tablet formulation compared with DRV/COBI 800/150 mg administered as 2 DRV 400-mg tablets (F030) and 1 COBI 150-mg tablet. The effect of food (high-fat breakfast) on the oral bioavailability of the DRV/COBI G006 FDC tablet was also investigated.

Table 5 PK Parameters of DRV Following Single-Dose Administrations of a DRV/COBI 800/150-mg FDC Tablet (G006) Compared With DRV/COBI 800/150 mg Administered as Single Agents Under Fasted and Fed Conditions (Study TMC114IFD1003)

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

N=maximum number of subjects with data; $t_{1/2term}$=terminal elimination half-life.

Influence of food

TMC114-C143

This was a Phase 1, open-label, randomized, 2-panel, 3-way crossover study to investigate the effect of food and different types of meals on the bioavailability of a single dose of DRV (400 mg, tablet formulation F014) co-administered with multiple doses of rtv 100 mg twice daily. Darunavir was taken immediately after 1 of 4 types of meals at breakfast, or under fasted conditions.

Table 6 PK Parameters of DRV Following a Single Oral Dose of DRV 400 mg. Coadministered With rtv 100 mg Twice Daily. Administered With Different Meal Types (Study TMC114-C143)

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

N=maximum number of subjects with data; $t_{1/2term}$=terminal elimination half-life.

GS-US-236-0105

This was a Phase 1, open-label, randomized, 3-period, 6-way crossover study to investigate the effect of 2 different fed conditions (high-calorie/high-fat meal or light meal) versus fasted conditions on the PK of a single dose of the EVG/COBI/FTC/TDF 150/150/200/300 mg STR tablet. The COBI exposure parameters C_{max}, AUC_{last}, and AUC_{∞} were bioequivalent following a light meal compared with fasted conditions. For the high-calorie/high-fat meal condition, C_{max}, AUC_{∞}, and AUC_{last}, were decreased by 27%, 19%, and 20% relative to the light meal condition and were decreased by 24%, 17%, and 18% relative to the fasted condition. These lower values in COBI exposures did not result in lower EVG exposures. Relative to fasted conditions, EVG C_{max}, AUC_{∞}, and AUC_{last} were increased by 22%, 34%, and 36%, respectively, when the STR tablet was administered following a light meal and were increased by 56%, 87%, and 91%, respectively, following a high-calorie/high-fat meal. Elvitegravir C_{max}, AUC_{∞}, and AUC_{last} were increased by 28%, 39%, and 40%, respectively, when the STR was administered with a high-calorie/high-fat meal relative to a light meal. Mean FTC C_{max}, AUC_{∞}, and AUC_{last} estimates and median FTC t_{max} estimates were similar under all treatment conditions. All 90% CIs were contained within the 80% to 125% bounds. Relative to fasted conditions, tenofovir AUC_{∞} and AUC_{last} were increased by 24% and 25%, respectively, following a light meal and by 23% and 25%, respectively, following a highcalorie/ high-fat meal. AUC estimates were bioequivalent between the 2 fed conditions (ie, light meal versus high-calorie/high-fat meal). Tenofovir C_{max} was increased by 20% with a light meal relative to fasted conditions, but was similar between the high-calorie/high-fat meal and fasted conditions. Tenofovir C_{max} was decreased by 14% with a high calorie/high fat meal relative to a light meal.

Distribution

Darunavir

The binding of DRV to human plasma proteins was assessed in studies TMC114-NC113 and TMC114-NC215 (see non-clinical report for further details). In study TMC114-NC113, the mean protein binding of DRV in human plasma was 92.3% to 96.1% across all concentrations, which covered the range of plasma concentrations that occur at therapeutic doses of DRV. According to the applicant, liquid chromatography with tandem mass-spectrometry (LC-MS/MS) analysis of buffer quality control samples indicated that the observed concentrations of DRV were systematically lower than the nominal concentrations, which was most probably caused by adsorption to the polypropylene containers. As this adsorption may have also occurred in the buffer compartment of the equilibrium dialysis system, the concentration of DRV in this matrix, and thereby the free fraction of DRV as well, may have been underestimated. Therefore, these protein binding data have to be interpreted with caution.

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

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

Cobicistat

Blood:plasma ratio

When [14C] COBI (150 mg COBI dose) was administered on the last day of a multiple-dose period (150 mg once daily for 6 days) in healthy subjects in a Phase 1 open-label, mass-balance study (GS-US-216-0111) the blood-to-plasma ratio of total 14C-radioactivity was time-independent and ~ 0.5, indicating that COBI is excluded from the cellular components of the blood.

Protein binding

Based on equilibrium dialysis studies COBI was ~97% to 98% bound to human plasma proteins regardless of concentration and binding was independent of concentration.

DRV Plasma PK Parameters	Treatment A DRV+GS-9350 (N=31)	Treatment B DRV+RTV (N=31)	Geometric Least-Squares Means Ratio (%) of Test/Reference (Treatment A/Treatment B) (90% CI)
C_{max} (ng/mL) Mean (%CV)	7737.1 (21.8)	7464.2 (20.3)	103.36 (100.34, 106.48)
AUC_{tau} (ng·h/mL) Mean (%CV)	81,084.2 (31.0)	79,987.0 (34.0)	101.78 (97.40, 106.36)
C_{tau} (ng/mL) Mean (%CV)	1332.7 (66.8)	1866.7 (83.3)	69.43 (59.02, 81.68)
C_{0h} (ng/mL) Mean (%CV)	2395.5 (50.7)	2483.8 (34.3)	89.39 (80.36, 99.44)

C_{0h}, predose concentration following observed, multiple doses of study drug at steady-state; CI, confidence interval; CV, coefficient of variation; DRV, darunavir; PK, pharmacokinetic; RTV, ritonavir.
Treatment A: DRV (2 × 400 mg tablets) + GS-9350 (1 x 150 mg tablet); Treatment B: DRV (2 × 400 mg tablets) + RTV (1 × 100 mg capsule)
Note: Ratios were estimated as the geometric LSmeans ratio of Test vs. Reference.

Cobicistat PK

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

Elimination

Darunavir

In a clinical mass-balance study (TMC114-C109), the majority of 14C-DRV-related radioactivity was excreted in faeces (81.7% and 79.5% at 168 hours in the absence and presence of rtv, respectively); 12.2% and 13.9% of the radioactivity was recovered in urine in the absence and presence of rtv, respectively, including 1.2% and 7.7% as unchanged drug.

Darunavir was extensively metabolized in the absence of rtv (only 8% of the dose was excreted unchanged after 48 hours), while co-administration of rtv markedly reduced metabolism (48.8% of the dose excreted unchanged after 48 hours). Unchanged drug was mainly excreted in faeces, both with and without rtv co-administration.

Cobicistat

In the steady state mass balance study GS-US-216-0111 radiolabeled COBI (150 mg dose of [14C]COBI) was given on day 7 following administration of 150 mg daily for 6 days. All dosing was once daily in the fed state and was followed by sampling for 4-21 days depending on recovery of radiolabeled material. Data were obtained from six evaluable male subjects.

Peak [14C] COBI plasma concentrations were observed at 4.5 h post-dose. The estimates for C_{max} and AUC_{-tau} were similar to values seen in other studies (e.g. GS-US-216-0120, 0115 and 0116) but the half-life was longer (e.g. median T1/2 was ~ 3 h in GS-US-216-0120 and 0115 and ~ 5 h in 0116).

COBI was the predominant species in plasma in the first 24 h, representing 98.6% of the circulating radioactivity, and with no quantifiable metabolites. In most subjects, plasma radioactivity was not detectable beyond 32 h and was BLQ in all subjects by 96 h.

Total recovery of radioactivity was 94%.

Most (86.2%) of the dose was recovered in faeces, consistent with hepatobiliary excretion. A mean of 62.3% of the total radioactive dose was quantified and comprised primarily the parent drug or the oxidative metabolites M21 (GS-9454 or E1) or M31 (GS-9612 or E3). COBI was the major species in the faeces (27%) followed by E3 (14%), which results from hydroxylation of isopropyl thiazole, and E1 (5.5%), which results from carbamate cleavage. All other metabolites detected in the faeces were in trace amounts, with no values exceeding 3% of the dose.

Only 8.2% of the administered dose was recovered in urine, primarily as unchanged parent drug (5.45%) and with low levels of metabolites M21 and M31 (each < 1%). Most of the recovered dose in urine (8.06%) appeared within 48h.

COBI displayed both dose- and time-dependent changes in apparent clearance (CL/F), consistent with the properties of a mechanism-based inhibitor.

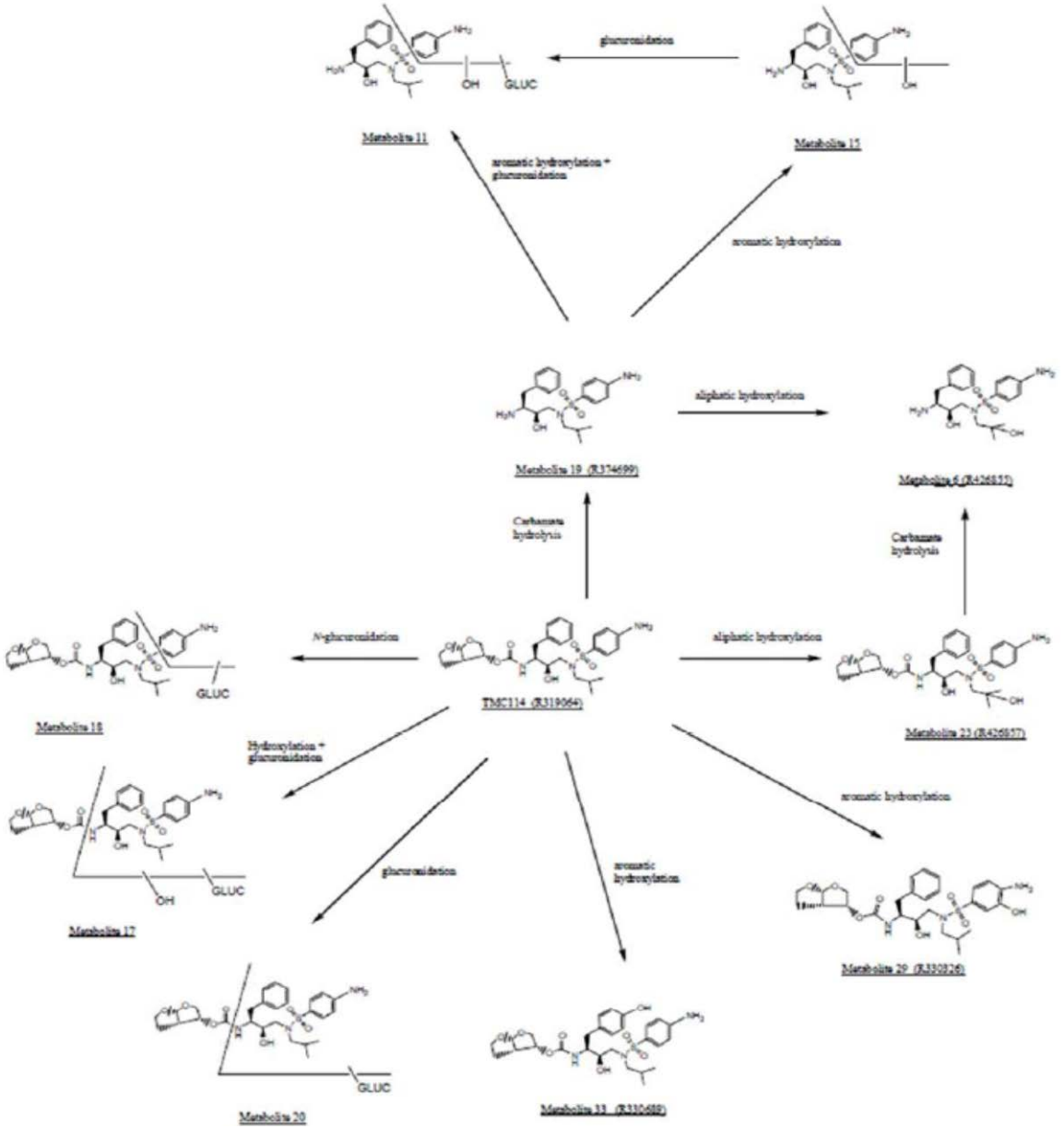
A mass-balance study of the DRV/COBI FDC has not been conducted.

Metabolism

Darunavir

A non-clinical study in human liver subcellular fractions and/or hepatocytes detected a relatively large number of metabolites for DRV (study TMC114-NC154). Major metabolic pathways identified were aliphatic (M21, M23), aromatic (M24, M29), alicyclic hydroxylation (M12, M27, and M28), and carbamate hydrolysis (M19, which was then metabolized further via various pathways to M2, M6, M15, M1, M11, and M3). Minor pathways included glucuronidation (M18, M20, and M17), N-dealkylation (M14), and N-acetylation (M30). In a nonclinical study (TMC114-NC213) using samples from the clinical mass-balance study TMC114-C109, in the absence of rtv, biotransformation of DRV occurred through aliphatic and aromatic hydroxylation, carbamate hydrolysis, and glucuronidation (Section 1.2.1.2.1). The predominant metabolic pathway was carbamate hydrolysis, accounting for 13.2% of the dose. Aliphatic hydroxylation at the isobutyl moiety towards the tertiary alcohol function (9.8%) and aromatic hydroxylation at the aniline moiety (4.5%) were other major pathways.

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



In the presence of rtv, the carbamate hydrolysis, isobutyl aliphatic hydroxylation, and aniline aromatic hydroxylation pathways were significantly inhibited, accounting for 0.67%, 2.26%, and 1.42% of the dose, respectively.

In 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. 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.

In a clinical mass-balance study (TMC114-C109), the majority of 14C-DRV-related radioactivity was excreted in faeces (81.7% and 79.5% at 168 hours in the absence and presence of rtv, respectively); 12.2% and 13.9% of the radioactivity was recovered in urine in the absence and presence of rtv, respectively, including 1.2% and 7.7% as unchanged drug Darunavir was extensively metabolized in the absence of rtv (only 8% of the dose was excreted unchanged after 48 hours), while co-administration of rtv markedly reduced metabolism (48.8% of the dose excreted unchanged after

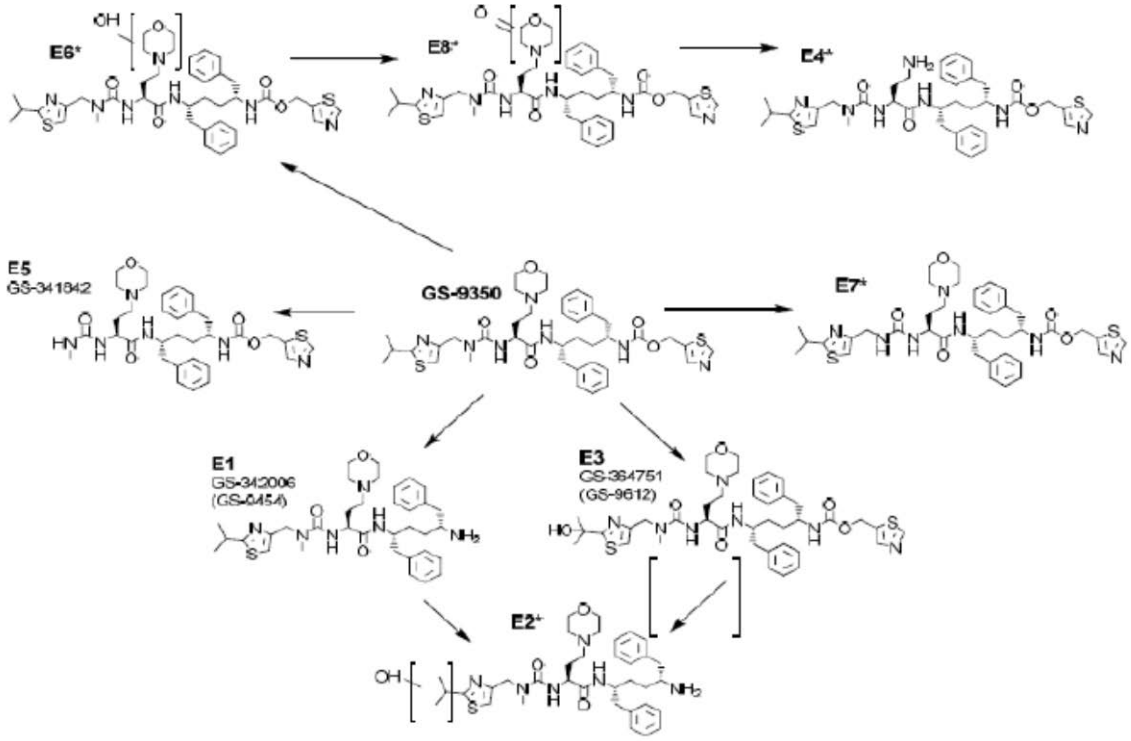
48 hours). Unchanged drug was mainly excreted in faeces, both with and without rtv co-administration.

Cobicistat

In-vitro studies showed that COBI is extensively metabolised via CYP3A (major) and CYP2D6 (minor) mediated oxidation and does not undergo glucuronidation. There are no unique or major (>10%) human metabolites. Primary metabolites include isopropyl oxidation (E3=M31, GS-9612), cleavage at the N-methylurea (E5=M26, GS-341842), cleavage of the carbamate (E1=M21, GS-9454) and cleavage and deethylation of the morpholine (M39). CYP3A can catalyse all reactions, while CYP2D6 contributes to the generation of M31. Mean plasma exposures of M31 were < 3% of COBI exposure (AUC) after a single 150 mg dose (GS-US-216-0111 mass-balance study; see above) or multiple doses (GS-US-236-0101 using the QUAD STR).

A proposed biotransformation pathway for radiolabeled COBI is shown below.

Figure 2. Proposed Biotransformation Pathway of COBI in Humans



E1=M21; E3=M31; E5=M26.
E1, E3, and E5 were generated by humans, mice, rats, and dogs; E2, E4, E6, E7, and E8 were generated exclusively by dogs.

The three most abundant human metabolites of COBI are weaker inhibitors of CYP3A compared to COBI. Due to their low systemic concentrations they are not considered likely to contribute to CYP3A inhibition.

Dose proportionality and time dependencies

There is no discussion by the applicant regarding the dose proportionality of DRV alone or in combination with Cobi. There is also no discussion of the dose proportionality of Cobi, however, studies GS-US-216-0101and GS-US-216-0113 are considered to be relevant to cobi.

GS-US-216-0101

This was a Phase 1, double-blind, randomized, placebo- and active-controlled, single- and multiple-dose escalation study to investigate the PK, PD, safety, and tolerability of COBI (25- and 100-mg tablets) in 60 healthy adult subjects. Cobicistat exhibited nonlinear PK with respect to dose and time (Table 7). Single-dose escalation from COBI 50 mg to 100 mg and from COBI 100 mg to 200 mg resulted in dramatic decreases in COBI apparent clearance (CL/F); the least square (LS) means ratio of CL/F for COBI 100 mg versus 50 mg was 23.6% and for COBI 200 mg versus 100 mg, the ratio was 38.4%. Similarly, the CL/F of COBI at steady state (CLss/F) following multiple-dose administration of COBI decreased with increasing dose; the LS means ratio of CLss/F for COBI 100 mg versus 50 mg was 33.5% and for COBI 200 mg versus 100 mg was 42.5%. When CL/F was compared following single versus multiple doses, lower values were observed following multiple doses of COBI at all dose levels versus single doses; the LS means ratios of single versus multiple doses were 312%, 219%, and 199% for 50, 100, and 200 mg, respectively.

At steady-state, systemic exposure of COBI 100 mg was 60% lower than that of rtv 100 mg.

Table 7. PK Parameters of COBI After Single- and Multiple-Dose Administration of COBI at 50 to 200 mg Under Fed Conditions in Healthy Subjects (Study GS-US-216-0101)

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

Q=quartile.
[a] Reported as AUC-

GS-US-216-0113

This was a Phase 1, open-label, single- and multiple-dose, staggered dose escalation study to investigate the PK, safety, and tolerability of COBI (100-mg tablet) in 24 healthy adult subjects. Cobicistat exhibited nonlinear PK with respect to time and dose (Table 8). Single-dose escalation from 300 to 400 mg resulted in statistically significant decreases in COBI CL/F and corresponding increases in AUC and Cmax without changes in t1/2, term, consistent with higher COBI bioavailability. Comparison of single-dose administration of 300 mg COBI with multiple dose administration of 300 mg COBI revealed a large decrease in CL/F and increases in t1/2,term, AUC, and C_{max}.

Table 8 PK Parameters of COBI After Single- and Multiple-Dose Administration of COBI at 300 and 400 mg Under Fed Conditions in Healthy Subjects (Study GS-US-216-0113)

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

Q=quartile; qd=once daily.

[a] AUC=AUC_{∞} for Day 1 and AUC_{τ} for Days 4 and 7.

Pharmacokinetics in target population

The non-compartmental PK of DRV following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents in HIV-1 infected subjects were assessed in a sub-study of GS-US-216-0130. Sixty HIV-1 infected subjects (57 ART-naïve and 3 ART-experienced) were enrolled. The mean DRV exposure (C_{max} and AUC_{24h}) following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents was generally higher than for DRV following multiple-dose administration of DRV/rtv 800/100 mg once daily co-administered as single agents in ART-naïve HIV-1 infected subjects (TMC114-C211) (Table 9). The rate of absorption of DRV was similar; the median t-max ranged from 3.0 to 3.5 hours. The mean DRV exposure (C_{max} and AUC_{24h}) following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents in study GS-US-216-0130 were generally lower than for DRV following multiple-dose administration of DRV/rtv 800/100 mg once daily co-administered as single agents in ART-experienced HIV-1 infected subjects in studies TMC114-C202 and TMC114-C213.

