20 July 2017
EMA/496527/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Symtuza

International non-proprietary name: darunavir / cobicistat / emtricitabine / tenofovir alafenamide

Procedure No. EMEA/H/C/004391/0000

Note

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

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List of abbreviations

AAG	α1-acid glycoprotein
ADR	adverse drug reaction
AE	adverse event
aGFR	actual glomerular filtration rate
AhR	aryl hydrocarbon receptor
AIDS	acquired immunodeficiency syndrome
APV	amprenavir
ARV	antiretroviral
ART	antiretroviral therapy
AST	aspartate aminotransferase
ATV	atazanavir
AUC	area under the curve
AUC_{24h}	area under the plasma concentration-time curve over 24 hours
AUClast	area under the curve from 0h up to the time of the last measurable concentration after dosing
AUCinf	area under the curve from time 0h to infinity
BMD	bone mineral density
BMI	body mass index
CatA	cathepsin A
CCDS	Company Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	clearance
Cmax	maximum observed analyte concentration
COBI	cobicistat
CPT	Child-Pugh-Turcotte
CR	child resistant
CSR	clinical study report
%CV	coefficient of variation

CPP(s)	critical process parameter(s)
CQAs	critical quality attributes
CYP	cytochrome P450
d4T	stavudine
DAIDS	division of AIDS
D/C/F/TAF	darunavir/cobicistat/emtricitabine/tenofovir alafenamide
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DoE	Design of experiments
DRV	darunavir
DRV/COBI	darunavir/cobicistat fixed dose combination
DSC	differential scanning calorimetry
DVS	dynamic vapor sorption
E/C/F/TAF	elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide
E/C/F/TDF	elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate
EC50	50% effective concentration
EFV	efavirenz
(e)GFR	(estimated) glomerular filtration rate
eGFRCG	eGFR calculated using the Cockcroft-Gault method
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EVG	elvitegravir
F/TAF	emtricitabine/tenofovir alafenamide
FC	fold change
FDC	fixed dose combination
FTC	emtricitabine
FTC/TDF	emtricitabine/tenofovir disoproxil fumarate
GC	Gas Chromatography
HDL	high density lipoprotein
HDPE	High Density Polyethylene
HIV-1/2	human immunodeficiency virus type 1 or type 2

HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IDV	indinavir
INSTI	integrase strand-transfer inhibitor
IPC	In-process control
IR	Infrared
KF	Karl Fischer
LDL	low density lipoprotein
LDPE	low density polyethylene
LoA	Letter of Access
LPV	lopinavir
LS	least square
MAA	Marketing Authorization Application
MS	Mass Spectrometry
(^{1}H/^{13}C-) NMR	Nuclear Magnetic Resonance
NNRTI	non-nucleoside reverse transcriptase inhibitor
N(t)RTI	nucleoside/nucleotide reverse transcriptase inhibitor
OBR	optimized background regimen
PBMC	peripheral blood mononuclear cell
PK/PD	pharmacokinetic/pharmacodynamic
PD	pharmacodynamic
PE	Polyethylene
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PI	protease inhibitor
PP	Polypropylene
PRAC	Pharmacovigilance Risk Assessment Committee
PRT	proximal renal tubulopathy
PT	preferred term

PXR	human pregnane X receptor
QbD	Quality by Design
QWBA	quantitative whole-body autoradiography
RAM	resistance associated mutation
RH	Relative Humidity
RNA	ribonucleic acid
RPV	rilpivirine
RT	reverse transcriptase
RTV	ritonavir
Rtv	low-dose ritonavir
SAE	serious adverse event
SD	standard deviation
SmPC	Summary of Product Characteristics
SOC	system organ class
SQV	saquinavir
TAF	tenofovir alafenamide
TDF	tenofovir disoproxil fumarate
TFV	tenofovir
TFV-DP	tenofovir-diphosphate
TLOVR	time to loss of virologic response
tmax	actual sampling time to reach the maximum observed analyte concentration
TPV	tipranavir
UGT	uridine diphosphate glucuronosyltransferase
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
U(H)PLC	ultra-high performance liquid chromatography
UV	Ultraviolet
V_p/F	peripheral volume of distribution
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 9 September 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Symtuza, 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 28 January 2016.

The applicant applied for the following indication:

Symtuza is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) (see sections 4.2, 4.4 and 5.1).