Table 9 Across-Study Comparison of PK Parameters of DRV in HIV-1 Infected Subjects After Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents of DRV/rtv 800/100 mg Once Daily Coadministered as Single Agents (Fed Conditions) (Studies GS-US-216-0130, TMC114-C211, TMC114-C202, TMC114-C213)

	Mean (SD); t_{max}: Median (Range)			
	DRV/COBI Single Agents 800/150 mg qd (ART Naïve and Experienced [a])	DRV/rtv Single Agents 800/100 mg qd (ART Naïve)		
Parameter	Weeks 2-8 GS-US-216-0130	Week 4 TMC114-C211	Week 24 TMC114-C211	Week 48 TMC114-C211
DRV formulation	F030	F021	F021	F021
N	59	9	13	10
t_{max}, h	3.5 (1.0-6.0)	3.0 (1.0-4.1)	3.0 (0.9-4.0)	3.5 (0.8-6.0)
C_{0h}, ng/mL	1,560 (1,328)	1,826 (1,003)	1,786 (838)	2,133 (1,220)
C_{min}, ng/mL	-	1,189 (410)	1,419 (671)	1,352 (688)
C_{max}, ng/mL	7,663 (1,920)	5,471 (1,320)	5,804 (1,558)	6,756 (1,683)
AUC_{24h}, ng.h/mL	81,646 (26,322)	64,230 (18,210)	66,950 (18,610)	75,620 (26,440)
$C_{ss,av}$, ng/mL	-	2,675 (758)	2,808 (767)	3,156 (1,100)
$t_{1/2, term}$, h	10.8 (10.0)	-	-	-

	DRV/rtv Single Agents 800/100 mg qd (ART Experienced)	
	Week 4 TMC114-C202 + TMC114-C213	Week 24 TMC114-C202 + TMC114-C213
DRV formulation	F001	F001
N	9	14
t_{max}, h	4.0 (1.0-6.0)	4.0 (2.0-6.0)
C_{0h}, ng/mL	2,385 (1,178)	2,667 (3,048)
C_{min}, ng/mL	1,898 (945)	1,956 (2,131)
C_{max}, ng/mL	7,534 (2,209)	7,091 (4,400)
AUC_{24h}, ng.h/mL	93,220 (34,677)	91,485 (81,305)
$C_{ss,av}$, ng/mL	3,884 (1,445)	3,812 (3,388)
$t_{1/2, term}$, h	-	-

N=maximum number of subjects with data; qd=once daily.
[a] Only 3 subjects were ART-experienced.

The non-compartmental PK of COBI following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents in HIV-1 infected subjects were assessed in a sub-study of GS-US-216-0130, following multiple-dose administration of DRV/COBI 800/150 mg once daily co-administered as single agents in 60 subjects, maximum COBI concentrations were observed 3.5 hours post-dose. The mean PK values for COBI following multiple-dose administration of DRV/COBI 800/150 mg are summarized in Table 10. The PK values for COBI were modestly lower than those observed in the study GS-US-216-0115 in healthy subjects (mean [SD] AUC_{24h}: 10,370 [2,150] ng.h/mL; C_{max}: 1,376 [268] ng/mL), but comparable with those observed in HIV-1 infected subjects treated with the EVG/COBI/FTC/TDF STR, which contains 150 mg COBI (mean [SD] AUC_{24h}: 8,300 [3,800] ng.h/mL; C_{max}: 1,100 [400] ng/mL).

Table 10 Non-compartmental PK Parameters of COBI Following Multiple-Dose Administration of DRV/COBI 800/150 mg Once Daily Coadministered as Single Agents + Background Regimen in HIV-1 Infected Subjects (GS-US-216-0230 Substudy)

Parameter	Mean (SD); t_{max}: Median (Range)
N	60
t_{max}, h	3.5 (0.9-6.0)
C_{0h}, ng/mL	76 (186)
C_{max}, ng/mL	991 (331)
C_{24h}, ng/mL[a]	33 (95)
AUC_{24h}, ng.h/mL[b]	7,596 (3,657)
$t_{½,term}$, h	3.8 (3.5)

N=maximum number of subjects with data.

[a] Reported as C_τ.

[b] Reported as AUC_τ.

Impaired renal function

The DRV/COBI FDC has not been investigated in patients with renal impairment. Results from a mass balance study with 14C DRV/rtv showed that approximately 7.7% of the administered dose of DRV is excreted in the urine unchanged.

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).

GS-US-216-0124 evaluated the PK of EVG and COBI in subjects with severe renal impairment (eGFR < 30 mL/min) not on dialysis and matched [age ± 10 years, sex and BMI ± 15%, 18 ≤ BMI ≤ 34 kg/m2] healthy controls (eGFR ≥ 90 mL/min). The actual mean $eGFR_{CG}$ values at baseline were 23.5 mL/min and 97.2 mL/min, respectively. EVG 150 mg and COBI 150 mg were co-administered (using 150 mg tablets of each) once daily in the fed state for 7 days with a 7-day follow-up.

The LS means ratios for C_{24h}, C_{max}, and AUC_{24h} of COBI when EVG/COBI 150/150 mg once daily was administered to subjects with severe renal impairment relative to matched healthy control subjects were 113%, 122%, and 125%, respectively (Table 11). The LS means ratios for C_{24h}, C_{max}, and AUC_{24h} of EVG when EVG/COBI 150/150 mg was administered to subjects with severe renal impairment relative to healthy control subjects were 69%, 67%, and 76%, respectively. Notably, EVG exposure on Day 7 among subjects with normal renal function was substantially higher than that observed in previous clinical studies with EVG/COBI (GS-US- 216-0123; and GS-US-183-0133).

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

Table 11 PK Parameters of COBI and EVG Following Coadministration of COBI 150 mg and EVG 150 mg Once Daily in Healthy Subjects and Subjects With Severe Renal Impairment (Study GS-US-216-0124)

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

qd=once daily.

[a] Reported as C_{τ}.

[b] Reported as AUC_{τ}.

Impaired hepatic function

The effect of hepatic impairment on the PK of DRV when co-administered with COBI has not been investigated. The effect of hepatic impairment on the PK of DRV and Cobi as single agents was investigated.

Darunavir

Study **TMC114-C134** investigated the steady-state PK of DRV, administered as the 300-mg tablet formulation F016, together with rtv in non-HIV-1 infected subjects with mild to moderate hepatic impairment compared with matched healthy subjects with normal hepatic function. The study population included 32 subjects divided into 2 panels: 8 subjects with mild hepatic impairment and 8 healthy matched control subjects in Panel A, and 8 subjects with moderate hepatic impairment and 8 healthy matched control subjects in Panel B. Panels A and B were conducted sequentially. Subjects in both panels received DRV/rtv at a dose of 600/100 mg twice daily for 6 days and on the morning of Day 7; subjects also received rtv on the evening of Day 7 and in the morning and evening of Days 8 and 9.

On Days 1 and 7, relative to the healthy matched control subjects, the mean exposure to DRV (C_{max}, AUC_{12h}, and C_{min}) was lower in subjects with mild hepatic impairment and higher in subjects with moderate hepatic impairment.

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

On Day 7, the LS mean ratios for C_{max} and AUC_{12h} of DRV were 88% and 94%, respectively, in subjects with mild hepatic impairment relative to healthy control subjects, and were 122% and 120%, respectively, in subjects with moderate hepatic impairment relative to healthy control subjects. For all comparisons, the 90% CIs of the LS means ratios were outside of the 80.00% to 125.00% bounds.

Table 12 PK Parameters of DRV Following Administration of DRB/rtv in Healthy Subjects and Subjects With Mild Hepatic Impairment (Study TMC114-C134)

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

bid=twice daily; N=maximum number of subjects with data.

Table 13 PK Parameters of DRV Following Administration of DRB/rtv in Healthy Subjects and Subjects With Moderate Hepatic Impairment (Study TMC114-C134)

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

bid=twice daily; N=maximum number of subjects with data.

The effect of severe hepatic impairment on the PK of DRV has not been studied.

Cobicistat

Study **GS-US-183-0133** investigated the steady-state PK of EVG and COBI when co-administered in non HIV-1 infected subjects with normal and impaired hepatic function. A total of 20 subjects (10 healthy subjects and 10 subjects with moderate hepatic impairment) received a single 150 mg EVG tablet and a single 150 mg COBI tablet once daily for 10 days. Elvitegravir and COBI were co-administered in the morning immediately after consuming a standard meal. Each subject in the moderate hepatic impairment group was matched for age (±5 years), sex, and BMI (±15%) with a subject in the healthy control group.

The AUC_{24h} and C_{max} of COBI were comparable in subjects with moderate hepatic impairment relative to healthy control subjects. The C_{24h} of COBI was increased (LS means ratio of 208%). Elvitegravir exposure was modestly increased in subjects with moderate hepatic impairment relative to healthy control subjects. However, the observed increases were well below the protocol-defined clinically significant increase of 100% in EVG AUC_{24h} or C_{max} for subjects with moderate hepatic impairment compared to healthy matched control subjects according to the applicant, exploratory analyses indicated no clinically relevant correlations between the EVG or COBI exposure and Child-Pugh-Turcotte score or its individual laboratory components (i.e., albumin, total bilirubin, prothrombin time, and international normalized ratio) for subjects with moderate hepatic impairment. The mean (SD) % free fraction (unbound concentration) for EVG in the healthy control subjects and subjects with moderate hepatic impairment was 1.15 (0.14) and 1.22 (0.23) respectively, Similar results were observed for COBI; corresponding values were 2.71 [0.56] and 3.23 [0.63], respectively.

Table 14 PK Parameters of COBI and EVG Following Administration of EVG/COBI in Healthy Subjects and Subjects With Moderate Hepatic Impairment (Study GS-US-183-0133)

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

qd=once daily.

[a] Reported as C_{τ}.

[b] Reported as AUC_{τ}.

Interactions

No drug-drug interaction studies have been performed using DRV/COBI FDC tablet formulations, or using DRV co-administered with COBI as separate agents. The drug-drug interaction potential of the FDC of DRV/COBI has been evaluated on the basis of interactions observed with each of the single agents, in the case of DRV, when co-administered with rtv. This was considered acceptable by the CHMP.

In vitro

Darunavir

According to the applicant, comprehensive drug-drug interaction program has been conducted with DRV/rtv, including a cocktail study to assess the effects of DRV/rtv co-administered as single agents on the metabolism of probe substrates (TMC114-C173-CRR11). Interactions are most likely a result of the rtv component because of its inhibitory effects on CYP2D6, CYP3A, and certain transporters, and/or its induction effects on CYP2C9, CYP2C19, and UGT.

Cobicistat

COBI inhibits human CYP3A and so it is expected to substantially increase the systemic levels of co-administered drugs whose bioavailability and elimination are affected by CYP3A enzymes. CYP3A inducers are expected to lower COBI exposures Assessor's comment and strong inhibitors of CYP3A enzymes may increase COBI exposures. Cobi does not significantly inhibit CYP1A2, CYP2C9, and CYP2C19 and it mildly inhibits CYP2B6 (similar to rtv). Cobi is a milder inhibitor of CYP2C8 and UGT1A1 activities when compared with rtv. Like rtv, COBI was found to be primarily an inhibitor of CYP3A and CYP2D6.

The effects of COBI on human transporters is summarised in the Table 15.

Table 15 Summary of the Effect of COBI on the Activity of Human Transporters

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

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

At human concentrations following 150 mg COBI would not be expected to inhibit the drug transporters MDR1, MRP1, MRP2, BCRP, OAT1 or OAT3 ($[I]1/IC_{50} < 0.1$). However, at concentrations achievable briefly in the intestinal lumen during absorption ([I]2 = 770 μM) COBI is expected to inhibit intestinal efflux transporters such as MDR1 and BCRP ($[I]2/IC_{50} > 10$).

On this basis COBI may modestly increase exposures of substrates of P-gp. In addition, high concentrations of COBI in the intestinal lumen during absorption can increase systemic TFV exposure due to inhibition of P-gp-dependent efflux of TDF.

COBI is expected to weakly-modestly increase exposures of substrates of MATE1 and OATP1B1/3.

Inhibition of OCT2 and MATE1 is associated with disrupted active renal secretion of creatinine, resulting in a reduction in creatinine clearance in the absence of changes in true GFR. This phenomenon has previously been described for a variety of other agents.

The potential for COBI to induce human drug metabolizing enzymes and transporters through the activation of aryl hydrocarbon receptor (AhR) and pregnane X receptor (PXR) was evaluated using

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

In vivo

According to the applicant, 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. It is considered by the applicant that 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). The applicant did a summary of the interactions and recommendations to use DRV/rtv in combination with various drugs in DRV SmPC based on previous studies conducted with darunavir/ritonavir.

The applicant considers that COBI like rtv, is an inhibitor of CYP3A and is also an inhibitor of CYP2D6, albeit to a lesser extent than rtv. Therefore, most data generated with DRV/rtv relating 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.

According to the applicant, 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. The applicant considers that 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.

The applicant considers that 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. This is endorsed by CHMP.

A number of studies were conducted with DRV/rtv and other drugs.

TMC114-C123

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

TMC114-C124

This study investigated the PK interaction between steady-state concentrations of TDF and steady-state concentrations of DRV, coadministered with rtv. The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with TDF relative to administration of DRV/rtv alone were 116% and 121%, respectively. For all comparisons, the upper limit of the 90% CIs of the LS means ratios was above 125%. There was no change in the median t_{max} of DRV.

TMC114-C111

This study investigated the PK interaction between steady-state concentrations of efavirenz (EFV) and repeated doses of DRV/rtv. The LS mean ratios for Cmax and AUC12h of DRV when DRV/rtv was coadministered with EFV relative to administration of DRV/rtv alone were 85% and 87%, respectively. For all comparisons, the lower limit of the 90% CIs of the LS means ratios was below 80.00%. There was no relevant change in the median t_{max} of DRV.

TMC114-C119

This was a Phase 1, open-label, randomized, crossover study in HIV-1 infected subjects to investigate the PK interaction between NVP (an NNRTI and CYP3A substrate and inducer) and DRV co-administered with rtv. The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV (TF019)/rtv 300/100 mg twice daily was co-administered with NVP relative to administration of DRV (TF019)/rtv 300/100 mg twice daily alone were 84% and 109%, respectively. When DRV (F001)/rtv 400/100 mg twice daily was co-administered with NVP, relative to administration of DRV (TF036)/rtv alone, the LS means ratios were 140% and 124%, respectively.

TMC125-C176

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

TMC278-C112

This study investigated the PK interaction between steady-state concentrations of rilpivirine and steady-state concentrations of DRV, co-administered with rtv. The LS mean ratios for C_{max} and AUC_{24h} of DRV when DRV/rtv was coadministered with rilpivirine relative to administration of DRV/rtv alone were 90% and 89%, respectively. For C_{max} and AUC_{24h}, the 90% CIs of the LS means ratios were contained within the 80.00% to 125.00% bounds; for C_{min}, the lower limit of the 90% CIs was below 80.00%. There was no relevant change in the median t_{max} of DRV.

TMC114-MK0518

Investigated the effect of DRV/rtv on the PK of raltegravir. The LS mean ratios for C_{max} and AUC_{12h} of raltegravir when raltegravir was co-administered with DRV/rtv relative to administration of raltegravir alone were 67% and 71%, respectively. There was no relevant change in the median t_{max} of raltegravir.

TMC114-A4001052

Investigated the effect of steady-state concentrations of DRV, co-administered with rtv, on the PK of maraviroc at steady-state. The LS mean ratios for C_{max} and AUC_{12h} of maraviroc when maraviroc was co- administered with DRV/rtv relative to administration of maraviroc alone were 229% and 405%, respectively. There was no relevant change in the median t_{max} of maraviroc.

TMC114-C122

Investigated the effect of omeprazole and ranitidine on the PK of DRV at steady-state, coadministered with rtv. The PK of DRV was unaffected by coadministration of ranitidine or omeprazole. The LS mean ratios for C_{max} and AUC_{12h} of DRV when DRV/rtv was coadministered with ranitidine relative to administration of DRV/rtv alone were 96% and 95%, respectively.

TMC114-C150

Investigated the effect of steady-state concentrations of DRV, coadministered with rtv, on the PK of a single dose of digoxin. The LS mean ratios for C_{max} and AUC_{24h} of digoxin when digoxin was coadministered with DRV/rtv relative to administration of digoxin alone were 129% and 135%, respectively. The 90% CIs of the LS means ratios were large because of the substantial intersubject variability (ISV).

Furthermore, 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 below.

Table 16 Potentially Significant and Theoretical Drug-Drug Interactions for DRV/COBI FDC

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
HIV-1-Antiviral Agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs)		
didanosine	↔ darunavir ↔ cobicistat ↔ didanosine	Didanosine should be administered on an empty stomach 1 hour before or 2 hours after DRV/COBI (administered with food).
tenofovir disoproxil fumarate	↔ darunavir ↔ cobicistat ↑ tenofovir	Coadministration of DRV/COBI with tenofovir disoproxil fumarate may increase concentrations of tenofovir (inhibition of P-gp). The increase in tenofovir is not expected to be clinically relevant and no dose adjustment of tenofovir disoproxil fumarate is needed. Monitoring of renal function may be indicated when DRV/COBI is given in combination with tenofovir disoproxil fumarate, particularly in patients with underlying systemic or renal disease, or in patients taking nephrotoxic agents.
Other NRTIs: abacavir, emtricitabine, lamivudine, stavudine, zidovudine	↔ darunavir	Based on the different elimination pathways of the other NRTIs, which are primarily renally excreted, no drug interactions are expected between these drugs and DRV/COBI. Darunavir/COBI can be used with these NRTIs without dose adjustment.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
HIV-1-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
efavirenz, etravirine, nevirapine	↓ darunavir ↓ cobicistat ↑ nevirapine	Coadministration of DRV/COBI with these NNRTIs may decrease DRV and/or COBI concentrations (induction of CYP3A) which may result in loss of therapeutic effect to DRV. Nevirapine concentrations may be increased when coadministered with DRV/COBI (inhibition of CYP3A). Coadministration of DRV/COBI with these NNRTIs is not recommended.
rilpivirine	↔ darunavir ↔ cobicistat ↑ rilpivirine	Coadministration of DRV/COBI with rilpivirine may increase concentrations of rilpivirine (inhibition of CYP3A). The increase in rilpivirine is not expected to be clinically relevant, and no dose adjustment of rilpivirine is needed.
HIV-1-Antiviral Agents: HIV-Protease Inhibitors (PIs)		
atazanavir, fosamprenavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, tipranavir	-	The appropriate dose of DRV/COBI with other HIV PIs have not been established. Coadministration of DRV/COBI with HIV PIs is not recommended.
HIV-1-Antiviral Agents: CCR5 Co-receptor Antagonist (CCR5RA)		
maraviroc	↑ maraviroc	Coadministration of DRV/COBI with maraviroc may increase concentrations of maraviroc (inhibition of CYP3A). When used in combination with DRV/COBI, the recommended dose of maraviroc is 150 mg twice daily.
HIV-1-Antiviral Agents: Integrase Strand Transfer Inhibitors		
dolutegravir	-	Darunavir/COBI and dolutegravir can be coadministered without dose adjustment.
elvitegravir	-	Coadministration of DRV/COBI and elvitegravir/COBI is not recommended.
raltegravir	↓ darunavir	Some clinical studies suggest raltegravir may cause a modest decrease in DRV concentrations (mechanism unknown). At present the effect of raltegravir on DRV concentrations does not appear to be clinically relevant. Darunavir/COBI and raltegravir can be used without dose adjustments.
Other Agents		
α_1-Adrenoreceptor Antagonists: alfuzosin	↑ alfuzosin	Coadministration of DRV/COBI with alfuzosin may increase alfuzosin concentrations (inhibition of CYP3A). Coadministration of DRV/COBI with alfuzosin is contraindicated.
Antacids: aluminum/magnesium hydroxide, calcium carbonate	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (decreased gastric acidity), no interaction is expected between antacids and DRV/COBI. Darunavir/COBI and antacids can be used without dose adjustment.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antiangina/ Antiarrhythmics: bepridil, disopyramide, flecainide, lidocaine (systemic), mexiletine, propafenone	↑ antiarrhythmics	Coadministration of DRV/COBI with these antiarrhythmics may increase concentrations of the antiarrhythmic (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring, if available, is recommended for the antiarrhythmics when coadministered with DRV/COBI.
digoxin	↑ digoxin	Coadministration of DRV/COBI with digoxin may increase concentrations of digoxin (inhibition of P-gp). The lowest possible dose of digoxin should initially be prescribed. Digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect, while assessing the overall clinical state of the subject.
amiodarone, dronedarone, quinidine, ranolazine		Coadministration of DRV/COBI with amiodarone, dronedarone, quinidine, or ranolazine is contraindicated.
Antibacterials: clarithromycin	↑ darunavir ↑ cobicistat ↑ clarithromycin	Coadministration of DRV/COBI with clarithromycin may increase concentrations of DRV, COBI and/or the clarithromycin (inhibition of CYP3A). Caution should be exercised when clarithromycin is combined with DRV/COBI.
Anticoagulants: apixaban, dabigatran etexilate, rivaroxaban, warfarin	↑ anticoagulants	Coadministration of DRV/COBI with these anticoagulants may increase concentrations of the anticoagulant (inhibition of CYP3A and/or P-gp). Coadministration of DRV/COBI and rivaroxaban is not recommended. When used in combination with DRV/COBI, the recommended dose of apixaban is 2.5 mg twice daily. Clinical monitoring, including a coagulation test, is recommended when DRV/COBI is coadministered with dabigatran etexilate. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure. Coadministration of DRV/COBI with warfarin may affect warfarin concentrations. The international normalized ratio should be monitored when DRV/COBI is coadministered with warfarin.
Anticonvulsants: carbamazepine, phenobarbital, phenytoin	↓ darunavir ↓ cobicistat	Coadministration of DRV/COBI with carbamazepine, phenobarbital, or phenytoin may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect to DRV. Coadministration of DRV/COBI and these anticonvulsants is contraindicated.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antidepressants: (selective serotonin reuptake inhibitors or tricyclics) desipramine, paroxetine, sertraline, trazodone	↑ antidepressant	Coadministration of DRV/COBI and these antidepressants may increase concentrations of the antidepressant (inhibition of CYP2D6 and/or CYP3A). If these antidepressants are to be used with DRV/COBI, the combination should be used with caution, and a lower dose of antidepressant should be considered.
Antidiabetic metformin	↑ metformin	Coadministration of DRV/COBI with metformin may increase concentrations of metformin (inhibition of MATE1). Clinical monitoring and dose adjustment of metformin may be needed.
Antifungals: fluconazole, itraconazole, ketoconazole, posaconazole	↑ darunavir ↑ cobicistat ↑ antifungal	Coadministration of DRV/COBI with these antifungals may increase concentrations of DRV, COBI, and/or the antifungal (inhibition of CYP3A and/or P-gp). Clinical monitoring is recommended when coadministering DRV/COBI with these antifungals. When used in combination with DRV/COBI, the dose of itraconazole or ketoconazole should not exceed 200 mg per day.
voriconazole		Voriconazole should not be used unless the possible benefit is considered to outweigh the risks associated with the unpredictable effect on plasma concentrations.
Antigout Agents: colchicine	↑ colchicine	Coadministration of DRV/COBI with colchicine may increase concentrations of colchicine (inhibition of CYP3A and/or P-gp inhibition). A reduction in colchicine dose is recommended in patients with normal renal or hepatic function if treatment with DRV/COBI is required. The combination of colchicine and DRV/COBI is contraindicated in patients with renal or hepatic impairment.
Antimalarials: artemether/lumefantrine	↑ artemether ↑ lumefantrine	Coadministration of DRV/COBI with artemether/lumefantrine may increase concentrations of artemether and lumefantrine (inhibition of CYP3A). Darunavir/COBI and artemether/lumefantrine can be used without dose adjustment; however, due to the expected increase in lumefantrine exposure, the combination should be used with caution.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Antimycobacterials: rifabutin, rifapentine	↓ darunavir ↓ cobicistat ↑ rifabutin	Coadministration of DRV/COBI with rifabutin, rifampicin, or rifapentine may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DRV. Rifabutin concentrations may be increased when coadministered with DRV/COBI. Coadministration of DRV/COBI and rifabutin or rifapentine is not recommended. If the combination of DRV/COBI and rifabutin is needed, the recommended dose of rifabutin is 150 mg 3 times per week on set days (eg, Monday-Wednesday-Friday). Increased monitoring for rifabutin-associated adverse reactions including neutropenia and uveitis is warranted due to an expected increase in exposure to rifabutin. Further dose reduction of rifabutin has not been studied. It should be kept in mind that a twice weekly dose of 150 mg may not provide an optimal exposure to rifabutin, thus leading to a risk of rifabutin resistance and treatment failure.
rifampicin		Coadministration of DRV/COBI with rifampicin is contraindicated.
Antineoplastic Agents: dasatinib, nilotinib, vinblastine, vincristine	↑ antineoplastic agents	Coadministration of DRV/COBI with these antineoplastic agents may increase their concentrations (inhibition of CYP3A), resulting in the potential for increased adverse events usually associated with these antineoplastic medicinal products. Caution should be exercised when coadministering one of these antineoplastic agents with DRV/COBI.
Antipsychotics: quetiapine	↑ quetiapine	Coadministration of DRV/COBI with quetiapine may increase quaetiapine concentrations (inhibition of CYP3A) and therefore quetiapine-related toxicity. Coadministration of DRV/COBI with quetiapine is contraindicated.
Beta-Blockers: carvedilol, metoprolol, timolol	↑ beta-blocker	Coadministration of DRV/COBI and beta-blockers may increase concentrations of the beta-blocker (inhibition of CYP2D6). Clinical monitoring is recommended when coadministering DRV/COBI with beta-blockers and a lower dose of the beta-blocker should be considered.
Calcium Channel Blockers: amlodipine, diltiazem, felodipine, nicardipine, nifedipine, verapamil	↑ calcium channel blocker	Coadministration of DRV/COBI with calcium channel blockers may increase concentrations of the calcium channel blocker (inhibition of CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with calcium channel blockers.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Contraceptives: ethinyl estradiol, norethindrone	-	No dosing recommendations can be made on the use of DRV/COBI with contraceptives. Alternative methods of nonhormonal contraception are recommended.
Corticosteroids, Inhaled/Nasal: budesonide, fluticasone	↑ corticosteroid	Coadministration of DRV/COBI with inhaled or nasal corticosteroids may increase concentrations of the corticosteroid (inhibition of CYP3A). Coadministration of DRV/COBI and budesonide or fluticasone is not recommended unless the potential benefit of treatment outweighs the risk of systemic corticosteroid side effects.
Corticosteroid, Systemic: dexamethasone	↓ darunavir ↓ cobicistat ↑ corticosteroid	Coadministration of DRV/COBI with systemic dexamethasone may decrease DRV and/or COBI concentrations (induction of CYP3A). Systemic dexamethasone should be used with caution when combined with DRV/COBI.
prednisone		Corticosteroid concentrations may be increased when coadministered with DRV/COBI (inhibition of CYP3A). Concomitant use may increase the risk for development of systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Clinical monitoring is recommended when coadministering DRV/COBI with corticosteroids.
Endothelin Receptor Antagonist: bosentan	↓ darunavir ↓ cobicistat	Coadministration of DRV/COBI with bosentan may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DRV. Bosentan concentrations may be increased when coadministered with DRV/COBI.
	↑ bosentan	Coadministration of DRV/COBI with bosentan is not recommended.
Ergot Derivatives: dihydroergotamine, ergometrine, ergotamine, methylergonovine	↑ ergot derivative	Coadministration of DRV/COBI with ergot derivatives may increase ergot derivative concentrations (inhibition of CYP3A). Coadministration of DRV/COBI with ergot derivatives is contraindicated.
Gastrointestinal Motility Agent: cisapride	↑ cisapride	Coadministration of DRV/COBI with cisapride may increase cisapride concentrations (inhibition of CYP3A). Coadministration of DRV/COBI with cisapride is contraindicated.
H_2-Receptor Antagonists: cimetidine, famotidine, nizatidine, ranitidine	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (decreased gastric acidity), no interaction is expected between H_2-receptor antagonists and DRV/COBI. Darunavir/COBI and H_2-receptor antagonists can be coadministered without dose adjustments.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Hepatitis C Virus (HCV) Direct-Acting Agents, NS3-4A Protease Inhibitors: boceprevir, telaprevir	↓ darunavir ↓ cobicistat ↓ HCV PI	Coadministration of DRV/COBI with boceprevir or telaprevir may decrease DRV, boceprevir, and/or telaprevir concentrations (mechanism unknown). Coadministration of DRV/COBI with boceprevir or telaprevir is not recommended.
Herbal Product: St. John's wort (*Hypericum perforatum*)	↓ darunavir ↓ cobicistat	Coadministration of DRV/COBI with St. John's wort may decrease DRV and/or COBI concentrations (induction of CYP3A), which may result in loss of therapeutic effect of DRV. Coadministration of DRV/COBI with St. John's wort is contraindicated.
HMG-CoA Reductase Inhibitors: atorvastatin, pitavastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitor	Coadministration of DRV/COBI with HMG-CoA reductase inhibitors may increase concentrations of the lipid lowering agent (inhibition of CYP3A and/or transport), which may lead to AEs such as myopathy. When administration of HMG-CoA reductase inhibitors and DRV/COBI is desired, it is recommended to start with the lowest dose and titrate up to the desired clinical effect while monitoring for safety.
lovastatin, simvastatin		Coadministration of DRV/COBI with lovastatin or simvastatin is contraindicated.
Immunosuppressants: ciclosporin, everolimus, sirolimus, tacrolimus	↑ immunosuppressant	Coadministration of DRV/COBI and these immunosuppressants may increase concentrations of the immunosuppressants (inhibition of CYP3A). Caution is warranted and therapeutic concentration monitoring is recommended for the immunosuppressant when coadministered with DRV/COBI.
Inhaled Beta Agonist: salmeterol	↑ salmeterol	Coadministration of DRV/COBI with salmeterol may increase concentrations of salmeterol (inhibition of CYP3A). The combination may result in increased risk of cardiovascular AEs associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. Coadministration of DRV/COBI with salmeterol is not recommended.
Narcotic Analgesics: fentanyl, oxycodone, tramadol	↑ analgesic	Coadministration of DRV/COBI with these analgesics may increase concentrations of the analgesic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with these analgesics.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Narcotic Analgesics/Treatment of Opioid Dependence: buprenorphine, buprenorphine/naloxone, naloxone, methadone	↑ buprenorphine ↑ norbuprenorphine ↔ naloxone ↑ methadone	No dose adjustment of buprenorphine, methadone, and/or naloxone may be required when coadministering with DRV/COBI. However, clinical monitoring is recommended as the dose of buprenorphine, methadone, and/or naloxone may need to be adjusted in some patients. For buprenorphine, careful clinical monitoring for signs of opiate toxicity is recommended.
Neuroleptics: perphenazine, risperidone, thioridazine	↑ neuroleptic	Coadministration of DRV/COBI and these neuroleptics may increase concentrations of the neuroleptic (inhibition of CYP2D6 and/or CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with perphenazine, risperidone, or thioridazine, and a lower dose of the neuroleptic should be considered.
pimozide, sertindole		Coadministration of DRV/COBI with pimozide or sertindole is contraindicated.
Phosphodiesterase (PDE)-5 Inhibitors: sildenafil, tadalafil, vardenafil avanafil	↑ PDE-5 inhibitor	Coadministration of DRV/COBI and PDE-5 inhibitors may increase concentrations of the PDE-5 inhibitor (inhibition of CYP3A), which may lead to AEs such as hypotension, syncope, visual disturbances, and priapism. *Use of PDE-5 inhibitors for pulmonary arterial hypertension (PAH)*: Coadministration of DRV/COBI with sildenafil for the treatment of PAH is contraindicated. Coadministration of tadalafil with DRV/COBI for the treatment of PAH is not recommended. *Use of PDE-5 inhibitors for erectile dysfunction*: Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased clinical monitoring for PDE-5 inhibitor-associated AEs. Coadministration of DRV/COBI with avanafil is contraindicated.
Proton Pump Inhibitors: dexlansoprazole esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole	↔ darunavir ↔ cobicistat	Based on mechanistic considerations (decreased gastric acidity and CYP2C19 inhibition), no interaction is expected between proton pump inhibitors and DRV/COBI. Darunavir/COBI and proton pump inhibitors can be coadministered without dose adjustment.

Concomitant Drug Class: Drug Name	Effect on Concentration of Darunavir, Cobicistat, or Concomitant Drug	Clinical Comment
Sedatives/Hypnotics: buspirone, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, zolpidem	↑ sedatives/hypnotics	Coadministration of DRV/COBI with these sedatives/hypnotics may increase concentrations of the sedative or hypnotic (inhibition of CYP3A). Clinical monitoring is recommended when coadministering DRV/COBI with these sedatives/hypnotics and a lower dose of the sedatives/hypnotics should be considered. Caution should be used with co administration of DRV/COBI and parental midazolam. Coadministration of parenteral midazolam should be done in a setting that ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Dose reduction for parenteral midazolam should be considered, especially if more than a single dose of midazolam is administered. Coadministration of DRV/COBI with oral midazolam or triazolam is contraindicated.

2.4.3. Pharmacodynamics

Mechanism of action

The darunavir/cobicistat (DRV/COBI) fixed dose combination (FDC) tablet is a combination of 2 single agents, DRV and COBI. Darunavir is an approved human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI). Cobicistat has recently been registered to be co-administered as a pharmacokinetic enhancer of DRV and atazanavir (ATV). Comprehensive drug development programs have been conducted for the individual compounds DRV (in combination with low-dose ritonavir [rtv] as pharmacokinetic enhancer) and COBI.

Darunavir

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (PR) (dissociation constant [Kd] of 4.5 x 10-12M). It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles.

Cobicistat

Cobicistat, a structural analogue of RTV and it is a potent mechanism-based inhibitor of human hepatic microsomal cytochrome P450 (CYP)3A activity. Cobicistat is devoid of anti-HIV and exhibited no antiviral activity against 17 HIV-1 and 2 HIV-2 primary isolates.

Primary and Secondary pharmacology

Primary pharmacology

Darunavir exhibits activity against laboratory strains and clinical isolates of HIV-1 and laboratory strains of HIV-2 in acutely infected T-cell lines, human peripheral blood mononuclear cells (PBMCs) and human monocytes/macrophages (M/Ms) with median 50% effective concentration (EC_{50}) values ranging from 1.2 to 8.5 nM (0.7 to 5.0 ng/mL). The DRV EC_{50} values observed in primary cells were comparable to these observed in cell lines.

Table 17 In Vitro Antiviral Activity of DRV in T-cell lines

	HIV-1/IIIB or NL4-3[a]	HIV-2/ROD[a]	SIV/MAC251[a]	HIV-1/LAI[b]	HIV-2/ROD and EHO[b]
Median EC_{50} values (nM)	2.29-6.26	4.70-8.49	9.28	3[c]	3 and 6[c]

SIV: Simian immunodeficiency virus
[a] MT4-cells
[b] MT2 cells
[c] Mean

Table 18 In Vitro Antiviral Activity of DRV in HIV-1 Infected Primary Cells (PBMCs and M/Ms)

Median EC_{50} value (nM)	1.2 (0.7 ng/mL) to 5.0 (2.7 ng/mL)
Median EC_{90} value (nM)	2.8 (1.5 ng/mL) to 8.0 (4.4 ng/mL)

PBMCs: human peripheral blood mononuclear cells; M/Ms: human monocytes/macrophages

Darunavir demonstrates antiviral activity in vitro against a broad panel of HIV-1 group M (A, B, C, D, E, F, G) and group O primary isolates with EC_{50} values ranging from <0.1 to 4.3 nM. These EC_{50} values are well below the 50% cellular toxicity concentration range of 87 µM to >100 µM. In addition, DRV is not an inhibitor of human cellular PRs.

Table 19 In Vitro Antiviral Activity of DRV Against Primary Isolates in Human PBMCs

	HIV-1 Group M	HIV-1 Group O
EC_{50} range (nM)	<0.10–4.28	1.59–2.54

PBMCs: human peripheral blood mononuclear cells

Darunavir is able to bind tightly to HIV-1 protease to form a highly stable complex with both WT and mutant proteases. Crystal structures suggested that darunavir might maintain activity against mutant proteases because of:

- formation of several hydrogen bonds, mostly with main chain atoms of the HIV-1 protease;
- close fit within the substrate consensus volume;
- flexibility that appeared to compensate for any potential reduction in interaction resulting from mutations in the HIV-1 PR.

The antiviral activity of DRV was determined on a screening panel of 20 PI resistant recombinant viruses. Eighteen of the 20 (90.0%) viruses were susceptible to DRV showing no significant increases in EC50 value compared with HIV-1/IIIB (EC_{50} ≤10nM, FC≤4).

The antiviral activity of DRV was determined against 3,309 recombinant HIV-1 isolates with a decreased susceptibility (FC>4) to at least 1 of the following PIs: APV, ATV, IDV, LPV, NFV, RTV, SQV, or TPV. Darunavir EC_{50} values were ≤ 10 nM for 78% of the isolates, while an EC50 >100 nM was observed for only 3% of the isolates. Eighty percent of the isolates exhibited a DRV FC≤4 and 10% a DRV FC>10. Genotypic data were available for 1,113 of the PI resistant viruses. Subgroups of the

viruses with up to 3 primary PI mutations and/or up to 8 PI resistance-associated mutations had a median fold change ≤ 4 for DRV.

The antiviral activity of DRV has been determined against 14 HIV-1 PI-resistant primary isolates in PBMCs. Only 14% (2 of 14) of the isolates had a FC>4 for DRV compared with 57% (8 of 14) for SQV and 65% (9 of 14) for APV, 93% (13 of 14) for NFV, 100% (14 of 14) for RTV, and 100% (7 of 7) for LPV.

The combination of DRV with HIV-1 inhibitors was studied in an anti-HIV-1/IIIB MT4 cell-based assay. A combination index was calculated using the isobologram model for combinations. DRV did not show antagonism when studied in combination with the PIs APV, ATV, IDV, LPV, NFV, RTV, SQV, or TPV, NRTIs abacavir (ABC), didanosine (ddI), FTC, lamivudine (3TC), stavudine, TFV, zalcitabine, or zidovudine (AZT), the non-nucleoside reverse transcriptase inhibitors (NNRTIs) delavirdine, efavirenz (EFV), etravirine, nevirapine (NVP), or rilpivirine1 and the fusion inhibitor enfuvirtide (T-20). The data indicate additivity with all NRTIs and NNRTIs. A modest synergistic effect with APV, NFV and RTV was observed whereas additive effect was described for the combination with ATV, IDV, LPV SQV, and TPV and with T-20.

Cobicistat

Inhibition of HIV-1 Proteases

COBI (GS-9350) and RTV were evaluated in an in vitro enzymatic assay for their inhibitory effect on HIV-1 PR enzymatic activity. COBI did not have any effect on the HIV-1 PR enzymatic activity at concentrations up to 30 µM. In comparison, the IC_{50} for RTV was 0.6 nM when tested in parallel under the same assay conditions. These enzyme inhibition data indicate that COBI is not an inhibitor of the HIV-1 PR.

Inhibition of the Activity of Human Proteases

The potential inhibitory activity of COBI was evaluated against cathepsin. Unlike RTV, COBI did not exhibit any activity towards this enzyme.

In Vitro Antiviral Activity

There was no inhibition (100% activity remaining) of HIV replication in the presence of 30 µM COBI relative to the untreated control. The EC_{50} values of COBI in the presence of 40% human serum were >90 µM. None of the tested metabolites of COBI, M21, M26, and M31, were found to have HIV-1 antiviral activity, up to a concentration of 30 µM.

The antiviral activity of COBI was tested in PBMCs against a panel of 17 HIV-1 and 2 HIV-2 primary isolates. Different groups of HIV-1 (M, N, and O), as well as the most prevalent group M subtypes (A, B, C, D, E, F, and G), were represented among the tested isolates. There was no inhibition of HIV-1 replication in the presence of COBI. Ritonavir was used as a control and exhibited the expected level of antiviral activity across all tested isolates. Two HIV-2 isolates were also evaluated; no selective antiviral activity of COBI was observed against the tested isolates.

In Vitro Cytotoxicity

COBI was less cytotoxic (CC_{50} = 89 µM) than RTV (CC_{50} = 38 µM) in MT-2 cells and showed a level of cytotoxicity similar to RTV in HepG2 cells (CC_{50} of 44 µM and 64 µM, respectively).

Darunavir/Cobicistat Fixed Dose Combination

No *in vitro* virology studies have been performed with the DRV/COBI FDC. The resistance profile of DRV/COBI FDC is driven by DRV. Due to its lack of antiviral activity, COBI does not select any HIV resistance mutations.

Secondary pharmacology

TMC114-C153

This was a Phase 1, open-label, randomized, placebo- and active-controlled (moxifloxacin), 4-way crossover study to assess the cardiac safety of DRV (400-mg tablet formulation F001), together with rtv, in 40 healthy adults, with particular attention to the QT/QTcF interval duration and the influence of DRV/rtv on other electrocardiogram (ECG) parameters, such as QRS and PR intervals. Each subject received treatment in 4 sessions: DRV/rtv 1600/100 mg once daily for 7 days (Treatment A), DRV/rtv 800/100 mg twice daily for 7 days (Treatment B), moxifloxacin 400 mg once daily for 7 days (Treatment C), and placebo once daily for 7 days (Treatment D).

Eleven 12-lead time-matched triplicate ECGs on Day -1 (pre-treatment baseline), Day 1 (first dose), and Day 7 (last dose at steady-state) at 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12 hours after the morning dose of each treatment period plus 1 additional 12-lead triplicate ECG after 24 hours on Day 2 and Day 8 were recorded. Subsequent sessions were separated by a washout period of 7 days. All treatments were administered under fed conditions and pharmacokinetic data were obtained on days 1 and 7.

The Fridericia correction (QTcF) was used as the primary correction method for statistical evaluation of the QT interval. However, Bazett's correction (QTcB) and Sagie's (Framingham) correction (QTcS) were also employed

The primary statistical comparison was the maximum mean change vs placebo for the 1600/100 mg q.d. group using the Fridericia correction.

QTc data

Time-matched differences in QTcF were increased for DAR/RTV vs placebo at most time points.

On Day 1, the largest time-matched mean changes in QTcF vs placebo were observed at 3 h after 1600/100 mg and at 2 h after 800/100 mg with values of 3.0 ms and 2.9 ms, respectively.

On Day 7, the largest values time-matched mean changes in QTcF vs placebo were observed at 4 h post-dose in both DAR/RTV groups with values of 6.1 ms and 5.0 ms, respectively.

The upper two-sided 90% CIs on the time-matched mean changes vs placebo did not exceed 10 ms on either Day 1 or Day 7.

After moxifloxacin on Day 1 post-dose differences in QTcF *vs* placebo were 4.5 to 10 ms and Day 7 values were 5.5 to 14.1 ms. The time-matched difference *vs* pre-dose was 5.2 ms at 2 h post-moxifloxacin but –4.7 ms for placebo, giving a maximal difference of 9.9 ms.

At 4 h post-moxifloxacin on Day 7 the time-matched difference was 8.4 ms compared to –5.3 ms for placebo, giving a maximal difference of 13.7 ms.

The upper two-sided 90% CI on the mean difference in QTcF *vs* placebo were 12.19 ms and 16.82 ms on Days 1 and 7, respectively.

It was concluded that moxifloxacin was an appropriate positive control according to E14 ICH.

With 14 females (2 discontinued) and 26 males (2 discontinued) the small sample size in females gave less accurate estimates for the mean time-matched change vs pre-dose and wider CIs. On Day 7 at 3 and 4 h post-placebo the mean decrease in QTcF was more extreme in females than in males so the difference for DAR/RTV *vs* placebo was larger in females. However, there was little or no increase in QTcF *vs* pre-dose at around C_{max} on Day 7 for females given 1600 mg darunavir.

Data derived from application of QTcB, QTcS, individually linear (QTcIL), individually non-linear (QTcINL), trial specific linear (QTcL) and trial specific non-linear correction (QTcNL) have been summarised.

For 1600/100 mg q.d. the upper two-sided 90% CIs for the greatest observed changes vs placebo control remained below 10 ms for all QT corrections and for QT uncorrected on Day 1.

On Day 7 the upper 90% CI for QTcL, QTcS and uncorrected QT slightly exceeded 10 ms at 10.0, 10.4 and 10.9 ms, respectively, while that for QTcB was 12.9 ms at 4 hours after dosing. The upper bounds resulting from the linear model were < 10 ms except for QTcB at 11.8 ms at 4 hours after dosing.

For 800/100 mg b.i.d. only the two-sided 90% CI upper bound of QTcB and uncorrected QT on Day 7 exceeded 10 ms (12.7 ms at 2 h and 14.8 ms at 10 h after dosing, respectively). The upper bound of the two-sided 90% CI resulting from the linear mixed model was > 10 ms for uncorrected QT (10.2 ms at 10 h) but < 10 ms for QTcB (9.3 ms).

For moxifloxacin, two-sided 90% CIs' upper bounds of the maximum mean QT changes exceeded 10 ms at all time points (from 10.4 to 14.9 ms on Day 1 and 14.7 to 22.0 ms on Day 7). This was confirmed by the estimates resulting from the linear mixed model, for which upper bounds were above 10 ms for all QT corrections and uncorrected QT.

There were no QT values that exceeded 500 ms and no increases in QT larger than 60 ms.

Treatment-emergent increases of 30-60 ms (using QTcF) occurred in three (8%) subjects during moxifloxacin treatment but one with 800/100 mg b.i.d. and in none during other treatments.

Treatment-emergent prolonged QTc (i.e. to 450 ms/470 ms by gender) was seen for all corrections in one subject during moxifloxacin treatment and in two subjects based on QTcB data during 800/100 mg b.i.d.

Day 7 data showed a trend for greater maximum change in QTcF with higher darunavir and moxifloxacin plasma concentrations. Using a linear mixed model the observed and predicted time matched changes QTcF *vs* concentration gave a non-significant interaction between gender and concentration with a p-value of 0.064. The estimated slope of QTcF vs plasma darunavir was 0.000659 (90% CI 0.000184 to 0.001135) but the applicant pointed out that the relationship was shallow since for every 1000 ng/mL increase in darunavir concentration the predicted shift in QTcF is only 0.66 ms. At the mean maximum darunavir concentration observed (6599 ng/mL) the mean increase in QTcF was 2.2 ms (90% CI –2.0 to 6.3 ms).

PR interval data

Maximum increases in PR on Day 1 were similar between treatment groups but on Day 7 the DAR/RTV groups showed a higher maximum increase (12.2 and 14.7 ms) compared to placebo (8.9 ms). The overall mean change was higher in the DAR/RTV groups (3.3 and 5.7 ms) compared to placebo (0.3 ms). Similar conclusions can be drawn from the mean time-matched differences in PR versus Day –1.