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 a new fixed combination medicinal product, composed of administrative information, complete quality data and with appropriate own applicant's non-clinical and clinical data and with a letter from a MAH Gilead allowing the cross 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/0123/2016 on the granting of a waiver.

At the time of submission of the application, the P/0123/2016 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.

Scientific Advice

The applicant did not receive Scientific Advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Alexandre Moreau

- The application was received by the EMA on 9 September 2016.
- The procedure started on 29 September 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 16 December 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 21 December 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 3 January 2016.
- During the meeting on 26 January 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 March 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 26 April 2017.
- During the PRAC meeting on 5 May 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 May 2017.
- During the CHMP meeting on 18 May 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 June 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 July 2017.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 14 July 2017.
- During the meeting on 20 July 2017, 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 Symtuza on 20 July 2017.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) (see sections 4.2, 4.4 and 5.1).

2.1.2. Epidemiology

Since the beginning of the epidemic, more than 70 million people have been infected with HIV, of which about 35 million people have died. Globally, 36.7 million [34.0–39.8 million] people were living with HIV at the end of 2015. An estimated 0.8% [0.7-0.9%] of adults aged 15–49 years worldwide are living with HIV, although the burden of the epidemic continues to vary considerably between countries and regions. Sub-Saharan Africa remains most severely affected, with nearly 1 in every 25 adults (4.4%) living with HIV and accounting for nearly 70% of the people living with HIV worldwide (WHO Global Health Observatory [GHO] data).

2.1.3. Biologic features, aetiology and pathogenesis

HIV-1 infection results in chronic activation of the immune system and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (viral load). The aim of treatment of HIV-1 infection is therefore to suppress the HIV-1 viral load to levels that are at least below 50 copies/mL of blood.

2.1.4. Clinical presentation and diagnosis

Acute HIV-1 infection is often missed, as it usually presents with nonspecific signs and symptoms, or goes without clinical symptoms. Diagnosis therefore most often occurs during chronic infection. Diagnostic tests for HIV-1 infection include assays for HIV-1 RNA, p24 antigen, and HIV-1 and HIV-2 antibodies.

2.1.5. Management

Antiretroviral therapy (ART) is recommended in all adults with chronic HIV infection, irrespective of CD4 counts. For ART-naïve HIV-infected patients, treatment guidelines recommend that initial therapy consists of 2 N[t]RTIs and either a nonnucleoside reverse transcriptase inhibitor (NNRTI), a boosted PI, or an integrase strand-transfer inhibitor (INSTI).

The main goal of ART is to suppress viral replication to below detectable limits, increase CD4+ cell counts, and stop disease progression and prevent transmission. It is a life-long treatment, as the viral load will rebound as soon as an individual stops taking effective antiretroviral therapy.

The available treatment options for HIV-1 infected individuals have greatly improved in the last two decades. Current treatment options are generally considered to be potent, with an overall acceptable toxicity profile.

Mutations in the viral genome can however occur when the virus replicates, which can make the virus resistant to antiretroviral drugs or classes of drugs. Therefore, there is a need for development of new antiretroviral treatment options.

About the product

The Applicant has developed the FDC tablet Symtuza, for oral once-daily use for the treatment of HIV-1 infection. It contains the PI DRV (800 mg), the PK enhancer COBI (150 mg), the NRTI FTC (200 mg), and the NtRTI TFV prodrug TAF (10 mg) as active substances. Two FDCs of the components (DRV/COBI and F/TAF) are already approved in the European Union, respectively, as REZOLSTA and Descovy, for combined administration. The D/C/F/TAF FDC is the first complete protease inhibitor (PI)-based HIV-1 regimen in a single tablet to be taken once daily.

The co-formulation with TAF, a prodrug of the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TFV), instead of tenofovir disoproxil fumarate (TDF), offers an improved renal and bone safety profile compared to TDF, with similar efficacy.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film coated tablets, containing 800 mg darunavir (as ethanolate), 150 mg cobicistat, 200 mg emtricitabine and 10 mg of tenofovir alafenamide (as fumarate) in a fixed dose combination.

Other ingredients of the tablets core are cellulose microcrystalline, croscarmellose sodium, silica colloidal anhydrous and magnesium stearate. The film coating comprises poly(vinyl alcohol)– partially hydrolysed, macrogol 4000, titanium dioxide, talc and yellow ferric oxide.