The maximum time-matched change in PR interval *vs* placebo was found at 1 h post-dose on Day 7 of 800/100 mg b.i.d., when PR had increased by 6.3 ms. However, the Day 7 maximum change *vs* placebo in the 1600/100 mg q.d. group was observed before dosing (4.9 ms). In contrast, the largest mean changes vs placebo on Day 1 in the two DAR/RTV groups were 2.6 and 2.3 ms.

This was a Phase 1, open-label, randomized, placebo- and active-controlled (moxifloxacin), partially-blinded, 4-way crossover study to assess the cardiac safety of COBI (100- and 150-mg tablets) in 48 healthy adults. Subjects were randomized to 1 of 2 Williams squares, and then to 1 of 4 possible treatment sequences within each Williams square (6 subjects per treatment sequence). Treatments were separated by a 6-day washout period. Subjects received a single dose of the following treatments on Days 1, 8, 15, and 22 as follows:

Treatment A: COBI 250 mg (1 COBI 150-mg active tablet, 1 COBI 100-mg active tablet, and 1 placebo 150-mg tablet).

Treatment B: COBI 400 mg (2 COBI 150-mg active tablets, 1 COBI 100-mg active tablet).

Treatment C: Placebo control (2 placebo 150-mg tablets, 1 placebo 100-mg tablet).

Treatment D: Moxifloxacin 400 mg (1 moxifloxacin 400-mg tablet).

All treatments were administered under fed conditions within 5 minutes after a meal. Cobicistat exhibited nonlinear PK, with an approximately 2.1-fold increase in AUC_{∞} and a 1.8-fold increase in C_{max} following administration of COBI 400 mg relative to COBI 250 mg. Exposure to COBI (AUC and C_{max}) following administration of COBI 250 mg and 400 mg was higher than the steady-state exposure following administration of COBI 150 mg when administered once daily as a pharmacoenhancer (AUC_{24h} approximately 11,000 ng.h/mL; C_{max} approximately 1,500 ng/mL).

Table 20 PK Parameters of COBI Following Single-Dose Administration of 250 or 400 mg COBI (Study GS-US-216-0107)

Parameter	Mean (%CV); t_{max} and $t_{1/2,term}$: Median (Q1; Q3)	
	Treatment A COBI 250 mg	Treatment B: COBI 400 mg
N	48	48
t_{max}, h	3.50 (3.00; 4.00)	4.00 (3.50; 4.50)
C_{max}, ng/mL	2,301 (22.7)	4,027 (18.3)
AUC_{∞}, ng.h/mL	20,178 (35.0)	41,660 (28.4)
$t_{1/2,term}$, h	4.46 (3.76; 5.01)	4.64 (4.11; 5.53)
CL/F, mL/h	14,056 (39.1)	10,462 (32.5)

Q=quartile.

Evaluation of the baseline-adjusted mean differences between COBI 250 and 400 mg and placebo and their associated 2-sided 90% CIs demonstrated a lack of prolongation effect on the QTcF interval following COBI administration; the upper bounds of the 2-sided 90% CIs were < 10 ms at all time-points after dosing. The upper bounds of the 2-sided 90% CIs were also <10 ms for the COBI 250-mg and 400-mg doses at all timepoints for QT interval corrected for heart rate using population-specific correction factor and QT interval corrected for heart rate using subject-specific correction factor.

An upper bound of the 2-sided 90% CI for QT interval corrected for heart rate using the Bazett formula was >10 ms (10.1 ms) at a single time-point (12 hours) with the COBI 400 mg dose. No subject had an absolute QTc interval >480 ms at any post-dose assessment, or change from pre-dose baseline QTc >60 ms using any of the correction factors following any of the treatments. The lower bound of the 2-sided 90% CI for the mean difference between the positive control and placebo was >5 ms at more than 1 time-point after dosing, thereby establishing assay sensitivity.

According to the applicant, in the ART-naïve group of study GS-US-216-0130, in which subjects were treated with DRV/COBI 800/150 mg once daily co-administered as single agents in combination with 2 NRTIs, there was no apparent relationship between the decrease in log10 plasma viral load from baseline at Week 24 and DRV exposure. Virologic success (plasma viral load of <50 HIV-1 RNA copies/mL) was comparable across the first to third DRV exposure quartiles (93.8% to 97.2% for AUC_{24h} and 93.7% to 97.3% for C_{0h}) and was modestly lower in the fourth (i.e., highest) DRV

exposure quartile (86.2% for AUC_{24h} and 86.4% for C_{0h}). Apparently, a similar result was observed in study TMC114-C211, in which ART-naïve HIV-1 infected subjects were treated with DRV/rtv 800/100 mg once daily co-administered as single agents in combination with a fixed background regimen of TDF and FTC. There was no apparent relationship between the PK of DRV and the decrease in log10 viral load from baseline at Week 48 or virologic response, defined as a plasma viral load of <50 or <400 HIV-1 RNA copies/mL. A GAM analysis, exploring the relationship between DRV C_{0h} and virologic response in study TMC114-C211, showed no indication that lower values within the observed DRV C_{0h} range lead to lower estimated virologic response. The mean predicted virologic response was 92.8% in the total population.

In study GS-US-216-0130, a GAM analysis was used to generate predictions of a smoothed spline for virologic response (defined as a plasma load of <50 HIV-1 RNA copies/mL) at Week 24 by DRV AUC_{24h} or C_{0h} in ART-naïve subjects. Inverse relationships were observed among ART-naïve subjects for both DRV AUC_{24h} and C_{0h}. This inverse relationship disappeared at week 48 as virologic response was comparable across all the different quartiles of exposure with no significant effect of exposure on response. This inverse relationship has previously been noted and is not considered to be clinically relevant.

Inverse exposure-response relationships for virologic success have been observed previously in ART-experienced subjects treated with DRV/rtv 800/100 mg once daily co-administered as single agents. In study TMC114-C229, the decrease in log10 viral load from baseline at Week 48 tended to be smaller in subjects with higher AUC_{24h} values, while no relevant relationship between AUC_{24h} and the decrease in log_{10} viral load was observed in the DRV/rtv 600/100 twice daily group. A similar trend was seen for virologic success, defined as a plasma viral load of <50 HIV-1 RNA copies/mL, at Week 48.

A GAM analysis exploring the relationship between DRV C0h and virologic response in study TMC114-C229 showed an inverse relationship between DRV C_{0h} and virologic response in the ART-experienced HIV-1 infected population of study TMC114-C229; virologic response was somewhat lower in the highest 2 deciles of the observed DRV C_{0h} range, suggesting a counterintuitive. However, in the first 8 deciles (DRV C_{0h} values up to 2,961ng/mL), there was no clear relationship between DRV C0h and virologic response at the observed rate, and variability was higher in the last 2 deciles.

Because DRV C_{tau} was notably lower when co-administered with COBI relative to rtv in the Phase 1 studies (ie, GS-US-0216-0115 and TMC114IFD1001), the impact of a potential reduction of DRV C_{0h} was further explored using the GAM. The same model used to predict virologic response was used to simulate a similar population with a 10%, 20%, 30%, 40%, and50% reduction in DRV C_{0h}. Based on this analysis, a reduction in DRV C0h of up to 50% did not negatively impact the mean predicted response.

2.4.4. Discussion on clinical pharmacology

In order to characterise the pharmacokinetics of this fixed dose combination (FDC), the applicant relies on studies conducted with the single agents, studies conducted with Darunavir (DRV) and ritonavir (rtv), a bioequivalence study of the FDC and single dose DRV with COBI and a bioequivalence study of DRV co-administered with COBI and DRV with rtv.

This approach is considered acceptable in principle as the pharmacokinetic of the single agents have previously been characterised.

DRV co-administered with COBI was demonstrated to be bioequivalent to DRV co-administered with rtv in study GS-US-216-0115, the 90% confidence interval for AUC_{tau} and C_{max} lie within 80-125%however the C_{tau} for DRV when co-administered with cobi was lower than DRV

o-administered with rtv the reason for this is not absolutely clear but not considered to be an issue (this was discussed during the assessment of cobicistat and will not be pursued any further).

Study TMC114IFD1001 also demonstrated bioequivalence of two FDC formulations of DRV + Cobi and DRV + rtv.

Additionally, study TMC114IFD1003 demonstrated bioequivalence of a FDC formulation with 2X 400mg DRV and 150 mg COBI administered as single agents.

The pharmacokinetic characteristics of DRV alone, DRV+rtv and COBI as have previously been well-characterised and there are no particular issues to highlight.

No drug-drug interaction studies have been performed using DRV/Cobi FDC tablet formulations or DRV co-administered with Cobi as separate agents and the applicant bases the drug interaction potential on the interactions observed with each single agent and DRV when co-administered with rtv. This is considered to be acceptable as the differences between Cobi and rtv appear to have been taken into account.

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease (PR) and it selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. While Cobicistat a structural analogue of RTV and a potent mechanism-based inhibitor of human hepatic microsomal cytochrome P450 (CYP) 3A activity). Cobicistat is devoid of anti-HIV activity and exhibits no antiviral activity against 17 HIV-1 and 2 HIV-2 primary isolates.

The results of study TMC114-C153 suggest that darunavir causes small increases in QTc and PR intervals when compared to placebo which are probably not clinically relevant. For COBI the results of study GS-US-216-0107 demonstrated modest increases in PR interval at around 3.5 h post-dose which are probably not clinically important or relevant changes.

One topic that merits attention is the further reduction of DRV exposure in case of co-medication with inductive effect on CYP3A4, such as efavirenz. Co-administration is not recommended because of both reduced DRV and COBI exposures. When switching from an EFC containing regimen to DRV/COBI the inductive effect of efavirenz could affect exposure to DRV/COBI. Two categories of patients who will switch from efavirenz to DRV/cobi based regimens must be considered: 1) patients intolerant to efavirenz but with virologic suppression, and 2) patients failing on efavirenz without virologic suppression. For the first category the concentration of DRV is far above the EC_{50} regardless of waning induction by EFV. In combination with the effect of the backbone ARVs DRV concentration will be sufficient to maintain virologic suppression.

The second patient category has been studied in the ODIN study with convincing results if no DRV-associated mutations are present and viral load < 100,000 copies/ml. Although efficacy data was not provided separately from this particular subgroup of virologic failures on EFV, the efficacy in the once daily DRV arm in the ODIN study is comforting. The mean DRV C0h in HIV-infected subjects in study GS-US-216-0130 was >37-fold above the protein binding corrected EC_{50} for wild-type virus (55 ng/mL). It is anticipated that the DRV exposure will be lowered by no more than 15-30%. Therefore, the DRV concentration above the EC_{50} is probably sufficient in patients with treatment failure on EFV, with the known caveats (specific DRV mutations and viral load restriction) that are now pronounced in the SmPC for this patient category.

2.4.5. Conclusions on clinical pharmacology

Due to pharmaco-enhancement of liver enzymes by COBI the exposure of DRV is similar to that when RTV is used as pharmaco-enhancer of DRV. From the PK studies is was demonstrated that DRV C_{tau} was ~30% lower.

The Applicant demonstrated during the application of COBI as a separate medicinal product that decreases of C_{tau} were not associated with virologic outcome, neither in the registration studies – when RTV was used - nor in the currently submitted study GS-US-216-0130 with COBI. This is considered acceptable.

Although EFV-containing regimens through induction of CYP3A4 could reduce DRV exposure levels, this is unlikely to be problematic in case of switch from EFV-containing regimens to DRV/COBI in the first weeks after switch. Although the DRV exposure could be reduced, the DRV concentration above the EC50 is likely to be sufficient in patients with treatment failure on EFV, with the known caveats (specific DRV mutations and viral load restriction) that are now pronounced in the SmPC for this patient category.

Efficacy is not affected by differences in DRV exposure, and also safety is not. There was no evidence that COBI exposures were higher and there is no evidence of an association between COBI plasma concentrations and the presence of rash, drug hypersensitivity or discontinuation due to an adverse event (AE).

2.5. Clinical efficacy

The clinical program for DRV/COBI FDC is primarily based on the comprehensive development programs of the 2 individual compounds and on the pharmacokinetic bridging clinical program. As the DRV/COBI FDC 800/150 mg is indicated as a 'substitution indication' of an already approved regimen, no comparative efficacy study was conducted. The efficacy data provided in support of DRV/COBI FDC in adult subjects consists of the following:

(1) A Phase 1 study TMC114IFD1001, investigating the relative oral bioavailability of 2 FDC formulations (G003 and G004) of DRV/COBI 800/150 mg once daily and that of DRV/rtv 800/100 mg once daily co-administered as single agents under fed conditions.

(2) A Phase 1 study TMC114IFD1003, assessing the bioequivalence of DRV when co-administered with COBI either as the FDC (formulation G006) or the single agents under fed and fasted conditions.

(3) An on-going Phase 3b, open-label, single-arm study GS-US-216-0130 assessing safety (primary objective), efficacy and pharmacokinetic parameters (secondary objectives) in HIV-1 infected adult subjects treated with DRV/COBI 800/150 mg once daily co-administered as single agents for at least 48 weeks.

(4) A brief summary of the virologic response and immunologic benefit of DRV/rtv 800/100 mg once daily as established in the historical studies TMC114-C211 (also referred to as ARTEMIS) in antiretroviral therapy (ART)-naïve HIV-1 infected adult subjects, and TMC114-C229 (also referred to as ODIN) in ART-experienced HIV-1 infected adult subjects with no DRV RAMs are also provided in support of DRV/COBI FDC.

Cobistat

The proof-of-concept study (GS-US-216-0115) and the pharmacokinetic bridging studies TMC114-IFD1001 and TMC114IFD1003 provide evidence of the primary pharmacodynamics properties of COBI as a pharmacokinetic enhancer of DRV.

2.5.1. Main study

GS-US-216-0130

A Phase 3b open-label, single-arm, multicenter study in HIV-1 infected, ART-naïve adult subjects or ART-experienced adult subjects with no DRV RAMs.

Methods

Study Participants

A total of 314 subjects were enrolled, and 313 subjects received at least 1 dose of study medication DRV/COBI 800/150 mg once daily co-administered as single agents. Of these 313 subjects, 295 (94.2%) were ART-naïve and 18 (5.8%) were ART-experienced. Subjects were considered treatment-naïve if they had never received treatment with an approved or investigational ARV drug. Subjects were considered treatment-experienced if they had been on a stable ARV regimen for at least 12 weeks prior to screening. After 48 weeks of treatment, subjects were given the option to participate in an open-label rollover extension of the study to receive COBI, DRV, and investigator-selected NRTIs, and attend study visits every 12 weeks until COBI becomes commercially available, or until Gilead elects to terminate development of COBI. Subjects who completed the Week-48 visit and did not wish to participate in the rollover part of the study were required to complete a follow-up visit 30 days after the Week-48 visit.

Eligibility criteria

Subjects enrolled in this study were HIV-1 infected subjects, ≥ 18 years of age, who were either treatment-naive (no ARV drugs for any length of time) or treatment-experienced (stable ARV treatment for at least 12 weeks prior to screening) and met the following criteria:

Plasma HIV-1 RNA levels ≥ 1000 copies/mL at screening

Screening genotype report shows full sensitivity to two nucleoside analogue reverse transcriptase inhibitors (NRTIs) and none of the following DRV-associated resistance mutations (RAMs): V11I, V32I, L33F, I47V, I50V, I54M, I54L, T74P, L76V, I84V or L89V.

Treatments

DRV/COBI 800/150 mg once daily co-administered as single agents plus 2 fully active investigator-selected NRTIs selected after resistance testing at screening. In subjects with the M184V/I reverse transcriptase mutation present at screening, FTC or lamivudine (3TC) could be included as a third (not-fully active) NRTI for the purpose of maintaining the M184V mutation.

Objectives

Primary objective

To evaluate the safety and tolerability of DRV/COBI 800/150 mg plus 2 NRTIs in the studied population through 24 weeks of treatment.

Secondary objectives

- 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
- To assess the change from baseline in CD4+ cell count at Weeks 24 and 48.

Outcomes / endpoints

Primary efficacy endpoint

The proportion of subjects who reached HIV-1 RNA <50 copies/mL at Week 24 and 48 using the snapshot analysis.

Safety endpoint

The primary safety endpoint is adverse events and clinical laboratory tests through 24 weeks of treatment.

PK

The population pharmacokinetics of darunavir and cobicistat will be explored.

Virology:

Analysis of the development of genotypic and phenotypic resistance in subjects experiencing virologic failure.

Results

Participant flow

Table 21 GS-US-216-0130: Disposition of Subjects Through Week 24 (All Screened Subjects)

Subject Disposition	Treatment-Naive (N = 361)	Treatment-Experienced (N = 36)	Total (N = 397)
Subjects Screened[a, b, c]	361	36	397
Screen Failures	65	18	83
Subjects Enrolled in Study	296	18	314
Subjects Enrolled in Study But Never Dosed	1	0	1
Subjects in the Full Analysis Set[d]	295	18	313
Subjects still on Study Drug up to the Week 24 Analysis Data Cut Date	259 (87.8%)	15 (83.3%)	274 (87.5%)
Subjects still on Study Drug through the Week 24 Visit Window	259 (87.8%)	15 (83.3%)	274 (87.5%)
Subjects Prematurely Discontinuing Study Drug prior to the Week 24 Analysis Data Cut Date	36 (12.2%)	3 (16.7%)	39 (12.5%)
Reasons for Prematurely Discontinuing Study Drug			
Adverse Event	15 (5.1%)	0	15 (4.8%)
Death	0	0	0
Pregnancy[e]	0	0	0
Lack of Efficacy	0	0	0
Investigator's Discretion	1 (0.3%)	0	1 (0.3%)
Withdrew Consent	4 (1.4%)	1 (5.6%)	5 (1.6%)
Lost to Follow-Up	9 (3.1%)	2 (11.1%)	11 (3.5%)
Subject Noncompliance	6 (2.0%)	0	6 (1.9%)
Protocol Violation	1 (0.3%)	0	1 (0.3%)
Study Discontinued by Sponsor	0	0	0
Subjects still in Study up to the Week 24 Analysis Data Cut Date	267 (90.5%)	15 (83.3%)	282 (90.1%)
Subjects still in Study through the Week 24 Visit Window	267 (90.5%)	15 (83.3%)	282 (90.1%)
Subjects Prematurely Discontinuing from Study prior to the Week 24 Analysis Data Cut Date	28 (9.5%)	3 (16.7%)	31 (9.9%)
Reasons for Prematurely Discontinuing from Study			
Adverse Event	9 (3.1%)	0	9 (2.9%)
Death	0	0	0

Pregnancy	1 (0.3%)	0	1 (0.3%)
Lack of Efficacy	0	0	0
Investigator's Discretion	1 (0.3%)	0	1 (0.3%)
Withdrew Consent	4 (1.4%)	1 (5.6%)	5 (1.6%)
Lost to Follow-Up	9 (3.1%)	2 (11.1%)	11 (3.5%)
Subject Noncompliance	3 (1.0%)	0	3 (1.0%)
Protocol Violation	1 (0.3%)	0	1 (0.3%)
Study Discontinued by Sponsor	0	0	0
Subjects in the PK Analysis Set[f]	284 (96.3%)	17 (94.4%)	301 (96.2%)
Subjects in the PK Substudy Analysis Set[f]	57 (19.3%)	3 (16.7%)	60 (19.2%)

a All screened subjects: those who signed the informed consent form.

b All percentages are based on the number of subjects in the full analysis set (subjects who took at least one dose of study drug).

c Subjects completed 24 weeks of study if (date of last clinical visit [eg, excluding follow up visit] - Study Day 1) + 1 is ≥ 141 days.

d Full Analysis Set includes subjects who were enrolled into the study, received at least one dose of study drugs (DRV+COBI).

e Subject 0091-4067 discontinued the study drug due to an AE. The subject elected to continue attending study visits; however, was later found to be pregnant and discontinued the study due to pregnancy

f PK analysis sets for DRV and COBI will include subjects treated with study drugs who have respective, evaluable DRV and COBI PK data.

Programming Details: .../version2/prog/t-disposit.sas v9.2 09NOV2012:13:41

Conduct of the study

A total of 35 protocol deviations occurred in 31 subjects during the study. Of the 31 subjects, 2 had 2 deviations and 1 had 3 deviations. The majority of deviations (15 of 35) were for incorrect dispensing/dosing of study drugs. Deviations were proportionally distributed among study centres. A total of 15 subjects were incorrectly dispensed/dosed study drugs, 14 were in the treatment-naive cohort and 13 achieved virologic success according the FDA Snapshot algorithm. A total of 9 subjects had procedural protocol deviations. The majority of these subjects had retesting of required laboratory tests out of window. Subjects were retested as soon as possible and were not discontinued from the study.

A total of 8 subjects violated at least 1 eligibility criterion. All of these violations were identified after treatment had commenced. One subject was asked to come in for an ESDD visit and a 30-day follow-up visit due to an exclusionary eGFR. All other subjects were not discontinued from the study.

Baseline data

The majority of subjects in the treatment-naive cohort were male (266 of 295 subjects,90.2%). The mean age was 36 years (range, 18 to 72 years), most were white (176 of 295 subjects, 59.7%) or black (101 of 295 subjects, 34.2%), and non-Hispanic/Latino (231 of 295 subjects, 78.3%). The mean value for BMI at baseline was 26.2 kg/m2. In the treatment-experienced cohort, 13 of 18 subjects (72.2%) were male. The mean age was 45 years (range, 22 to 69 years), most were white (11 of 18 subjects, 61.1%) or black (7 of 18 subjects, 38.9%), and non-Hispanic/Latino (14 of 18 subjects, 77.8%). The mean value for BMI at baseline was 25.6 kg/m2.

Baseline disease characteristics

For subjects in the treatment naive cohort, the mean (SD) baseline HIV-1 RNA value was 4.8 (0.76) log10 copies/mL, CD4 cell count was 378.2 (199.94) cells/µL, and CD4% was 22.6% (9.99%). The most common HIV risk factor category was homosexual sex (238 of 295 subjects, 80.7%). The majority of subjects had asymptomatic HIV-1 infection (241 of 295 subjects, 81.7%), 26 of 295 subjects (8.8%) had symptomatic HIV-1 infection, and 28 of 295 subjects (9.5%) were diagnosed with AIDS. A small percentage of subjects were HBsAg positive (1.7%, 5 of 295 subjects) or HCV seropositive (2.4%, 7 of 295 subjects). The mean (SD) baseline $eGFR_{CG}$ (calculated using observed

body weight) was 119.0 (28.71) mL/min, the mean (SD) baseline eGFRMDRD was 99.3 (19.73) mL/min/1.73m2, and the mean (SD) baseline cysGFR was 97.6 (21.87) mL/min/1.73m^2.

For subjects in the treatment-experienced cohort, the mean (SD) baseline HIV-1 RNA value was 4.8 (1.04) log10 copies/mL, CD4 cell count was 197.8 (214.30) cells/µL, and CD4% was 11.9% (10.25%). At the time of initial ARV treatment, the CD4 cell count was 229.6 (225.89) and the HIV-1 RNA value was 5.1 (0.87) log10 copies/mL. The mean (SD) number of years since HIV diagnosis in the treatment-experienced cohort was 10.8 (7.13). The most common HIV risk factor category was homosexual sex (9 of 18 subjects, 50.0%).

The majority of subjects had asymptomatic HIV-1 infection (10 of 18 subjects, 55.6%),

Two of 18 subjects (11.1%) had symptomatic HIV-1 infection, and 6 of 18 subjects (33.3%) were diagnosed with AIDS. No subjects were HBsAg positive and 1 subject was HCV seropositive (5.6%). The mean (SD) baseline $eGFR_{CG}$ (calculated using observed body weight) was 103.6 (37.77) mL/min, the mean (SD) baseline eGFRMDRD was 92.5 (19.09) mL/min/1.73m2, and the mean (SD) baseline cysGFR was 81.5 (25.80) mL/min/1.73m^2.

Table 22 GS-US-216-0130: Baseline HIV Disease Characteristics (Full Analysis Set)

Disease Characteristic[a]	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Baseline CD4 (cell/mm^3)			
N	295	18	313
Mean (SD)	378.2 (199.94)	197.8 (214.30)	367.8 (204.79)
Median	370.0	107.0	361.0
Q1, Q3	249.0, 495.0	42.0, 294.0	239.0, 487.0
Min, Max	6.0, 1473.0	5.0, 643.0	5.0, 1473.0
Baseline CD4 Cell Count Category			
<= 50	17 (5.8%)	5 (27.8%)	22 (7.0%)
51 to <= 200	30 (10.2%)	7 (38.9%)	37 (11.8%)
201 to <= 350	85 (28.8%)	2 (11.1%)	87 (27.8%)
351 to <= 500	94 (31.9%)	1 (5.6%)	95 (30.4%)
> 500	69 (23.4%)	3 (16.7%)	72 (23.0%)
Baseline CD4 (%)			
N	295	18	313
Mean (SD)	22.6 (9.99)	11.9 (10.25)	21.9 (10.29)
Median	23.8	7.8	23.2
Q1, Q3	15.5, 29.5	3.8, 19.3	14.8, 29.1
Min, Max	0.8, 47.4	0.8, 30.6	0.8, 47.4
CD4 Cell Count at Initial ARV Treatment (cells/µL)			
N		7	
Mean (SD)		229.6 (225.89)	
Median		199.0	
Q1, Q3		60.0, 293.0	
Min, Max		44.0, 700.0	
Baseline HIV-1 RNA (log_{10} copies/mL)			
N	295	18	313
Mean (SD)	4.8 (0.76)	4.8 (1.04)	4.8 (0.78)
Median	4.8	5.0	4.8
Q1, Q3	4.2, 5.3	4.0, 5.5	4.2, 5.3
Min, Max	2.6, 7.0	2.7, 6.8	2.6, 7.0
Baseline HIV-1 RNA Category			
≤ 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%)
HIV-1 RNA at Initial ARV Treatment (log_{10} copies/mL)[c]			
N		5	
Mean (SD)		5.1 (0.87)	
Median		5.5	
Q1, Q3		4.2, 5.8	
Min, Max		4.1, 5.9	
Years Since HIV Diagnosis[c]			
N		18	
Mean (SD)		10.8 (7.13)	
Median		8.5	
Q1, Q3		6.0, 14.0	
Min, Max		2.0, 24.0	
Years Since Start of First HIV Treatment[c]			
N		16	
Mean (SD)		7.5 (5.06)	
Median		7.0	
Q1, Q3		4.0, 10.5	
Min, Max		1.0, 19.0	

Disease Characteristic[a]	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
HIV Disease Status			
Asymptomatic	241 (81.7%)	10 (55.6%)	251 (80.2%)
Symptomatic HIV Infection	26 (8.8%)	2 (11.1%)	28 (8.9%)
AIDS	28 (9.5%)	6 (33.3%)	34 (10.9%)
HIV Risk Factors			
Heterosexual Sex	69 (23.4%)	6 (33.3%)	75 (24.0%)
Homosexual Sex	238 (80.7%)	9 (50.0%)	247 (78.9%)
IV Drug Use	3 (1.0%)	1 (5.6%)	4 (1.3%)
Transfusion	0	0	0
Vertical Transmission	0	1 (5.6%)	1 (0.3%)
Other	1 (0.3%)	0	1 (0.3%)
Unknown	4 (1.4%)	1 (5.6%)	5 (1.6%)
HBV Surface Antigen Status			
Positive	5 (1.7%)	0	5 (1.6%)
Negative	289 (98.0%)	18 (100.0%)	307 (98.1%)
Undetermined	1 (0.3%)	0	1 (0.3%)
HCV Antibody Status			
Positive	7 (2.4%)	1 (5.6%)	8 (2.6%)
Negative	288 (97.6%)	17 (94.4%)	305 (97.4%)

Full Analysis Set includes subjects who were enrolled into the study, received at least one dose of study drugs (DRV+COBI).

Only applicable to subjects in the treatment-experienced cohort.

Programming Details: .../version2/prog/t-basechar.sas v9.2 09NOV2012:13:41

Of the 314 subjects who were enrolled, 313 were included in the full analysis set (295 in the treatment-naive cohort and 18 in the treatment-experienced cohort). The PK and PK substudy sets were comprised of 284 and 57 subjects from the treatment-naive cohort and 17 and 3 subjects from the treatment-experienced cohort, respectively.

Table 23 GS-US-216-0130: Demographics and Baseline Characteristics (Full Analysis Set)

Characteristic	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Age (Years)			
N	295	18	313
Mean (SD)	36 (10.3)	45 (10.9)	36 (10.6)
Median	34	48	35
Q1, Q3	27, 43	38, 52	28, 45
Min, Max	18, 72	22, 69	18, 72
Sex			
Male	266 (90.2%)	13 (72.2%)	279 (89.1%)
Female	29 (9.8%)	5 (27.8%)	34 (10.9%)
Race			
White	176 (59.7%)	11 (61.1%)	187 (59.7%)
Black or African Heritage	101 (34.2%)	7 (38.9%)	108 (34.5%)
American Indian or Alaska Native	4 (1.4%)	0	4 (1.3%)
Asian	4 (1.4%)	0	4 (1.3%)
Native Hawaiian or Pacific Islander	2 (0.7%)	0	2 (0.6%)
Other	8 (2.7%)	0	8 (2.6%)
Ethnicity			
Hispanic or Latino	64 (21.7%)	4 (22.2%)	68 (21.7%)
Not Hispanic or Latino	231 (78.3%)	14 (77.8%)	245 (78.3%)
Baseline Weight (kg)			
N	295	18	313
Mean (SD)	80.6 (14.22)	78.0 (20.76)	80.4 (14.64)
Median	80.3	75.3	79.9
Q1, Q3	70.5, 89.8	67.9, 86.6	70.5, 89.3
Min, Max	51.4, 147.3	41.7, 128.1	41.7, 147.3
Baseline Height (cm)			
N	295	18	313
Mean (SD)	175.5 (8.41)	173.9 (8.08)	175.4 (8.39)
Median	175.3	175.3	175.3
Q1, Q3	170.2, 181.6	172.7, 177.8	170.2, 180.3
Min, Max	149.9, 210.8	152.4, 185.4	149.9, 210.8
Baseline Body Mass Index (kg/m^2)[a]			
N	295	18	313
Mean (SD)	26.2 (4.21)	25.6 (6.32)	26.1 (4.35)
Median	25.9	24.3	25.7
Q1, Q3	23.0, 28.8	21.5, 28.2	23.0, 28.8
Min, Max	16.5, 45.3	18.0, 43.0	16.5, 45.3

a Body Mass Index (kg/m^2) = Weight (kg)/[(Height (cm)/100)^2].

Programming Details: .../version2/prog/t-demog.sas v9.2 09NOV2012:13:41

Outcomes and estimation

Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 and 48; Snapshot Analysis

Virologic success at Week 24 was achieved by 83.7% (247 of 295 subjects) of subjects in the treatment naive cohort. Virologic success at Week 48 was achieved by 82.7% (244 of 295 subjects). The percentage of subjects with virologic failure at Week 24 was 9.8% (29 of 295 subjects) and the percentage of subjects with no virologic data in the Week 24 window was 6.4% (19 of 295 subjects).

For the treatment-naïve subjects, of the 29 subjects who were virologic failure at Week 24, 9 gained response by Week 48. As 17 subjects of the 19 subjects with no virologic data at Week 24 discontinued the study before Week 24, the outcome of these subjects remained unchanged by Week 48.

The number of subjects in the treatment-experienced cohort was small (n = 18). In this cohort, virologic success was achieved by 61.1% (11 of 18 subjects) at Week 24 and by 50.0% (9 out of 18 subjects) at Week 48. The percentage of subjects with virologic failure at Week 24 was 38.9% (7 of 18 subjects) and no subjects had no virologic data in the Week 24 window. Of the 5 subjects with virologic failure at Week 24 due to HIV-1 RNA ≥ 50 copies/mL, 1 was lost to follow up, 3 did not have additional HIV-1 RNA levels after Week 24 at the data cut-off date for this CSR, and 1 subject had < 50 copies/mL at Week 36.

For the treatment-experienced subjects, of the 7 virologic failures at Week 24, 1 subject became a responder at Week 48.

Table 24 GS-US-216-0130: Treatment Outcomes at Week 24 for HIV-1 RNA Cut-off at 50 copies/mL (Snapshot Analysis; Full Analysis Set)

HIV-1 RNA Category	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Virologic Success at Week 24			
HIV-1 RNA < 50 copies/mL	247 (83.7%)	11 (61.1%)	258 (82.4%)
95% CI[a]	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 Study Drug Due to Lack of Efficacy	0	0	0
Discontinued Study Drug 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	19 (6.4%)	0	19 (6.1%)
Discontinued Study Drug Due to AE/Death	14 (4.7%)	0	14 (4.5%)
Discontinued Study Drug 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 Drug	2 (0.7%)	0	2 (0.6%)

a 95% CI is the 2-sided exact 95% CI for binomial proportions.

Table 25 GS-US-216-0130: Treatment Outcomes at Week 48 for HIV-1 RNA Cut-off at 50 copies/mL (Snapshot Analysis; Full Analysis Set)

	Treatment-Naive (N=295)	Treatment-Experienced (N=18)	Total (N=313)
Virologic Success at Week 48			
HIV-1 RNA < 50 copies/mL	244 (82.7%)	9 (50.0%)	253 (80.8%)
95% CI	77.9% to 86.8%	26.0% to 74.0%	76.0% to 85.0%
Virologic Failure at Week 48	24 (8.1%)	9 (50.0%)	33 (10.5%)
HIV-1 RNA >= 50 copies/mL	9 (3.1%)	5 (27.8%)	14 (4.5%)
Discontinued Study Drug Due to Lack of Efficacy	0	0	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA >= 50 copies/mL	15 (5.1%)	4 (22.2%)	19 (6.1%)
No Virologic Data in Week 48 Window	27 (9.2%)	0	27 (8.6%)
Discontinued Study Drug Due to AE/Death	15 (5.1%)	0	15 (4.8%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	10 (3.4%)	0	10 (3.2%)
Missing Data During Window but on Study Drug	2 (0.7%)	0	2 (0.6%)

Proportion of Subjects with HIV-1 RNA < 50 copies/mL at Week 24 and Week 48 by baseline viral load (≤ 100,000 copies/mL vs. >100,000 copies/mL); Snapshot Analysis

In the treatment-naive cohort, the percentage of subjects who achieved virologic success at Week 24 was higher in subjects who had a baseline viral load of ≤ 100,000 copies/mL (87.9% [152 of 295 subjects]) compared with those who had a baseline viral load of > 100,000 copies/mL (77.9% [95 of 122]).

In the Week-48 analysis, there was a 2.7% difference in the response rates between subjects with a baseline viral load ≤ 100,000 copies/mL (83.8%) versus subjects with a baseline viral load >100,000 copies/mL (81.1%).

Table 26 GS-US-216-0130: Treatment Outcomes at Week 24 and 48 by Baseline Viral Load Category (Snapshot Analysis; Full Analysis Set)

	Week 24 (Week-24 Analysis)		Week 48 (Week-48 Analysis)	
	Treatment-naïve N=295		Treatment-naïve N=295	
HIV-1 RNA Category, Number of Subjects, n (%)	HIV-1 RNA ≤100,000 copies/mL N=173	HIV-1 RNA >100,000 copies/mL N=122	HIV-1 RNA ≤100,000 copies/mL N=173	HIV-1 RNA >100,000 copies/mL N=122
Virologic Response				
HIV-1 RNA <50 Copies/mL	**152 (87.9)**	**95 (77.9)**	**145 (83.8)**	**99 (81.1)**
95% CIs[a]	82.0 to 92.3	69.5 to 84.9	77.5 to 89.0	73.1 to 87.7
Virologic Failure	**6 (3.5)**	**23 (18.9)**	**8 (4.6)**	**16 (13.1)**
HIV-1 RNA ≥50 Copies/mL	1 (0.6)	16 (13.1)	2 (1.2)	7 (5.7)
Discontinued due to Lack of Efficacy	0	0	0	0
Discontinued due to Other Reasons and Last Available HIV-1 RNA ≥50 Copies/mL	5 (2.9)	7 (5.7)	6 (3.5)	9 (7.4)
No Virologic Data in Week 24 or 48 Window[b]	**15 (8.7)**	**4 (3.3)**	**20 (11.6)**	**7 (5.7)**

N=total number of subjects; n=number of observations.
[a] 95% CI is the 2-sided exact 95% CI for binomial proportions.
[b] Week-24 window: 20-30 weeks; Week 48 window: 42-54 weeks.

The Applicant highlighted that in study TMC114-C211 (ARTEMIS study), discussed under supportive studies, the difference in response between patients with a baseline viral load ≤ 100,000 copies/mL versus subjects with a baseline viral load >100,000 copies/mL too decreased with time, although at Week 48 study baseline viral load remained predictive of response: 85.8% (194/226) in the patients with < 100,000 copies/ml and 79.5% (93/117) in patients with > 100,000 copies/ml at baseline. These results indicate that patients with higher viral loads at start therapy possibly respond slower.

Achievement and Maintenance of HIV-1 RNA < 50 copies/mL Through Week 24; TLOVR analysis

The treatment outcomes through week 24 according to the time to loss of virologic response (TLOVR) analysis as initially submitted are presented in table 27 below.

Table 27 Treatment outcomes through Week 24 for HIV-1 RNA Cut-off at 50 copies/mL (TLOVR Analysis) Full Analysis Set (Submitted with initial application)

	Treatment-Naive (N=295)	Treatment-Experienced (N=18)	Total (N=313)
Responder	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	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%)
Drug Discontinuation Due to Lack of Efficacy	0	0	0
Death	0	0	0
Drug Discontinuation Due to AEs	15 (5.1%)	0	15 (4.8%)
Drug Discontinuation Due to Other Reasons	18 (6.1%)	3 (16.7%)	21 (6.7%)

The treatment outcomes through week 24 according to the time to loss of virologic response (TLOVR) analysis as submitted with the reponse to LoQ are presented in Table 28 .

Table 28 Treatment outcomes through Week 24 for HIV-1 RNA Cut-off at 50 copies/mL (TLOVR Analysis) Full Analysis Set (submitted in response to D120 LoQ)

	Treatment-Naive (N=295)	Treatment-Experienced (N=18)	Total (N=313)
Responder	247 (83.7%)	9 (50.0%)	256 (81.8%)
95% CI	79.0% to 87.8%	26.0% to 74.0%	77.1% to 85.9%
Virologic Failure	15 (5.1%)	6 (33.3%)	21 (6.7%)
Rebound	2 (0.7%)	0	2 (0.6%)
Never Suppressed through Week 24	13 (4.4%)	6 (33.3%)	19 (6.1%)
Drug Discontinuation Due to Lack of Efficacy	0	0	0
Death	0	0	0
Drug Discontinuation Due to AEs	15 (5.1%)	0	15 (4.8%)
Drug Discontinuation Due to Other Reasons	18 (6.1%)	3 (16.7%)	21 (6.7%)

These are not consistent with each other. The response in the Treatment Naïve arm as seen in table 27 seems to mimic the snapshot analysis presented in table 24, and is unlikely the TLOVR analysis. It is unclear whether the Week-48 TLOVR analysis presented with de response to the D120 LoQ can be relied on. The Applicant was asked to check the TLOVR analyses submitted with the Week-48 efficacy analyses in their response and either confirm that they are correct, and if so then explain the discrepancy with the Week-24 TLOVR analyses submitted with the initial application, or if not then to submit the correct analyses. The difference in virologic response (time to loss of virologic response [TLOVR]) at the Week-24 time point in the Week-24 analysis (240 subjects, 76.7%) and the Week-24 time point in the Week-48 analysis (256 subjects, 81.8%) was due to 16 subjects who had achieved human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) <50 copies/mL at the Week-24 visit but for whom response was not yet confirmed (ie, HIV-1 RNA <50 copies/mL at 2 consecutive visits) at time of the Week-24 analysis. After receipt of the confirmation sample, these 16 subjects were accordingly classified as Week 24 responders / no responders in the Week-48 analysis.

A total of 78.6% of subjects (232 of 295 subjects) in the treatment-naive cohort achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 24 and were considered responders. The percentage of subjects classified as non-responders (those with virologic failure) was 10.2% (30 of 295 subjects). Reasons for virologic failure included viral rebound (0.7% [2 of 295 subjects]) and never suppressed through Week 24 (9.5% [28 of 295 subjects]). A total of 5.1% (15 of 295 subjects)

and 6.1% (18 of 295 subjects) of subjects were defined as non-responders due to study drug discontinuation due to AE and other reasons, respectively.

In the treatment naive-cohort, the percentage of responders at Week 24 was higher in subjects who had a baseline viral load of ≤ 100,000 copies/mL (83.8% [145 of 295 subjects]) compared with those who had a baseline viral load of > 100,000 copies/mL (71.3% [87 of 122]). The difference in virologic success between subgroups was primarily attributable to the higher number of subjects who were never suppressed through Week 24 in the > 100,000 copies/mL versus the ≤ 100,000 copies/mL category (18.9% [23 of 122 subjects] and 2.9% [5 of 173 subjects], respectively). The difference was offset by the higher number of subjects who discontinued study drug due to an AE in the ≤ 100,000 copies/mL category versus the > 100,000 copies/mL category (6.9% [12 of 173] and 1.6% [2 of 122], respectively).

In the treatment-experienced cohort, 44.4% of subjects (8 of 18 subjects) achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 24 and were considered responders. The percentage of subjects classified as non-responders was 38.9% (7 of 18 subjects). The only reason for virologic failure was no viral suppression through Week 24. A total of 16.7% (3 of 18 subjects) of subjects were considered non-responders as a result of drug discontinuation due to other reasons.

Table 29 GS-US-216-0130: Treatment Outcome at Week 24 (HIV-1 RNA Cut-off at 50 copies/mL, TLOVR Analysis)

HIV-1 RNA Category	Treatment-Naive (N = 295)	Treatment-Experienced (N = 18)	Total (N = 313)
Responder[a]	232 (78.6%)	8 (44.4%)	240 (76.7%)
95% CI	73.5% to 83.2%	21.5% to 69.2%	71.6% to 81.2%
Virologic Failure[b]	30 (10.2%)	7 (38.9%)	37 (11.8%)
Rebound	2 (0.7%)	0	2 (0.6%)
Never Suppressed through Week 24	28 (9.5%)	7 (38.9%)	35 (11.2%)
Drug Discontinuation Due to Lack of Efficacy	0	0	0
Death	0	0	0
Drug Discontinuation Due to AEs	15 (5.1%)	0	15 (4.8%)
Drug Discontinuation Due to Other Reasons[c]	18 (6.1%)	3 (16.7%)	21 (6.7%)

a Responder refers to subject who achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 24.

b Virologic failure includes confirmed viral rebound and failure to achieve confirmed < 50 copies/mL through Week 24. If there were more than one event at the earliest time of failure, the order for classification was viral rebound, did not complete protocol-planned duration of the study according to the study completion eCRF page, or added a new antiretroviral treatment prior to discontinuation from the study.

c Drug discontinuation due to other reasons includes lost to follow-up, subject withdrawal, noncompliance, protocol violation and other reasons.

Proportion of Subjects with Plasma HIV-1 RNA < 50 copies/mL at Week 24 and Week 48 (Missing = Failure, Missing = Excluded, and Last Observation carried Forward Analysis)

The percentage of subjects in the treatment-naive cohort with HIV-1 RNA levels of < 50 copies/mL at Week 24 was 93.6% (250 of 267 subjects) using the M = E method, 89.7% (253 of 282 subjects) using LOCF analysis, and 84.7% (250 of 295 subjects) using the M = F method. At Week 48 this was 95.8 % (250/261) using the M = E method, 91.5% (258/282) using LOCF analysis, and 84.7% (250 of 295 subjects) using the M = F method.

The percentage of subjects with HIV-1 RNA levels of < 50 copies/mL continued to increase throughout the duration of the study and had not achieved a plateau by Week 24.

The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and a baseline viral load of ≤ 100,000 copies/mL was 99.4% (155 of 156 subjects) using the M = E method, 96.3% (155 of 161 subjects) using LOCF analysis, and 89.6% (155 of 173 subjects) using the M = F method. The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and a baseline viral load of >

100,000 copies/mL was 85.6% (95 of 111 subjects) using the M = E method, 81.0% (98 of 121 subjects) using LOCF analysis, and 77.9% (95 of 122 subjects) using the M = F method.

The percentage of subjects in the treatment-experienced cohort with HIV-1 RNA levels of < 50 copies/mL at Week 24 was 68.8% (11 of 16 subjects) using the M = E method, 64.7% (11 of 17 subjects) using LOCF analysis, and 61.1% (11 of 18 subjects) using the M = F method. Consistent with the treatment-naive cohort, no plateau in response was achieved by Week 24. The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and a baseline viral load of ≤ 100,000 copies/mL was 62.5% [5 of 8 subjects] using the M = E method, 62.5% [5 of 8 subjects] using LOCF analysis, and 55.6% [5 of 9 subjects] using the M = F method. The percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 and a baseline viral load of > 100,000 copies/mL was 75.0% [6 of 8 subjects] using the M = E method, 66.7% [6 of 9 subjects] using LOCF analysis, and 66.7% [6 of 9] using the M = F method.

Change from Baseline in Plasma HIV-1 RNA

For subjects in the treatment-naive cohort, the mean (SD) baseline HIV-1 RNA level was 4.75 (0.759) $\log_{10}$ copies/mL. HIV-1 RNA levels decreased following initiation of study drugs with the greatest mean decrease occurring within the first 2 weeks of treatment. At Week 24, the mean (SD) decrease from baseline in HIV-1 RNA was −3.00 (0.788) $\log_{10}$ copies/mL. At week 48, the mean (SD) decrease was -3.01 (0.817). When stratified by baseline viral load, the mean (SD) decrease from baseline in HIV-1 RNA was −3.65 (0.614) and -3.68 (0.646) in subjects with a baseline viral load of > 100,000 copies/mL and −2.54 (0.532) and -2.53 (0.549) in subjects with a baseline viral load of ≤ 100,000 copies/mL at Week 24 and Week 48 respectively.