The product is available in white, high density polyethylene (HDPE) bottle, fitted with polypropylene (PP) child resistant closure with induction seal and a desiccant pouch, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

Darunavir (as ethanolate)

General information

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, corresponding to the molecular formula $C_{27}H_{37}N_3O_7S.C_2H_6O$ and has a relative molecular mass 593.73 g/mol and has the following chemical structure:

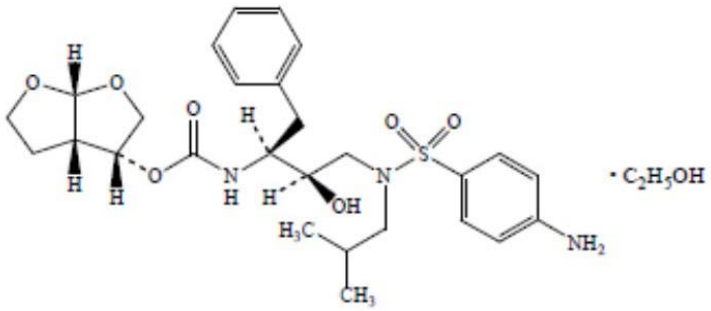


Figure 1. Structure of darunavir ethanolate

The structure of the active substance was elucidated by a combination of IR spectroscopy, ^{1}H- and ^{13}C-NMR spectroscopy, UV spectroscopy, mass spectrometry, elemental analysis and XRD. Darunavir ethanolate is sufficiently characterised and its structure is adequately elucidated.

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

It exhibits stereoisomerism due to the presence of five chiral centres. Enantiomeric purity is controlled routinely through the chiral identity and purity of the starting materials. The absence of interconversion during the manufacturing process and storage has been demonstrated. Darunavir ethanolate is presented in the solid state as a pseudo-polymorph (ethanolate solvate). 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 in Rezolsta 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 and are satisfactory.

The active substance is packed in one or two low density polyethylene (LDPE) bags (primary packaging material) placed into a hot-sealed aluminum polyethylene laminated bag (secondary functional), which is placed into a suitable container (secondary packaging). All components used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

Darunavir specification includes tests for identification (IR, UPLC), physical description (visual), 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). Specifications, analytical procedures and validation data are in accordance with those currently authorised in Rezolsta.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

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 manufacturer(s) stored in the intended commercial package for 36 months at 5 °C (3 commercial scale batches), at 25 ºC / 60% RH for up to 36 months (3 commercial scale batches), at 30 °C / 65% RH for up 36 months (3 commercial scale batches) and up to 60 months (7 commercial scale batches) and at 40 ºC / 75% RH for up 6 months (10 commercial scale batches) according to the ICH guidelines were provided. The parameters tested were physical description, assay, chromatographic purity, ethanol and heavy metals and the methods were stability indicating. All results meet the acceptance criteria after storage at 5 °C, 25 °C /60% RH and 30 °C /65% RH for a period of 36 months, at 30 °C /65% RH for a period of 60 months and 40 °C /75% RH for a period of 6 months. No trends were observed.

Results from a photostability study as per ICH guideline conditions show a decrease in ethanol content along with an increase in water content. These changes are due to the fact that the drug substance was removed from the hot-sealed aluminum laminated bag to be exposed to the light. No change in impurity profile was observed upon exposure to light.

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

Cobicistat on silicon dioxide

General information

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), corresponding to the molecular formula $C_{40}H_{53}N_7O_5S_2$ and has a relative molecular mass 776.0 g/mol and has the following chemical structure:

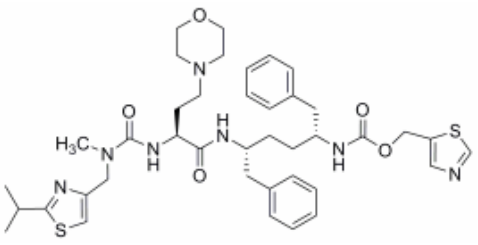


Figure 2. Structure of cobicistat

The structure of the active substance was elucidated by a combination of IR spectroscopy, 1H- and 13C-NMR spectroscopy, UV spectroscopy, mass spectrometry and XRD. Solid state properties were confirmed using X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), and dynamic vapor sorption (DVS). Comparison of the IR, UV, DSC and DVS data for cobicistat reference standard and a sample of cobicistat on silicon dioxide were also discussed. Cobicistat on silicon dioxide is sufficiently characterised and its structure is adequately elucidated.

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.