In the treatment-experienced cohort, the mean (SD) baseline HIV-1 RNA level was 4.83 (1.044) log10 copies/mL. HIV-1 RNA levels followed similar trends to that observed for subjects in the treatment-naive cohort. At Week 24, the mean (SD) decrease from baseline in HIV-1 RNA was −2.56 (1.459) log10 copies/mL. At Week 48 it was -2.39 (1.786). When stratified by baseline viral load, the mean (SD) decrease from baseline in HIV-1 RNA was −3.72 (0.523) and -3.70 (0.342) in subjects with a baseline viral load of > 100,000 copies/mL and −1.40 (1.108) and -0.89 (1.544) in subjects with a baseline viral load of ≤ 100,000 copies/mL at Week 24 and Week 48 respectively.

Change from Baseline in CD4 Cell Count

For subjects in the treatment-naive cohort, mean (SD) baseline CD4 cell count was 378 (199.9) cells/µL. CD4 cell counts increased following initiation of study drugs and continued to increase with increased duration of exposure to study drugs. At Week 24, the mean (SD) increase from baseline in CD4 cell count, based on observed data, was 145 (131.6) cells/µL. At Week 48 this was 194 (152.1) cells/µl. When stratified by baseline viral load, the baseline CD4 cell count was 431 (192.6) cells/µL in subjects with a baseline HIV-1 RNA of ≤ 100,000 copies/mL and 304 (186.7) cells/µL in subjects with a baseline HIV-1 RNA of > 100,000 copies/mL. At Week 24, the change in CD4 cell count was 165 (141.8) cells/µL in subjects with a baseline viral load of > 100,000 copies/mL and 130 (122.2) cells/µL in subjects with a baseline viral load of ≤ 100,000 copies/mL.

In the treatment-experienced cohort the mean (SD) baseline CD4 cell count was 198 (214.3) cells/µL. Similar trends in the change in CD4 cell count to those observed for the treatment-naive cohort were observed. At Week 24 and Week 48 the mean (SD) increase from baseline in CD4 cell count, based on observed data, was 99 (161.9) cells/µL and 121 (157.0) cells/µl respectively. When calculated using the LOCF method, it was 88 (155.4) cells/µL and 102 (149.3) cells/µl respectively.

Change from Baseline in CD4 Percentage

CD4% increased following initiation of study drugs and continued to increase with increased duration of exposure to study drugs. At Week 24 and Week 48, the mean (SD) increase from baseline in CD4%

was 7.2% (4.52%) and 9.0% (5.00%) respectively. The trends observed for CD4% when stratified by baseline viral load where similar to those observed for CD4 cell count.

In the treatment-experienced cohort, the mean (SD) baseline CD4% was 11.9% (10.25%) CD4% increased following initiation of study drugs and at Week 24 and Week 48 the mean (SD) increase from baseline in CD4% was 4.1% (3.31%) and 4.2% (3.88%) respectively. The trends observed for CD4% when stratified by baseline viral load where similar to those observed for CD4 cell count.

Resistance analysis

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).
- 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).

One ART-experienced subject who started with 5 CD4 cells and high viral load (6.6 million copies/ml) had poor adherence and developed a DRV RAM at position I84 as a mixture withwild type [WT] (I84I/V). Another subject had RT mutations that were not affecting his background ARVs.

Among the remaining 8 subjects, 3 subjects had no change in PR and RT, and the 5 other subjects only had singly occurring mutations at sites not associated with ARV resistance and were not associated with phenotypic fold changes to any ARV. None developed any other primary or secondary PI RAMs and also no phenotypic resistance to DRV or other PIs was observed.

Table 30 Summary of Efficacy for trial GS-US-216-0130

Title: A Phase 3b, open-label, single arm study to evaluate the safety and efficacy of cobicistat-boosted darunavir plus two fully active nucleoside reverse transcriptase inhibitors in HIV-1 infected, antiretroviral treatment-naïve and -experienced adults with no darunavir resistance associated mutations.		
Study identifier	**GS-US-216-0130**	
Design	The ongoing study is an open-label, single arm, multicenter, study that evaluates the safety and efficacy of a regimen of darunavir (DRV) + cobicistat (COBI) plus 2 fully active nucleoside reverse transcriptase inhibitors (NRTIs) in HIV-1 infected, antiretroviral (ARV) treatment-naïve and treatment-experienced adult subjects with no DRV resistance associated mutations (RAMs). The study consists of an eligibility screening (within 35 days before baseline/Day 1 visit), a 48-week open-label treatment period, and a follow-up visit 30 days after last drug intake. After 48 weeks of treatment, subjects will be given the option to participate in an open-label rollover study to receive DRV, COBI, and investigator-selected NRTIs, and attend study visits every 12 weeks until COBI becomes commercially available (or until Gilead Sciences, Inc [GSI] elects to terminate its development). Subjects who complete treatment through the Week-48 visit and decide not to participate in the rollover study will be required to complete the 30-day follow-up visit.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	48 weeks not applicable Until COBI becomes commercially available, or until GSI elects to terminate development of COBI.
Hypothesis	No hypothesis available for this study.	

Treatments groups	DRV/COBI		DRV/COBI 800/150 mg once daily coadministered as single agents plus 2 fully active investigator-selected NRTIs selected after resistance testing at screening, for 48 weeks.
Endpoints and definitions	Primary endpoint	Safety	The primary safety endpoint was any treatment-emergent grade 3 or grade 4 adverse events (AEs) that occurred through Week 24. The secondary safety endpoints included any treatment-emergent AEs through the data cu-offt date for the Week-24 analysis, including any that led to discontinuation of either DRV or COBI. Additional safety assessments included the monitoring of all AEs, clinical laboratory measures, 12-lead electrocardiograms (ECGs), and physical examinations.
	other:	Efficacy	The efficacy endpoints included the proportion of subjects who achieved HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA Snapshot algorithm, the time to confirmed achievement and maintenance of (2 consecutive) HIV-1 RNA <50 copies/mL through Week 24 (time to loss of virologic response [TLOVR]), the proportion of subjects with HIV-1 RNA <50 copies/mL at Week 24 using missing = failure (M=F), missing = excluded (M=E), and last observation carried forward (LOCF) methods, and the change in CD4+ cell count using M=E and LOCF methods at Week 24. Similar analyses were done at Week 48. Assessment of the development of genotypic and phenotypic resistance in subjects who experienced virologic failure was also performed.
	other:	PK	PK parameters were determined for DRV, COBI, emtricitabine (FTC), and tenofovir (TFV) based on intensive sampling between Weeks 2 and 8 in a subset of subjects (n=60) at selected sites (PK substudy) and a single PK blood sample at all visits through Week 48 was planned for all subjects. The population PK of DRV and the relationship between the DRV PK and pharmacodynamics (PD) were explored.
Database lock	16 August 2012 (cut-off date for primary analysis at Week 24) 8 February 2013 (cut-off date interim analysis at Week 48)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	other: full analysis set, snapshot Week 24			
Descriptive statistics	Treatment group	DRV/COBI Treatment-naïve	DRV/COBI Treatment-experienced	DRV/COBI Total
	Number of subjects	295	18	313
	Virologic Response HIV-1 RNA <50 copies/mL, n (%)	*247 (83.7)*	*11 (61.1)*	*258 (82.4)*
	95% CIs	79.0 to 87.8	35.7 to 82.7	77.8 to 86.5
	Virologic Failure	*29 (9.8)*	*7 (38.9)*	*36 (11.5)*

	HIV-1 RNA ≥50 copies/mL, n (%)	17 (5.8)	5 (27.8)	22 (7.0)
	Discontinued due to lack of efficacy, n (%)	0	0	0
	Discontinued due to other reasons and last available HIV-1 RNA ≥50 copies/mL, n (%)	12 (4.1)	2 (11.1)	14 (4.5)
	No virologic data in Week-24 window, n (%)	*19 (6.4)*	*0*	*19 (6.1)*
	Discontinued due to AE/death, n (%)	14 (4.7)	0	14 (4.5)
	Discontinued due to other reasons and last available HIV-1 RNA <50 copies/mL, n (%)	3 (1.0)	0	3 (1.0)
	Missing data during window but on study medication, n (%)	2 (0.7)	0	2 (0.6)

Analysis population and time point description	other: full analysis set, sensitivity analyses Week 24						
Descriptive statistics	Treatment group	DRV/COBI Treatment-naïve		DRV/COBI Treatment-experienced		DRV/COBI Total	
	Virologic Response HIV-1 RNA <50 copies/mL, n (%)						
	TLOVR	N=295	232 (78.6)	N=18	8 (44.4)	N=313	240 (76.7)
	M=E	N=267	250 (93.6)	N=16	11 (68.8)	N=283	261 (92.2)
	M=F	N=295	250 (84.7)	N=18	11 (61.1)	N=313	261 (83.4)
	LOCF	N=282	253 (89.7)	N=17	11 (64.7)	N=299	264 (88.3)
	Mean HIV-1 RNA log change from baseline (log10 copies/ml)						
		−3.00		-2.56		-2.98	
	CD4+ cell count mean change from baseline						
	M=E	+145		+99		+142	
	LOCF	+133		+88		+131	
	N=total number of subjects, n=number of responders.						
Notes	Resistance development to DRV or other PIs, and to the background NRTIs was rare in this study. Of the 313 treated subjects, 10 met the criteria for postbaseline resistance analysis (5 treatment-naïve and 5 treatment-experienced). No genotypic and phenotypic resistance development was seen in the ART-naïve subjects. One treatment-experienced subject with poor pill bottle returns indicative of poor adherence had developed a DRV RAM at position I84 as a mixture with wild-type (I84I/V) through 24 weeks. No phenotypic resistance to DRV or other PIs was observed. No subjects developed any other primary or secondary PI RAMs. No subjects developed an NRTI RAM (or phenotypic resistance) to their concomitant NRTI regimen.						

Analysis description	Interim Analysis at Week 48:			
Analysis population and time point description	other: full analysis set Week 48			
Descriptive statistics	Treatment group	DRV/COBI Treatment-naïve	DRV/COBI Treatment-experienced	DRV/COBI Total
	Number of subjects	295	18	313
	Virologic Response HIV-1 RNA <50 copies/ml, n(%)			
	TLOVR	245 (83.1)	8 (44.4)	253 (80.8)
	Mean HIV-1 RNA log change from baseline (log10 copies/ml)			
		-3.01	-2.39	-2.97
	CD4+ cell count mean change from baseline			
	LOCF	+174	+102	+170

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant has performed a comparison and analyses of results across studies given that the efficacy and resistance profiles of DRV have been established in the DRV/rtv development program, and the Phase 1 studies GS-US-216-0115 and TMC114IFD1001 demonstrated comparable pharmacokinetics of DRV/rtv and DRV/COBI with the proviso that these comparisons should be interpreted with caution because of the inherent inherent limitations associated with the use of historical data as control and the small sample size of the treatment-experienced subgroup further limits the interpretation of this historical comparison in this subgroup.

The Week-24 results of the 295 treatment-naïve HIV-1 infected adults in the GS-US-216-0130 study were compared with the Week-24 results of the treatment-naïve HIV-1 infected adults treated with DRV/rtv 800/100 mg once daily of the Phase 3b study TMC114-C211. The Week-24 results of the 18 treatment-experienced HIV-1 infected adults with no DRV RAMs in the GS-US-216-0130 study were compared with the Week-24 results of the DRV/rtv 800/100 mg once daily treatment group of the Phase 3b study TMC114-C229, which included adult treatment-experienced subjects with no DRV RAMs at baseline.

The treatment-naïve subject populations of TMC114-C211 and GS-US-216-0130 are similar with respect to demographic data and baseline disease and resistance characteristics. The treatment-experienced subjects of study GS-US-216-0130 are somewhat older (median age was 48 years, while it was 40 years in TMC114-C229), and the median number of years (range) since HIV diagnosis was 8.5 years (range 2 to 24 years) in the GS-US-216-0130 study, while it was 1.1 years (range 0 to 22 years) in study TMC114-C229. The treatment-experienced subjects in study GS-US-216-0130 also have a slightly higher baseline viral load (mean log10 viral load was 4.8 copies/mL) than those in study TMC114-C229 (mean log10 viral load 4.2 copies/mL), and a lower CD4+ cell count (mean cell count 198x106 cells/L) than those in study TMC114-C229 (mean cell count $250x10^6$ cells/L). The percentage of subjects with HIV-1 RNA ≥ 100,000 copies/mL was 50.0% in study GS-US-216-0130, and 13.3% in study TMC114-C229.

In treatment-naïve subjects, the efficacy of treatment with DRV/rtv 800/100 mg once daily in study TMC114-C211 is similar to that seen with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130. The percentage of subjects reaching virologic response at Week 24 (snapshot analysis) was 81.6% in the historical study TMC114-C211, and 83.7% in the treatment-naïve subgroup of study GS-US-216-0130. The change from baseline in log10 viral load at Week 24 was -3.11 copies/mL with DRV/rtv 800/100 mg once daily and -3.00 copies/mL with DRV/COBI 800/150 mg once daily. The change from baseline in CD4+ cell count at Week 24 was $+142x10^6$ cells/L and $+145x10^6$ cells/L with DRV/rtv and DRV/COBI, respectively.

In treatment-experienced subjects (n=18), the percentage of subjects reaching virologic response at Week 24 was 70.1% in the historical study TMC114-C229, and 61.1% in the treatment-experienced

subgroup of study GS-US-216-0130. The decrease in log10 viral load at Week 24 was -2.09 copies/mL with DRV/rtv 800/100 mg once daily, and -2.56 copies/mL with DRV/COBI 800/150 mg once daily. The change from baseline in CD4+ cell count was $+83x10^6$ cells/L and $+99x10^6$ cells/L with DRV/rtv and DRV/COBI, respectively.

Resistance development to DRV or other PIs, and to the background NRTIs was rare in the Week-24 analysis of study GS US-216-0130. These low levels of resistance development were comparable to those observed in the DRV/rtv 800/100 mg once daily arm of TMC114-C211 and TMC114-C229, confirming the clinical resistance profile of DRV/rtv 800/100 mg once daily in ART-naïve subjects and ART-experienced subjects with no DRV RAMs and the high genetic barrier of DRV whether boosted with COBI or rtv.

Supportive studies

Study TMC114-C211

A randomized, controlled open-label trial to compare the efficacy, safety and tolerability of TMC114/ritonavir compared with lopinavir/ritonavir in combination with a fixed background once daily regimen of FTC (200 mg) and TDF (300 mg) in treatment naive adult patients with HIV 1 RNA ≥ 5000 copies/mL.

The primary objective of this Week-48 analysis was to demonstrate non-inferiority in virologic response (time to loss of virologic response [TLOVR]), defined as a confirmed plasma viral load of < 50 copies/mL, with DRV/rtv (800 mg/100 mg q.d.) versus LPV/rtv (800 mg/200 mg total daily dose) at 48 weeks, when administered in combination with a fixed background regimen, consisting of tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) in a treatment-naïve, HIV-1 infected population with a predefined delta of non-inferiority of 12%. Secondary objectives were to evaluate other virologic parameters and immunologic parameters, to compare the quality of life, to assess pharmacokinetics, resistance characteristics, pharmacokinetic/pharmacodynamic relationships, and to evaluate safety and tolerability over time. Analyses were also performed at Week 96 (when all subjects had reached 96 weeks or discontinued earlier) and at Week 192, in support of the long-term use of DRV/rtv versus LPV/rtv in treatment-naïve HIV-1 infected subjects.

The efficacy results of this trial demonstrated non-inferiority in virologic response defined as a confirmed plasma viral load of < 50 copies/mL at Week 48 (primary efficacy parameter) with DRV/rtv 800/100 mg q.d. when compared to a daily dose of LPV/rtv 800/200 mg (both in combination with a fixed background regimen of TDF/FTC). The results for the primary efficacy parameter were supported by those for the secondary virologic parameters. These results were confirmed in the Week-96 analysis, and sustained up to 192 weeks of treatment of study TMC114-C211. Virologic response at Week 192 was achieved in 68.8% of subjects in the DRV/rtv group and 57.2% in the LPV/rtv group (ITT, TLOVR).

Table 31 Efficacy Summary – TMC114-C211 Week-48 and Week-96 Analyses

Parameter	Week 48[a] DRV/rtv 800/100 mg once daily N=343	Week 48[a] LPV/rtv 800/200 mg daily dose N=346	Week 48[a] Treatment Difference (95% CI of Difference)[d]	Week 96[b] DRV/rtv 800/100 mg once daily N=343	Week 96[b] LPV/rtv 800/200 mg daily dose N=346	Week 96[b] Treatment Difference (95% CI of Difference)[d]
Virologic Response						
HIV-1 RNA <50 Copies/mL[c] All Subjects,% (n/N)	83.7% (287/343)	78.3% (271/346)	5.3% (-0.5; 11.2)	79.0% (271/343)	70.8% (245/346)	8.2% (1.7; 14.7)
Baseline HIV-1 RNA <100,000 Copies/mL[c]	85.8% (194/226)	84.5% (191/226)	1.3% (-5.2; 7.9)	80.5% (182/226)	75.2% (170/226)	5.3% (-2.3; 13.0)
Baseline HIV-1 RNA ≥100,000 Copies/mL[c]	79.5% (93/117)	66.7% (80/120)	12.8% (1.6; 24.1)	76.1% (89/117)	62.5% (75/120)	13.6% (1.9; 25.3)
Baseline CD4+ Cell Count <200 Cells/L	79.4% (112/141)	70.3% (104/148)	9.2% (-0.8; 19.2)	78.7% (111/141)	64.9% (96/148)	13.9% (3.5; 24.2)
Baseline CD4+ Cell Count ≥200 Cells/L	86.6% (175/202)	84.3% (167/198)	2.3% (-4.6; 9.2)	79.2% (160/202)	75.3% (149/198)	4.0% (-4.3; 12.2)
Immunologic Change						
Median (Range) Change in CD4+ Cell Count, x10^6 Cells/L[e]	+137 (-182; 725)	+141 (95; 684)		+171 (-278; 921)	+188 (-179; 782)	

N=total number of subjects; n=number of observations.
[a] Data based on analyses at Week 48.
[b] Data based on analyses at Week 96.
[c] Imputations according to the TLOVR algorithm.
[d] Based on normal approximation to the difference in % response.
[e] Noncompleter is failure imputation: subjects who discontinued prematurely are imputed with a change equal to 0

The percentage of virologic failures, (rebounders and subjects who were never suppressed using the TLOVR [non-VF censored algorithm] defined as loss of or never achieving a plasma viral load < 50 copies/mL, respectively), was lower in the DRV/rtv group than in the LPV/rtv group. Of the 343 DRV/rtv subjects, 34 (9.9%) experienced virologic failure versus 49 of 346 (14.2%) LPV/rtv subjects. In the DRV/rtv group, 8 (2.3%) subjects were rebounders and 26 (7.6%) subjects were never suppressed. In the LPV/rtv group, 10 (2.9%) subjects were rebounders and 39 (11.3%) subjects were never suppressed. Development of resistance was assessed in the virologic failures for which matching baseline/endpoint genotypic profiles were available, 10 and 18 subjects in the DRV/rtv and LPV/rtv group, respectively. In the virologic failures of the DRV/rtv group, there were no emerging PI-RAMs identified. In one subject of the LPV/rtv group, 2 PI RAMs emerged by endpoint. In 1 subject of the DRV/rtv group and 2 subjects of the LPV/rtv group, 1 developing NRTI RAM was identified at endpoint, which was associated with a decreased susceptibility to FTC included in the background regimen.

Study TMC114-C229

A Phase 3, randomized, open-label, 48-week study comparing DRV/rtv 800/100 mg once daily versus DRV/rtv 600/100 mg twice daily in ART-experienced HIV-1 infected subjects with screening genotype resistance testing showing no DRV RAMs and with a viral load >1,000 HIV-1 RNA copies/mL and a CD4+ cell count >50x106 cells/L at screening. Both arms used an OBR of at least 2 NRTIs.

At baseline, the mean duration of HIV-1 infection was 8.5 years; the mean log viral load was 4.16 log10 copies/mL; 86.7% of the subjects had a viral load <100,000 copies/mL. The median CD4+ cell count was 228x106 cells/L; 57.5% of subjects had a baseline CD4+ cell count ≥ 200x10^6/L and 16.7% had a baseline CD4+ <100x10^6 cells/L.

At Week 48, virologic response, defined as the percentage of subjects with plasma HIV-1 RNA <50 copies/mL, with DRV/rtv 800/100 mg once daily was demonstrated to be noninferior (at the predefined 12% non-inferiority margin) compared to DRV/rtv 600/100 mg twice daily for the ITT and OP populations of treatment-experienced subjects carrying 0 DRV RAMs.

Table 32 Efficacy Summary – TMC114-C229 Week-48 Analysis

Parameter	DRV/rtv 800/100 mg Once Daily N=294	DRV/rtv 600/100 mg Twice Daily N=296	Treatment Difference (95% CI of Difference)[b]
Virologic Response[a], % (n/N)			
HIV-1 RNA <50 Copies/mL 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			
Median Change in CD4+ Cell Count, x10^6 Cells/L[e]	+108	+112	-5 (-25; 16)[d]

N=total number of subjects; n=number of observations.
[a] Imputations according to the TLOVR algorithm.
[b] Based on a normal approximation of the difference in % response.
[c] Clades A1, D, F1, G, K, CRF02_AG, CRF12_BF, and CRF06_CPX.
[d] Difference in means.
[e] Last Observation Carried Forward imputation

The virologic failure rate (HIV-1 RNA ≥ 50 copies/mL TLOVR non-VF-censored) was similar in the DRV/rtv once daily group (65/294, 22.1%) and DRV/rtv twice daily group (54/296, 18.2%). Development of resistance was infrequent among virologic failures in both treatment groups. Of all virologic failures with matching baseline/endpoint genotypes, only 1 subject (DRV/rtv once daily) developed primary (major) PI mutations, including DRV RAMs, and lost susceptibility to DRV. The proportion of virologic failure subjects who retained susceptibility to all currently available PIs was 96.6% for the DRV/rtv once daily group and 100% for the DRV/rtv twice daily group. In the DRV/rtv once daily group, 7/59 (11.9%) virologic failures, with available phenotypes at baseline and endpoint, lost susceptibility to an NRTI in the background regimen, compared to 4/41 (9.8%) in the DRV/rtv twice daily group.