Cobicistat exists as a white to pale yellow amorphous solid. Cobicistat on silicon dioxide is a white to pale yellow, hygroscopic powder. Amorphous cobicistat is practically insoluble in water. The solubility of both the amorphous and the adsorbed on silicon dioxide increases significantly in acidic pH, soluble/sparingly soluble respectively in 0.1N HCl.

Cobicistat exhibits stereoisomerism due to the presence of three chiral centres. It is produced as a single isomer. The stereochemical configurations at these chiral centres are controlled through the synthetic process and use of starting materials having suitably high chiral purities. One crystalline form has been identified for cobicistat free base. Cobicistat active substance is amorphous.

Manufacture, characterisation and process controls

Cobicistat is synthesized in multiple convergent steps using well-defined starting materials with acceptable specifications. The manufacturing process is the same as described in Rezolsta 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.

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

The active substance is packed in in double polyethylene bags. The bags are held in high-density polyethylene drums with lids (or other suitable secondary containment) and fitted with a tamper-evident security seal. All components used as primary packaging material are food grade and comply with the requirements of Ph. Eur. and European Directive 10/2011 as amended.

Specification

Cobicistat on silicon dioxide specification, re-produced in Table 2, includes tests for appearance (visual), identification of silicon dioxide (chemical reaction), identification of cobicistat (IR, HPLC, UV), water content (KF), assay (HPLC), impurity content (HPLC), chiral purity (HPLC), residual solvent (GC), heavy metals (ICP-MS) and crystallinity (PXRD). Specifications, analytical procedures and validation data are in accordance with those currently authorised in Rezolsta.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data of 20 representative batches of the active substance are provided (the crystalline content was tested in 3 batches). The results are within the specification and consistent from batch to batch.

Stability

Stability data on 3 commercial scale and 2 pilot scale batches of cobicistat from the proposed manufacturers stored in the intended commercial package for up to 60 months at 5 °C, for up 48 months at 25ºC/60% RH and for up to 12 months at 30°C/75% RH according to the ICH guidelines were provided. The parameters tested were appearance, assay, impurity content, chiral impurities and water content. The absence of crystalline form is monitored on long-term stability for one commercial scale batch (ongoing). The analytical methods used were the same as for release and were stability indicating. All stability attributes were well within the specified acceptance criteria and showed no discernible trends through 48 and 60 month time points.

A photostability study was conducted on one batch in accordance with ICH Q1B Guideline. Photostability Testing of New Drug Substances and Products Stress test studies were also conducted following the ICH Q1A (R2) Guideline, Stability Testing of New Drug Substances and Products. The data indicate that cobicistat on silicon dioxide is not sensitive to light.

Stress study has also been conducted at 30 °C/75% RH, to assess the stability of cobicistat on silicon dioxide at higher temperatures such as those that may occur during shipping and handling. Tested parameters remain within specification and the results support exposure to elevated temperatures up to 30 °C for a 3 month cumulative duration that may arise during shipping and handling.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period and storage conditions in the proposed container.

Emtricitabine

General information

The chemical name of emtricitabine is 4-amino-5-fluoro-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan -5-yl]-1,2-dihydropyrimidin-2-one , corresponding to the molecular formula $C_8H_{10}FN_3O_3S$ and has a relative molecular mass 247.24 g/mol and has the following chemical structure:

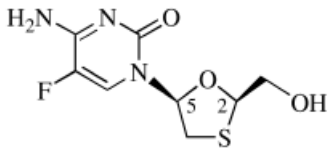


Figure 3. Structure of emtricitabine

The structure of the active substance was elucidated by a combination of ^{1}H- and ^{13}C-NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and single crystal x-ray determination.

Emtricitabine appears as a white to off-white non-hygroscopic crystalline powder, freely soluble in methanol and water. Its pKa is 2.65 and the partition coefficient Log P is -0.43.
It has 2 chiral centres at carbons 2 and 5 of the oxathiolane ring. Two enantiomeric pairs of diastereomers can exist: *cis*-(-)- emtricitabine and *cis*-(+)- emtricitabine, *trans*-(-)- emtricitabine and *trans*-(+)- emtricitabine. The synthetic route has been chosen to be stereoselective for the formation of the desired cis-(-) enantiomer, emtricitabine.

Three polymorphs of emtricitabine have been observed. However, the most stable thermodynamically form at room temperature, is consistently produced.

Manufacture, characterisation and process controls

Emtricitabine is manufactured by two possible synthetic routes sharing a common first step and followed by two options comprising either one or two extra steps. The active substance information is essentially the same as in the approved product Descovy. The synthesis was described in sufficient detail.