2.5.2. Discussion on clinical efficacy

The clinical program for DRV/COBI FDC is primarily based on a pharmacokinetic bridging clinical program and the comprehensive development programs of the 2 individual compounds (Darunavir and Cobicistat). The efficacy data provided therefore consists only of bioavailability studies investigating the relative oral bioavailability of 2 FDC formulations of DRV/COBI 800/150 mg once daily and that of DRV/rtv 800/100 mg once daily co-administered as single agents used used in combination and assessing the bioequivalence of DRV when co-administered with COBI either as the FDC (formulation G006) or the single agents under fed and fasted conditions and an on-going Phase 3b, open-label, single-arm study GS-US-216-0130 assessing safety (primary objective), efficacy and pharmacokinetic parameters (secondary objectives) in HIV-1 infected adult subjects treated with DRV/COBI 800/150 mg once daily co-administered as single agents for at least 48 weeks.

Additionally, data from the historical studies TMC114-C211 (also referred to as ARTEMIS) in antiretroviral therapy (ART)-naïve HIV-1 infected adult subjects, and TMC114-C229 (also referred to as ODIN) in ART-experienced HIV-1 infected adult subjects with no DRV RAMs using DRV/rtv are provided in support.

Design and conduct of clinical studies

An open label phase 3b, open-label, single-arm study GS-US-216-0130 is provided to support the proposed indication and is considered acceptable on this occasion as data from two historic studies TMC114-C211 (ARTEMIS) and TMC114-C229 are also provided in support. The primary objective of the study was to evaluate the safety and tolerability of DRV/cobi in combination with 2NRTIs through 24 weeks of treatment and secondarily to assess the efficacy of the regimen in terms of virologic response (plasma viral load <50 copies/mL) at 24 and 48 weeks using a snap-shot analysis.

In the open-label study GS-US-216-0130, a disparity in the reasons for discontinuing is noted, the Applicant was asked to clarify. The slight discrepancy was clarified by the applicant. Of the 295 subjects included in the treatment-naive cohort study GS-US-216-0130, 254 subjects in the FAS (86.1%) were still on study drugs whilst 261 subjects (88.5%) completed the study up to week 48; thus 41 subjects prematurely discontinued the study drug whilst 34 subjects prematurely discontinued the study.

There are no major concerns regarding the methodology of this study.

Efficacy data and additional analyses

Three hundred and fourteen (314) subjects were enrolled into the study: 296 treatment-naive subjects and 18 treatment-experienced subjects out of whom 313 subjects received at least one dose of both study medications. Majority of these subjects were ART-naïve (94.3%) while 5.7% were ART-experienced.

In the treatment naïve group the mean baseline log10 HIV-1 RNA value was 4.8 copies/ml and the mean baseline CD4+ cell count was 378 x 10^6 cells/L.

For the treatment experienced group, the mean baseline log10 HIV-1 RNA value was 4.8 copies/ml and the mean baseline CD4+ cell count was 198 x 106 cells/L. About 2/3rd of this group had CD4+ cell count less than 200 x 10^6 cells/L.

The results of this open-label study showed that virologic response at 24 weeks was achieved by 83% of the treatment naïve subjects and in treatment-experienced cohort (which had very small numbers) virologic response was achieved by 61.1% (11 of 18 subjects). At 48 weeks virologic response was achieved by 82.7% of the treatment naïve subjects and 50.0% in the treatment-experienced cohort.

Of the 29 subjects treatment-naïve subjects who were virologic failure at Week 24, 9 gained response by Week 48. As 17 subjects of the 19 subjects with no virologic data at Week 24 discontinued the study before Week 24, the outcome of these subjects remained unchanged by Week 48. For the treatment-experienced subjects, of the 7 virologic failures at Week 24, 1 subject became a responder at Week 48.

In the TLOVR analysis (a viral load <50 copies at 2 consecutive visits required), a total of 78.6% of subjects (232 of 295 subjects) in the treatment-naive cohort achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 24 and were considered responders. In the treatment-experienced cohort, 44.4% of subjects (8 of 18 subjects) achieved and maintained confirmed HIV-1 RNA < 50 copies/mL through Week 24 and were considered responders. The Week 24 TLOVR analyses provided with the response to the D120 LoQ were inconsistent with the analyses provided with the initial submission. The difference in virologic response (time to loss of virologic response [TLOVR]) at the Week-24 time point in the Week-24 analysis (240 subjects, 76.7%) and the Week-24 time point in the Week-48 analysis (256 subjects, 81.8%) was due to 16 subjects who had achieved human immunodeficiency virus type 1 (HIV-1) ribonucleic acid (RNA) <50 copies/mL at the Week-24 visit but for whom response was not yet confirmed (ie, HIV-1 RNA <50 copies/mL at 2 consecutive visits) at time of the Week-24 analysis. After receipt of the confirmation sample, these 16 subjects were accordingly classified as Week 24 responders / no responders in the Week-48 analysis.

Additionally, these results were compared with DRV/rtv data from studies TMC114-C211 (ART- naïve subjects) and TMC114-C229 (ART-experienced subjects). Overall, there was a suggestion that the response to DRV/cobi can be considered comparable to DRV/rtv. It should however be noted that such cross-study comparisons should always be viewed with extreme caution.

In the treatment-naive cohort, the percentage of subjects who achieved virologic success at Week 24 was higher in subjects who had a baseline viral load of ≤ 100,000 copies/mL (87.9% [152 of 295 subjects]) compared with those who had a baseline viral load of > 100,000 copies/mL (77.9% [95 of 122]), mainly due to delayed suppression, because in 6 from 17 virologic failures had HIV-RNA levels at week 36 of <50 copies/ml at the data cut-off analysis date. In the Week-48 analysis, there was a 2.7% difference in the response rates between subjects with a baseline viral load ≤ 100,000 copies/mL (83.8%) versus subjects with a baseline viral load >100,000 copies/mL (81.1%). These results indicate that patients with higher viral loads at start therapy possibly respond slower.

2.5.3. Conclusions on the clinical efficacy

Taking into consideration the results of the PK studies TMC114IFD1001 and Study GS-US-216-0115 which show bioequivalence of DRV/cobi compared to DRV/rtv, it is possible to conclude that the results of this single arm study of DRV/cobi+2 fully active NRTIs are demonstrative of efficacy.

Efficacy data for DRV/COBI 800/150 mg qd can be extrapolated to patients failing on other regimens with the same limitations as DRV/RTV 800/100 mg qd.

2.6. Clinical 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.

Patient exposure

Table 33 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.

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 the table below.

Table 34 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.

Adverse events

The most frequently reported AEs by preferred term were headache (72.2%), fatigue (61.1%), diarrhoea (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 rashes occurred both under DRV/COBI single agent treatment (grade 1) and DRV/COBI FDC treatment (grade 2) and were assessed as at least possibly related at the 2 occasions. No subject permanently stopped or temporarily interrupted the study medication due to an AE.

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. 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.

Table 35 Summary of Adverse Events – GS-US-216-0130 Week-24 Analysis

n (%) of Subjects Experiencing	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
≥1 AE	260 (88.1)	15 (83.3)	275 (87.9)
≥1 Grade 3 or 4 AE	16 (5.4)	2 (11.1)	18 (5.8)
≥1 Grade 2, 3, or 4 AE	133 (45.1)	6 (33.3)	139 (44.4)
≥1 AE related to DRV/COBI	117 (39.7)	6 (33.3)	123 (39.3)
≥1 Grade 3 or 4 AE Related to DRV/COBI	5 (1.7)	0	5 (1.6)
≥1 Grade 2, 3, or 4 AE Related to DRV/COBI	41 (13.9)	1 (5.6)	42 (13.4)
≥1 SAE	13 (4.4)	2 (11.1)	15 (4.8)
≥1 SAE Related to DRV/COBI	3 (1.0)	0	3 (1.0)
≥1 AE Leading to Study Medication Discontinuation	15 (5.1)	0	15 (4.8)
≥1 AE Leading to Study Medication Interruption	9 (3.1)	0	9 (2.9)

N=total number of subjects with data; n=number of subjects with observation.

Table 36 Incidence of Adverse Events Reported in More Than 5% of All Subjects – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Any Adverse Event	*260 (88.1)*	*15 (83.3)*	*275 (87.9)*
Gastrointestinal Disorders	**154 (52.2)**	**10 (55.6)**	**164 (52.4)**
Diarrhoea	73 (24.7)	5 (27.8)	78 (24.9)
Flatulence	18 (6.1)	1 (5.6)	19 (6.1)
Nausea	66 (22.4)	1 (5.6)	67 (21.4)
Vomiting	24 (8.1)	2 (11.1)	26 (8.3)
General Disorders and Administration Site Conditions	**46 (15.6)**	**2 (11.1)**	**48 (15.3)**
Fatigue	20 (6.8)	0	20 (6.4)
Infections and Infestations	**144 (48.8)**	**9 (50.0)**	**153 (48.9)**
Upper Respiratory Tract Infection	31 (10.5)	0	31 (9.9)
Nasopharyngitis	16 (5.4)	2 (11.1)	18 (5.8)
Sinusitis	16 (5.4)	1 (5.6)	17 (5.4)
Nervous System Disorders	**59 (20.0)**	**3 (16.7)**	**62 (19.8)**
Headache	27 (9.2)	2 (11.1)	29 (9.3)
Skin and Subcutaneous Tissue Disorders	**84 (28.5)**	**4 (22.2)**	**88 (28.1)**
Rash (preferred term)	27 (9.2)	0	27 (8.6)

N=total number of subjects with data; n=number of subjects with observation.

Overall, 39.3% of subjects experienced at least 1 AE that was considered related to DRV/COBI. Diarrhoea (14.7%) and nausea (14.4%) were the only AEs considered to be study drug-related in more than 5% of subjects, most drug-related AEs were recorded in 1 or 2 subjects. Five subjects (1.6%) experienced 1 or more grade 3 study drug-related AEs: hypersensitivity, peripheral neuropathy, immune reconstitution syndrome, allergic dermatitis, maculo-papular rash, and vesicular rash.

Table 37 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.

The results of the Week-48 ADR analysis of study GS-US-216-0130 are presented side-by-side with the DRV/rtv 800/100 mg once daily treatment arm of the Week-48 ADR (any grade) analyses of 2 historical controls, studies TMC114-C211 and TMC114-C229 in Table 38.

Table 38 Incidence of Adverse Drug Reactions – GS-US-216-0130, TMC114-211, TCM114-C229, Week-48 Analysis

n (%)	GS-US-216-0130 DRV/COBI 800/150 mg qd N=313	TMC114-C211 DRV/rtv 800/100 mg qd N=343	TMC114-C229 DRV/rtv 800/100 mg qd N=294
Any ADR	*208 (66.5)*	*226 (65.9)*	*125 (42.5)*
Gastrointestinal Disorders	**153 (48.9)**	**168 (49.0)**	**89 (30.3)**
Diarrhoea	87 (27.8)	116 (33.8)	42 (14.3)
Nausea	72 (23.0)	55 (16.0)	38 (12.9)
Vomiting	28 (8.9)	21 (6.1)	13 (4.4)
Abdominal Pain	25 (8.0)	32 (9.3)	14 (4.8)
Flatulence	20 (6.4)	8 (2.3)	6 (2.0)
Abdominal Distension	6 (1.9)	10 (2.9)	4 (1.4)
Dyspepsia	6 (1.9)	9 (2.6)	6 (2.0)
Pancreatic Enzymes Increased	1 (0.3)	4 (1.2)	2 (0.7)
Pancreatitis Acute	1 (0.3)	2 (0.6)	0
Skin and Subcutaneous Tissue Disorders	**56 (17.9)**	**57 (16.6)**	**24 (8.2)**
Rash	49 (15.7)	35 (10.2)	20 (6.8)
Pruritus	7 (2.2)	18 (5.2)	4 (1.4)
Angioedema	3 (1.0)	3 (0.9)	0
Urticaria	3 (1.0)	6 (1.7)	0
Stevens-johnson Syndrome	0	1 (0.3)	0
Nervous System Disorders	**38 (12.1)**	**60 (17.5)**	**20 (6.8)**
Headache	38 (12.1)	60 (17.5)	20 (6.8)
General Disorders and Administration Site Conditions	**23 (7.3)**	**26 (7.6)**	**5 (1.7)**
Fatigue	22 (7.0)	19 (5.5)	3 (1.0)
Asthenia	2 (0.6)	7 (2.0)	2 (0.7)
Metabolism and Nutrition Disorders	**18 (5.8)**	**33 (9.6)**	**25 (8.5)**
Hypertriglyceridaemia	7 (2.2)	6 (1.7)	5 (1.7)
Anorexia	6 (1.9)	11 (3.2)	4 (1.4)
Hypercholesterolaemia	4 (1.3)	7 (2.0)	3 (1.0)
Diabetes Mellitus	3 (1.0)	3 (0.9)	2 (0.7)
Hyperlipidaemia	1 (0.3)	4 (1.2)	3 (1.0)
Dyslipidaemia	0	1 (0.3)	2 (0.7)
Hyperglycaemia	0	2 (0.6)	3 (1.0)
Lipodystrophy	0	2 (0.6)	5 (1.7)
Low Density Lipoprotein Increased	0	4 (1.2)	1 (0.3)
Psychiatric Disorders	**11 (3.5)**	**3 (0.9)**	**0**
Abnormal Dreams	11 (3.5)	3 (0.9)	0
Immune System Disorders	**8 (2.6)**	**4 (1.2)**	**0**
(Drug) Hypersensitivity	7 (2.2)	3 (0.9)	0
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)	0
Hepatobiliary Disorders	**6 (1.9)**	**14 (4.1)**	**1 (0.3)**
Hepatic Enzyme Increased	6 (1.9)	13 (3.8)	1 (0.3)
Acute Hepatitis	0	1 (0.3)	0
Musculoskeletal and Connective Tissue Disorders	**6 (1.9)**	**10 (2.9)**	**4 (1.4)**
Myalgia	6 (1.9)	10 (2.9)	4 (1.4)
Investigations	**3 (1.0)**	**3 (0.9)**	**3 (1.0)**
Increased Blood Creatinine	3 (1.0)	3 (0.9)	3 (1.0)

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The incidence of skin and subcutaneous tissue disorders (ADRs of any grade) was similar after 48 weeks of treatment with DRV/COBI 800/150 mg once daily coadministered as single agents in study GS-US-216-0130 (17.9%) and after 48 weeks of treatment with DRV/rtv 800/100 mg once daily in the treatment-naïve subjects in study TMC114-C211 (16.6%). Skin and subcutaneous tissue disorders ADRs were less frequent in the treatment-experienced subjects treated with DRV/rtv in study TMC114-C229 (8.2%). The incidence of gastrointestinal disorders (ADRs of any grade or at least grade 2 ADRs) was similar between the GS-US-216-0130 and TMC114-C211 studies (48.9% and 49.0%, respectively).

Table 39 Incidence of Adverse Drug Reactions of at least Grade 2 – GS-US-216-0130, TMC114-211, TCM114-C229, Week-48 Analysis

n (%)	GS-US-216-0130 DRV/COBI 800/150 mg qd N=313	TMC114-C211 DRV/rtv 800/100 mg qd N=343	TMC114-C229 DRV/rtv 800/100 mg qd N=294
Any ADR at least grade 2	*64 (20.4)*	*100 (29.2)*	*58 (19.7)*
Gastrointestinal Disorders	**29 (9.3)**	**48 (14.0)**	**35 (11.9)**
Diarrhoea	17 (5.4)	22 (6.4)	17 (5.8)
Nausea	11 (3.5)	9 (2.6)	14 (4.8)
Vomiting	6 (1.9)	5 (1.5)	10 (3.4)
Abdominal Pain	4 (1.3)	12 (3.5)	9 (3.1)
Flatulence	3 (1.0)	2 (0.6)	2 (0.7)
Dyspepsia	1 (0.3)	1 (0.3)	1 (0.3)
Abdominal Distension	0	0	1 (0.3)
Pancreatic Enzymes Increased	0	4 (1.2)	2 (0.7)
Pancreatitis Acute	0	1 (0.3)	0
Skin and Subcutaneous Tissue Disorders	**19 (6.1)**	**13 (3.8)**	**7 (2.4)**
Rash	17 (5.4)	6 (1.7)	6 (2.0)
Pruritus	2 (0.6)	3 (0.9)	1 (0.3)
Angioedema	0	1 (0.3)	0
Stevens-johnson Syndrome	0	1 (0.3)	0
Urticaria	0	3 (0.9)	0
Nervous System Disorders	**9 (2.9)**	**18 (5.2)**	**10 (3.4)**
Headache	9 (2.9)	18 (5.2)	10 (3.4)
Immune System Disorders	**7 (2.2)**	**3 (0.9)**	**0**
(Drug) Hypersensitivity	6 (1.9)	2 (0.6)	0
Immune Reconstitution Syndrome	1 (0.3)	1 (0.3)	0
Metabolism and Nutrition Disorders	**5 (1.6)**	**22 (6.4)**	**17 (5.8)**
Diabetes Mellitus	2 (0.6)	2 (0.6)	1 (0.3)
Hypertriglyceridaemia	2 (0.6)	5 (1.5)	3 (1.0)
Hypercholesterolaemia	1 (0.3)	6 (1.7)	3 (1.0)
Hyperlipidaemia	1 (0.3)	2 (0.6)	3 (1.0)
Anorexia	0	4 (1.2)	1 (0.3)
Dyslipidaemia	0	1 (0.3)	2 (0.7)
Hyperglycaemia	0	2 (0.6)	3 (1.0)
Lipodystrophy	0	0	1 (0.3)
Low Density Lipoprotein Increased	0	4 (1.2)	1 (0.3)
Hepatobiliary Disorders	**3 (1.0)**	**12 (3.5)**	**0**
Hepatic Enzyme Increased	3 (1.0)	11 (3.2)	0
Acute Hepatitis	0	1 (0.3)	0
General Disorders and Administration Site Conditions	**2 (0.6)**	**4 (1.2)**	**2 (0.7)**
Fatigue	2 (0.6)	1 (0.3)	1 (0.3)
Asthenia	0	3 (0.9)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	**2 (0.6)**	**2 (0.6)**	**2 (0.7)**
Myalgia	2 (0.6)	2 (0.6)	2 (0.7)
Psychiatric Disorders	**1 (0.3)**	**1 (0.3)**	**0**
Abnormal Dreams	1 (0.3)	1 (0.3)	0
Investigations	**0**	**1 (0.3)**	**2 (0.7)**
Increased Blood Creatinine	0	1 (0.3)	2 (0.7)

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Serious adverse event / deaths / other significant events

There were no deaths in the Week-24 analysis of this study. Fifteen subjects (4.8%) experienced at least 1 SAE. All SAEs were reported in 1 subject except for pyrexia (n=2). Three SAEs were considered related to DRV/COBI, each occurring in 1 subject: immune reconstitution syndrome (grade 3), rash (preferred term, grade 1, led to treatment discontinuation), and maculo-papular rash (grade 3, led to treatment discontinuation).

Laboratory findings

There were no clinically relevant changes from baseline through Week 24 in mean values for the hematology parameters or clinical chemistry parameters, for the lipid parameters (fasting HDL

cholesterol, fasting LDL cholesterol, fasting total cholesterol to HDL cholesterol ratio, or fasting glucose), or for the liver-related laboratory tests (AST, ALT, bilirubin [direct, indirect and total]).

Renal Laboratory Parameters

An increase from baseline in serum creatinine was observed from Week 2 onwards (mean change 0.09 mg/dL, the increase remained stable till Week 24 (mean change 0.12 mg/dL).

The mean changes from baseline in the eGFR were calculated using the Cockcroft-Gault method ($eGFR_{CG}$), the modification of diet in renal disease method (eGFRMDRD), and by cystatin C clearance (eGFRCC). When using eGFR based on creatinine clearance (eGFRCG and eGFRMDRD), a decrease was noted from Week 2 onwards, the level remained relatively stable from then onwards.

The mean (SD) eGFRCG change from baseline was -9.6 (13.7) mL/min at Week 2, and – 11.5 (15.5) mL/min at Week 24. However, the eGFR calculated by cystatin C clearance (eGFRCC) did not change significantly over time. These results are consistent with the known COBI inhibitory effects on renal tubular creatinine secretion and an absence of effect on the glomerular filtration.

Incidence of Laboratory Abnormalities

The majority of grade 3 or 4 clinical laboratory abnormalities were associated with changes in creatine kinase (18 subjects or 5.8%) and ALT (7 subjects or 2.3%). All other grade 3 or 4 abnormalities occurred in less than 2% of subjects. There were no grade 3 or 4 abnormalities in creatinine levels. Creatinine was abnormally high in 23 subjects (7.4%), the increase was grade 1 in 22 subjects (7.1%) and grade 2 in 1 subject (0.3%). All graded creatinine levels were observed in treatment-naïve subjects, except for 1 grade 1 abnormality in a treatment-experienced subject.

Table 40 Incidence of Grade 3 or 4 Treatment-emergent Graded Laboratory Abnormalities in at Least 1% of Subjects – GS-US-216-0130 Week-24 Analysis

Laboratory Parameter Grouping Laboratory Parameter Grade [a], n (%)	Treatment-naïve	Treatment-experienced	All Subjects
General Hematology			
Neutrophils	**N=292**	**N=18**	**N=310**
Grade 3	2 (0.7)	0	2 (0.6)
Grade 4	2 (0.7)	0	2 (0.6)
Grade 3 or 4	4 (1.4)	0	4 (1.3)
General Clinical Chemistry			
ALT	**N=292**	**N=18**	**N=310**
Grade 3	5 (1.7)	0	5 (1.6)
Grade 4	2 (0.7)	0	2 (0.6)
Grade 3 or 4	7 (2.4)	0	7 (2.3)
Amylase	**N=292**	**N=18**	**N=310**
Grade 3	5 (1.7)	1 (5.6)	6 (1.9)
Grade 4	0	0	0
Grade 3 or 4	5 (1.7)	1 (5.6)	6 (1.9)
AST	**N=292**	**N=18**	**N=310**
Grade 3	3 (1.0)	1 (5.6)	4 (1.3)
Grade 4	2 (0.7)	0	2 (0.6)
Grade 3 or 4	5 (1.7)	1 (5.6)	6 (1.9)
Creatine Kinase	**N=292**	**N=18**	**N=310**
Grade 3	8 (2.7)	0	8 (2.6)
Grade 4	10 (3.4)	0	10 (3.2)
Grade 3 or 4	18 (6.2)	0	18 (5.8)
Gamma Glutamyl Transferase	**N=292**	**N=18**	**N=310**
Grade 3	4 (1.4)	0	4 (1.3)
Grade 4	1 (0.3)	0	1 (0.3)
Grade 3 or 4	5 (1.7)	0	5 (1.6)
Pancreatic Lipase	**N=292**	**N=18**	**N=310**
Grade 3	2 (0.7)	0	2 (0.6)
Grade 4	3 (1.0)	0	3 (1.0)
Grade 3 or 4	5 (1.7)	0	5 (1.6)
Total Cholesterol (Fasting)	**N=273**	**N=17**	**N=290**
Grade 3	3 (1.1)	0	3 (1.0)
Grade 4	0	0	0
Grade 3 or 4	3 (1.1)	0	3 (1.0)
Triglycerides (Fasting)	**N=273**	**N=17**	**N=290**
Grade 3	4 (1.5)	0	4 (1.4)
Grade 4	0	0	0
Grade 3 or 4	4 (1.5)	0	4 (1.4)
Urinalysis			
Urine Red Blood Cells (Hematuria, Quantitative)	**N=291**	**N=18**	**N=309**
Grade 3	3 (1.0)	1 (5.6)	4 (1.3)
Grade 4	0	0	0
Grade 3 or 4	3 (1.0)	1 (5.6)	4 (1.3)

N=total number of subjects with data; n=number of subjects with laboratory toxicity.
[a] GSI Grades.