The synthetic process results in the stereoselective formation of an intermediate and thus the formation of the desired emtricitabine enantiomer. Five manufacturing sites are involved. Adequate in-process controls (IPCs) are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. The process has been shown to consistently produce emtricitabine that meets the required quality standards. 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.

The active substance is packaged in double polyethylene (PE) bags inside HDPE drums; the PE bags comply with EC Regulation 10/2011 as amended.

Specification

Emtricitabine specification includes tests for appearance, identification (IR, HPLC), clarity of solution, water content (Ph. Eur.), assay (HPLC), impurity content (HPLC), enantiomeric purity (HPLC), organic volatile impurities (GC), heavy metals (ICP-MS), residue on ignition (Ph. Eur.) and particle size (laser scattering). The active substance specification is essentially the same as in the approved product Descovy.

The testing and the proposed limits applied, conform to current ICH guidelines and are acceptable from a toxicological and clinical perspective. Non compendial analytical methods have been validated in accordance with ICH guidelines.

Extended testing during development has demonstrated that only a single polymorphic form results from the synthetic process of emtricitabine. Therefore, as per ICH Q6A, testing for polymorphic form at release is not necessary. Development data demonstrate the absence of indicator organisms and therefore, as per ICH Q6A, microbial testing of the active substance is not required. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data on 22 commercial scale batches of the active substance from all proposed manufacturers were provided. The results comply with the specifications and confirm consistency and uniformity of the manufacturing process.

Stability

Thirteen commercial scale and additional pilot scale batches of emtricitabine manufactured using both synthetic routes and packaged in the proposed container were put on stability testing in accordance with the ICH Q1A (R2) Guideline under long-term conditions (25ºC/60% RH) for up to 36 months. Of the above batches, eight commercial scale and five pilot batches were stored under accelerated conditions (40ºC/75% RH) for up to 6 months. In addition, another three batches were stored under intermediate conditions (30ºC/65% RH) for up to 12 months. Samples were tested for appearance, impurities, assay, water content and enantiomeric purity by validated stability indicating methods. Stability data for emtricitabine manufactured by both synthetic routes was comparable. The majority of tested parameters remained within the specification limits throughout the study period for all three stability conditions. In one isolated batch, one degradation product exceeded the specification limit at the last time point (36 months). The same degradation product is observed in emtricitabine stored under accelerated conditions. Four batches stored under accelerated conditions exceeded the specification limit at 6 months. These data indicate that emtricitabine should not be exposed to elevated temperatures for extended periods of time.

A photostability study was conducted on one commercial batch of emtricitabine. The results showed no significant changes in appearance, purity, and impurity content and indicate that emtricitabine is not sensitive to light.

Based on the long-term stability data, the proposed re-test period and storage conditions when the active substance is packed in the proposed packaging materials is considered acceptable.

Tenofovir alafenamide fumarate

General information

The chemical name of tenofovir alafenamide fumarate (TAF fumarate) is propan-2-yl N-[(S)-({[(2R)-1-(6-amino-9H-purin-9-yl)propan-2-yl]-oxy}methyl)(phenoxy)phosphoryl]-L-alaninate, (2E)-but-2-enedioate (2:1) corresponding to the molecular formula $C_{23}H_{31}O_7N_6P$ and has a relative molecular mass 534.5 g/mol and has the following structure:

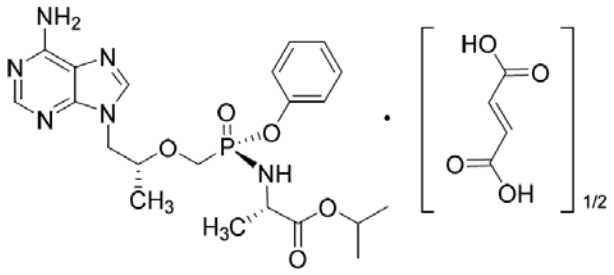


Figure 4. Structure of tenofovir alafenamide fumarate.

The chemical structure of TAF fumarate has been adequately demonstrated by infrared spectroscopy, nuclear magnetic resonance spectroscopy (^{1}H, ^{13}C, and ^{31}P), mass spectrometry, elemental analysis, ultraviolet absorption spectroscopy, and X-ray crystallography.