None of the laboratory-related AEs were reported as serious, and there were no permanent treatment discontinuations due to a laboratory-related AE in the Week-24 analysis of the study. Hypercholesterolemia and hypertriglyceridemia were the most frequent AEs, experienced by 4 subjects (1.3%) each. Increased blood creatinine was reported as an AE in 3 subjects (1.0%). In 1 of these subjects, this AE was considered related to DRV/COBI; the increased creatinine levels resolved with continued treatment. Other laboratory-related AEs considered by the investigator to be related to DRV/COBI were neutropenia, anemia, and hyperlipasemia. The events of neutropenia and anaemia resolved; the AE of hyperlipaemia was on-going at time of report writing, although the laboratory abnormality resolved with continued treatment and there was no report of pancreatitis.

Table 41 Clinical Laboratory Abnormalities Reported as an Adverse Event in at Least 1% of Subjects – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Investigations	**22 (7.5)**	**2 (11.1)**	**24 (7.7)**
Blood Creatinine Increased	3 (1.0)	0	3 (1.0)
Blood Triglycerides Increased	3 (1.0)	0	3 (1.0)
Hepatic Enzyme Increased	3 (1.0)	0	3 (1.0)
Metabolism and Nutrition Disorders	**18 (6.1)**	**3 (16.7)**	**21 (6.7)**
Hypercholesterolaemia	4 (1.4)	0	4 (1.3)
Hypertriglyceridaemia	3 (1.0)	1 (5.6)	4 (1.3)
Renal and Urinary Disorders	**8 (2.7)**	**2 (11.1)**	**10 (3.2)**
Hematuria	3 (1.0)	0	3 (1.0)
Proteinuria	2 (0.7)	1 (5.6	3 (1.0)
Dysuria	1 (0.3)	1 (5.6)	2 (0.6)

N=total number of subjects with data; n=number of subjects with observation.

Safety in special populations

Hepatic impairment

Darunavir or COBI have not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Paediatrics

The safety profile of the combined use of DRV and COBI has not been established in paediatric subjects.

Elderly

Limited information is available on the use of DRV or COBI in subjects aged 65 or more.

Discontinuation due to adverse events

Fifteen subjects (4.8%) discontinued the study drugs due to an AE. Most AEs leading to discontinuation were in the SOC of Skin and Subcutaneous Tissue Disorders (7 subjects; 2.2%).

The most common AEs that led to discontinuation were rash (preferred term) and maculo-papular rash, both of which were experienced by 3 subjects each (1.0%). Nausea and hypersensitivity each resulted in discontinuation of 2 subjects (0.6%). All AEs that led to discontinuation were considered by the investigators to be study drug-related, except for idiopathic thrombocytopenic purpura and mycobacterium avium complex infection.

Table 42 Incidence of Adverse Events Leading to Permanent Discontinuation – GS-US-216-0130 Week-24 Analysis

System Organ Class Preferred Term, n (%)	Treatment-naïve N=295	Treatment-experienced N=18	All Subjects N=313
Any AE Leading to Discontinuation	**15 (5.1)**	**0**	**15 (4.8)**
Blood and Lymphatic System Disorders	**1 (0.3)**	**0**	**1 (0.3)**
Idiopathic Thrombocytopenic Purpura	1 (0.3)	0	1 (0.3)
Gastrointestinal Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Dyspepsia	1 (0.3)	0	1 (0.3)
Nausea	2 (0.7)	0	2 (0.6)
Vomiting	1 (0.3)	0	1 (0.3)
Immune System Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Hypersensitivity	2 (0.7)	0	2 (0.6)
Infections and Infestations	**1 (0.3)**	**0**	**1 (0.3)**
Mycobacterium Avium Complex Infection	1 (0.3)	0	1 (0.3)
Nervous System Disorders	**2 (0.7)**	**0**	**2 (0.6)**
Headache	1 (0.3)	0	1 (0.3)
Dysgeusia	1 (0.3)	0	1 (0.3)
Skin and Subcutaneous Tissue Disorders	**7 (2.4)**	**0**	**7 (2.2)**
Dermatitis Allergic	1 (0.3)	0	1 (0.3)
Rash	3 (1.0)	0	3 (1.0)
Rash Maculo-papular	3 (1.0)	0	3 (1.0)
Rash Macular	1 (0.3)	0	1 (0.3)
Rash Vesicular	1 (0.3)	0	1 (0.3)

N=number of subjects with data; n=number of subjects with observation.

2.6.1. Discussion on clinical safety

The safety profile of the DRV/COBI FDC is based mainly on the data from the Phase 3b study GS-US-216-0130 in HIV-1 infected subjects and data from the Phase 1 studies in healthy subjects (TMC114IFD1001 and TMC114IFD1003). The safety profile of DRV given in combination with rtv and COBI given alone were also provided in support.

Overall therefore approximately 480 subjects have been exposed to DRV/COBI given as single entities with an median duration of exposure of about 31 weeks and 169 subjects have been exposed to the FDC for a period of 10 days only, it would appear that no subjects have been exposed to DRV/cobi for up to or beyond a year. Apparently around 78 subjects have also been exposed to DRV/cobi in studies conducted by Gilead, however these were not included in this application.

In the phase 1 studies in which the FDC was used, the most frequent adverse events were headache, fatigue, diarrhoea, nausea, skin irritation, pruritus and muscle fatigue.

In the phase 3b study GS-US-216-0130, 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%). Adverse events considered at least possibly related to study medication by the investigator were reported for 39,3 % of subjects.

Particularly striking is the high incidence of rash. In the Week-48 analysis from study GS-US-216-0130, rash (ADR) was reported for 49 subjects (42 out of 49 subjects with rash did not discontinue the study; these 42 subjects had grade 1 or 2 rash – of the seven subjects who did discontinue, two subjects experienced a grade 3 rash).

Table 43 Detailed analysis of the ADR rash in GS-US-216-130 and in the DRV/rtv 800/100 mg once daily arm of TMC114-C211 and TMC114-C229 (Week 48 analysis).

Rash[a] Characteristic n (%)	GS-US-216-0130 DRV/COBI 800/150 mg qd N=313	TMC114-C211 DRV/rtv 800/100 mg qd N=343	TMC114-C229 DRV/rtv 800/100 mg qd N=294
Any Rash ADR (Grouped Term)	***49 (15.7)***	***35 (10.2)***	***20 (6.8)***
Grade			
Grade 1	32 (10.2)	29 (8.5)	14 (4.8)
Grade 2	15 (4.8)	4 (1.2)	6 (2.0)
Grade 3	2 (0.6)	2 (0.6)	0
Rash ADR Leading to Discontinuation	7 (2.2)	2 (0.6)	1 (0.3)
Rash ADR Related to Study Medication[b]	23 (7.3)	12 (3.5)	11 (3.7)
Rash ADR Reported as SAE	2 (0.6)	0	0
Median Time to Onset of Rash (Days)	15.0 (2; 328)	25.0 (1; 337)	11.0 (1; 263)

N=total number of subjects with data; n=number of subjects with observation.
[a] Grouped term. The grouped preferred terms are described in Module 2.7.4/Appendix 3.
[b] Causality assessment by the investigator.

For registration of COBI as a pharmaco-enhancer of DRV no comparative study has been submitted. However, for the registration of COBI as booster of another PI, a comparative study has been performed, GS-US-216-0114 that compared ATV/COBI+Truvada (n=394) with ATV/RTV+Truvada (n=377). In that direct comparison of COBI versus RTV in both arms 6.1% of subjects experienced rash, thus COBI itself does not seem to be particularly prone to hypersensitivity disorders or rashes when compared to RTV. PK parameters were available for 60 subjects in study GS-US-216-0130. Of these, 9 subjects presented with a rash (ADR). Comparing the COBI exposures in these subjects to those who did not experience a rash provided no evidence of an association between COBI plasma concentrations and the presence of rash.

There were no serious adverse events or deaths reported in the studies. Only a small number of subjects discontinued the study drugs due to an adverse event.

It is considered that there are a few gaps regarding the safety of DRV/rtv given as a FDC or as single entities as follows;

- There is a lack of knowledge regarding the long-term safety of DRV/cobi as a FDC or administered as single agents. Currently there is up to 48 weeks safety data.
- There is no discussion by the applicant of safety issues which might result from drug-drug interactions especially with regards to differences between cobi and rtv. The Marketing Authorization Holder (MAH) for the COBI single agent is planning to conduct drug-drug interaction studies of COBI-boosted DRV with the estrogen and progestin component of oral contraceptives, with rosuvastatin, and with atorvastatin. In case the results of these studies warrant an update of the COBI SmPC, the DRV/COBI FDC SmPC will be updated accordingly.
- DRV/cobi has not been studied in patients with severe hepatic impairment or renal impairment. This is reflected in the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Adverse events considered to be of special interest to DRV/COBI were noted to be prevalent in the studies conducted with the FDC (Rash [grouped term], 16.3%), Lipid Abnormalities (2.9%) and Severe Skin Reactions (2.6%).

Overall, the data suggest that DRV/COBI is generally well tolerated. No particular concern has been identified with this fixed dose combination or DRV/cobi given as single agents to date.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2 is acceptable. The PRAC advice is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2 with the following content:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Table 44 Summary of the Safety Concerns

Summary of safety concerns	
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 • Renal Toxicity* • Off-label use in the paediatric population and in ARV treatment experienced patients with >100,000 copies/mL HIV-1 RNA
Missing information	• Elderly

Summary of safety concerns	
	• Pregnancy and breast-feeding women • Children < 18 years of age • Long-term safety of DRV/COBI in adults • Subjects with severe hepatic impairment (Child-Pugh C) • Subjects with renal impairment • Subjects co-infected with HIV and HBV and/or HCV.

* including potential worsening of TDF renal toxicity when REZOLSTA and TDF are coadministered

The PRAC agreed on the above list.

Pharmacovigilance plan

Table 45: Ongoing and planned studies in the PhV development plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status** (planned, started)	**Date for submission of interim or final reports (planned or actual)**
GS-US-216-0130 (Gilead) A Phase 3b, open-label, single arm trial to evaluate the safety and efficacy of COBI-boosted DRV plus two fully active NRTIs in HIV-1 infected, ART-naïve and –experienced adults with no DRV-RAMs. **Category 3**	To evaluate the safety and tolerability of DRV+COBI plus 2 fully active NRTIs through 48 weeks of treatment and beyond. After 48 weeks of treatment, subjects are 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.	potential risk: Renal Toxicity Missing information: Long-term safety of DRV/COBI in adults	Ongoing	Q3 2015 (Final report)
GS-US-216-0128 (Gilead) An open-label, multicentre, multi-cohort, 2-part trial evaluating the PK, safety and efficacy of ATV/COBI once daily or DRV/COBI twice daily administered with a BR in HIV-1 infected ART-experienced subjects aged 3 months to <18 years for the ATV/COBI regimen and 3 years to <18 years for the DRV/COBI regimen. **Category 3**	To evaluate PK, safety, and efficacy of ATV/COBI and DRV/COBI in children and adolescents	Missing information: Children <18 years of age	Planned	February 2018 (Week 48 report) February 2022 (Final report)
GS-US-236-0118 (Gilead) A Phase 3 open-label safety study of COBI-containing highly active ARV regimens in	To evaluate the effect (including long-term effects), safety, and tolerability of COBI	Important potential risk: Renal Toxicity	Ongoing	Q3 2015 (Final report)

HIV-1 infected patients with mild to moderate renal impairment. **Category 3**	containing regimens (STB, ATV/COBI or DRV/COBI) on renal parameters through 48 weeks of treatment and beyond	Missing information: Subjects with renal impairment		
GS-US-236-0140 (Gilead) A randomized, open-label, Phase 4 study evaluating the renal effect of elvitegravir/COBI/emtricitabine/TDF or other TDF-containing regimens (rtv-boosted atazanavir plus emtricitabine/TDF or efavirenz/emtricitabine/TDF) compared to rtv-boosted atazanavir plus abacavir/lamivudine in ARV treatment-naïve HIV-1 infected adults with eGFR ⩾70 mL/min **Category 3**	To evaluate the effect on TDF on renal function and markers of renal tubular function with and without COBI	Important identified risk: Drug-drug interaction Important potential risk: Renal Toxicity	Planned	May 2015 (Final report)
TMC114HIV3015 A single-arm, open-label trial to assess the pharmacokinetics of DRV/rtv, etravirine, and rilpivirine in HIV-1-infected pregnant women. (This study will be amended to include an evaluation of the pharmacokinetics of DRV/COBI during pregnancy as well.) **Category 3**	To assess the PK of DRV/rtv and DRV/COBI in HIV-1- infected pregnant women.	Missing information: Pregnant and breast-feeding women	Ongoing	Q2 2017 (Final report)
PBPK simulations of the effect of potent CYP3A4 inhibitors on COBI exposure (Gilead) **Category 3**	To evaluate the potential effect of potent CYP3A4 inhibitors on COBI exposure	Important identified risk: Drug-drug interaction	Planned	Q2 2014 (Final report)
In vitro studies of the individual STB components on the cytotoxicity of TFV in HEK-293 cells cotransfected with OAT1 and MRP4 (Gilead) **Category 3**	To evaluate the effect of individual STB components on the cytotoxicity of TFV	Important identified risk: Drug-drug interaction	Ongoing	Q3 2013 (Final report)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 46: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks:		
Severe Skin Reactions	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Hepatotoxicity	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Hyperglycaemia	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Lipid Abnormalities	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Pancreatitis	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Fat redistribution	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Immune Reconstitution Inflammatory Syndrome	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Development of Drug Resistance	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications) and 4.4 (Special warnings and precautions for use) of the SmPC.	None
Drug-Drug Interactions	Adequate information and guidance to help the prescriber is provided in Sections 4.3	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(Contraindications), 4.4 (Special warnings and precautions for use), and 4.5 (Interaction with other medicinal products and other forms of interaction) of the SmPC.	
Important potential risks:		
Coronary Artery Events	None proposed.	None
Cardiac Conduction Abnormalities	None proposed.	None
Convulsions	None proposed.	None
Renal Toxicity	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Off-label use in the paediatric population and in ARV treatment-experienced patients with >100,000 copies/mL HIV-1 RNA	Adequate information and guidance to help the prescriber is provided in Sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), and 4.4 (Special warnings and precautions for use) of the SmPC.	None
Missing information:		
Elderly (65 years and above)	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use), and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Pregnant and Breast-Feeding Women	Adequate information and guidance to help the prescriber is provided in Sections 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
Children (<18 years of age)	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration).	None
Long-Term Safety of DRV/COBI in Adults	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use) and 4.8 (Undesirable effects) of the SmPC.	None
Subjects with Sever Hepatic Impairment (Child-Pugh C)	Adequate information and guidance to help the prescriber	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	is provided in Sections 4.2 (Posology and method of administration), 4.3 (Contraindications), and 5.2 (Pharmacokinetic properties) of the SmPC.	
Subjects with Renal Impairment	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), and 4.4 (Special warnings and precautions for use).	None
Subjects Coinfected with HIV and HBV and/or HCV	Adequate information and guidance to help the prescriber is provided in Sections 4.4 (Special warnings and precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) of the SmPC.	None

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

2.9. Significance of paediatric studies

Not applicable.

2.10. Product information

2.10.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

- The PREZISTA (darunavir) leaflet serves as the parent leaflet for REZOLSTA;
- The proposed REZOLSTA leaflet contains currently approved active ingredients (darunavir and cobicistat), for which the individual leaflets have been user tested;
- The proposed new leaflet follows a similar layout as PREZISTA
  - no new route of administration is proposed;
  - no additional safety issues have been identified.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The most evident benefit of the FDC DRV/COBI is the reduction of pill burden: instead of 2 pills (DRV 800 mg and ritonavir 100 mg), one single tablet would suffice, in combination with other background ARVs.

The combination DRV/COBI as separate compounds showed high antiviral efficacy (83.7%, viral suppression < 50 c/ml) in treatment-naïve subjects at week 24 and adequate immunologic recovery. Development of DRV-RAMs was absent in treatment failures in the treatment-naïve subjects. The results obtained appear in line with those known for DRV/rtv in treatment-naïve subjects.

Antiretroviral activity will be optimal in a fixed dose of a PI and its boosting agent, because if either one is not adhered to, no antiretroviral activity of DRV (too low dose without boosting) or COBI (lack of antiretroviral activity) can be expected.

No cases of Proximal Tubular Nephrotoxicity (pre-Fanconi) were recorded in the 313 subjects receiving COBI mostly in combination with tenofovir that is associated with nephrotoxicity.

Tenofovir exposures were not higher due to the combined effects of DRV and COBI compared to the effects of DRV and RTV, thus that additional risk factor for nephrotoxicity is not present.

Uncertainty in the knowledge about the beneficial effects

The anticipated benefit of increased simplicity of administration with the current FDC might be limited: more benefit in simplicity can be achieved when also the background NRTIs, e.g. tenofovir and emtricitabine, were combined in the fixed dose combination.

Although antiviral efficacy appears in line with that known for DRV/rtv, the comparison of data is hampered by the lack of a comparator arm DRV/rtv in study GS-US-216-0130.

Very limited data were obtained about patients failing on other regimens (n=18).

Risks

Unfavourable effects

The study GS-US-216-0130 mainly focused on safety evaluation in 313 subjects during 48 weeks. No new Adverse Drug Reactions were recorded that were not yet part of the DRV list of AEs.

Rash (16%), diarrhoea (28%), nausea (23%) frequently complicate administration DRV/COBI and rash resulted in discontinuation in 2% of subjects.

COBI increases serum creatinine with about 10 nmol/L, due to inhibition of tubular secretion of creatinine, whereas RTV does not.

Next to inhibition of CYP3A4 enzyme COBI also inhibits various other hepatic and transporter enzymes which complicates administration of co-medication.

COBI is not lipid neutral.

Uncertainty in the knowledge about the unfavourable effects

A single arm study is not considered as the most optimal design to evaluate safety issues.

Benefit-risk balance

Importance of favourable and unfavourable effects

The introduction of a new pharmaco-enhancer of DRV in a FDC with DRV is considered a benefit in treatment simplification and in prevention of medication errors. Overall, use of COBI as a pharmaco-enhancer of DRV results in similar efficacy in treatment-naïve patients compared to use of RTV. No new AEs were recorded when COBI instead of RTV was used as a pharmaco-enhancer of DRV. COBI has a reduced potential of liver enzyme inhibition compared to RTV.

Several issues require consideration:

- The introduction of a FDC of DRV and a pharmaco-enhancer is only a marginal contribution in the reduction of pill burden, since in the cART-treatment naive patient category it would imply a reduction of 3 pills to 2 pills per day, which is not considered a fundamental change or breakthrough in simplicity of PI-based regimens, since the backbone is still a separate tablet.
- More benefit of increased simplicity of administration of a FDC of DRV and a boosting agent is to be achieved in treatment-experienced patients who require DRV/RTV 600/100 mg BID (i.e. 2 pills twice daily). That would imply a reduction of 4 pills to 2 pills per day. The Applicant has mentioned that they will not pursue a twice daily dosing simplification for other treatment-experienced populations as COBI is only indicated for once daily use. However there is no reason why COBI and DRV/cobi FDC could not be developed for treatment experienced patients requiring a twice daily regimen, and the Applicant is encouraged to do so.
- Substantial gains in antiretroviral efficacy cannot be expected, because only DRV 800 mg qd will be active in this respect and its effective plasma concentration is relatively similar with either 100 mg rtv or 150 mg COBI.

In fact, the application of the FDC DRV/COBI 800/150 mg qd based on results from study GS-US-216-0130 with DRV+COBI used as separate components is not required to establish the antiretroviral activity of DRV, since the separate substances have been approved. Most relevant data from this study are therefore related to safety, including nephrotoxicity issues due to interaction of COBI and tenofovir. These were however not evident in this study. Further on, a single arm study design complicates the interpretation of the observed signals. Increased frequency of patient discomfort was recorded: rash (16%) and nausea (23%), compared to data in DRV/RTV (10% and 16%).

Finally, COBI shares various interaction pathways with rtv, and commonly prescribed co-medication (e.g. contraceptives, beta blockers, methadone) remain subject to inhibition of liver enzymes by COBI, complicating management of co-morbidities.

Benefit-risk balance

Both substances, DRV and COBI, have already been registered. DRV boosted by RTV has been shown to be a potent antiretroviral agent with a high barrier to resistance. A fixed dose combination of DRV

combined with its pharmaco-enhancer is a logical step to a future application of a fixed dose combination of a protease-inhibitor, its booster and 2 NRTIs.

In a single arm study in 313 patients that mainly focused on safety of DRV/COBI during 48 weeks no new AEs were recorded apart from the known COBI-related increase of creatinine due to inhibition of secretion of creatinine in the tubular cells without nephrotoxicity AEs. The incidence of rash and nausea may be increased when DRV/COBI is used compared to use of DRV/RTV, but does not seem to be related to DRV exposures nor to COBI itself, since in direct comparison of COBI versus RTV in other studies these differences were not recorded.

Efficacy of DRV/COBI once daily was similar to that of DRV/RTV once daily.

Discussion on the benefit-risk balance

DRV in combination with its pharmaco-enhancer RTV has been approved in HIV patients who are ARV-naïve or who have been exposed to other ARVs but do not have DRV resistance associated mutations (RAMs) and who have plasma HIV-1 ribonucleic acid (RNA) <100,000 copies/mL and CD4+ cell count $\geq$ $100x10^6$ cells/L. COBI has been approved as a pharmaco-enhancer of DRV based on PK data. The observed reduction of DRV C_{tau} of ~30% compared to boosting by RTV, was not associated with reduced antiretroviral activity in earlier studies and not in the currently submitted study GS-US-216-0130. The bioequivalence study is pivotal in supporting the current submission of the FDC DRV/COBI 800/150 mg tablet.

Extrapolation from the current indication of DRV 800 mg once daily if boosted by RTV seems therefore rational for the (fixed dose) combination of DRV/COBI 800/150 mg qd. The confirmatory study GS-US-216-0130 in 313 subjects did not show major new safety concerns during the period of observation of 48 weeks.

Antiretroviral efficacy was demonstrated in 295 treatment-naïve subjects, which appeared in line with that known for DRV/rtv.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of REZOLSTA "indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus-1 (HIV-1) infection in adults aged 18 years or older.

Genotypic testing should guide the use of REZOLSTA (see sections 4.2, 4.3, 4.4 and 5.1)"

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription. (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.