The active substance is a white to off-white or tan, slightly hygroscopic powder. TAF fumarate has pH-dependent aqueous solubility decreasing with increasing pH. It is soluble at low pH (pH 2.0), sparingly soluble at pH 3.8, and slightly soluble at pH values up to 8.0. TAF fumarate is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol and slightly soluble in acetone.

Tenofovir alafenamide exhibits stereoisomerism due to the presence of three chiral centres. The chiral centre at the propyloxy- side chain is in the *R*-configuration. The absolute stereo-configuration of the carbonylethylamino-substituent has the *S*-configuration at the alpha-carbon. The remaining stereocentre is located at the phosphorus atom and is in the *S*-configuration. Enantiomeric purity is monitored routinely by chiral HPLC.

Polymorphism has been observed for TAF fumarate. A single form is consistently generated through the manufacturing process and this form has been adequately characterised and is consistently produced by the manufacturing process.

Manufacture, characterisation and process controls

TAF fumarate is obtained from two manufacturers using the same synthetic route. It is synthesized in multiple steps using well-defined starting materials with acceptable specifications.

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

The characterisation of the active substance and its impurities is 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. Critical process parameters were identified using a risk assessment approach.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double-lined PE bags which comply with the EC Regulation 10/2011 as amended. The bags are held in HDPE drums (or other suitable secondary container) with lids of appropriate size and fitted with a security seal.

Specification

The active substance specification includes tests for appearance (visual examination), identification (IR, HPLC), identity of fumaric acid (HPLC), clarity of solution (visual examination), water content (Ph. Eur.), assay (HPLC), impurities (HPLC, HPLC-MS, GC), L-alanine isopropyl ester content (HPLC), fumaric acid content (HPLC), residual solvents (GC), elemental impurities (ICP-MS), and melting point (Ph. Eur.). The active substance specifications are based on the active substance critical quality attributes (CQAs).

Impurities present at levels higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay testing has been presented.

Batch analysis data of 13 production and 3 pilot scale batches of the active substance, manufactured at both proposed manufacturing sites using the proposed commercial process were provided. Additional batch analysis data for development batches used in pre-clinical pharmacokinetics and toxicological studies are provided. The results are within the specification and consistent from batch to batch.

Stability

Stability data on 6 commercial scale batches of active substance from both proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions (5 ºC) and for up to 24 months under accelerated conditions (25 ºC/60% RH) according to the ICH guidelines were provided. Results under stressed conditions for up to 6 months at 40 ºC/75% RH on 5 batches were provided. Additionally, results for 4 days at 60 ºC / ambient RH, for 4 days at 50 ºC/ambient RH and for 4 days at -20 ºC were also provided on one batch.

Samples were tested for appearance, impurities, assay, water content, and solid state characteristics (XRD and melting point). The analytical methods used were the same as for release and were stability indicating.

All tested parameters remained within specification under long term and accelerated conditions. Degradation products increased under accelerated conditions but also remained within the specification.

Photostability testing following ICH guideline Q1B was performed on one commercial sale batch, indicating that the active substance is not photosensitive.

The stability results indicate that the active substance manufactured by the both proposed suppliers is sufficiently stable. The stability results justify the proposed retest period and storage conditions in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is an immediate release fixed-dose combination film-coated tablet intended for oral administration. The finished product contains 867.0 mg of darunavir (DRV) ethanolate (equivalent to 800 mg

darunavir free form), 288.5 mg of cobicistat (COBI) on silicon dioxide (equivalent to 150.0 mg cobicistat free form), 200 mg of emtricitabine (FTC), and 11.2 mg of tenofovir alafenamide (TAF) fumarate (equivalent to 10.0 mg tenofovir alafenamide free form). The tablets are yellow to yellowish brown capsule shaped measuring 22 mm x 10 mm, debossed with "8121" on one side and "JG" on the other side.

Fixed dose combinations of the components (DRV/COBI and FTC/TAF) are already approved, respectively as Rezolsta and Descovy, and can be used in combination.

The main objective of the pharmaceutical development was to develop a single tablet, containing all active substances, taking into account their different physical and chemical properties and stability, while keeping the tablet mass to a minimum.

The formulation development was based on prior experience with DRV tablets, the addition of the other active substances, and the need to minimize tablet weight.

Darunavir (DRV) is very slightly soluble at all pH and presents pseudo-polymorphism. It is isolated as ethanol solvate, however, it converts into hydrate at ambient conditions. The presence of darunavir hydrate in the finished product has no impact on clinical bioavailability because ethanolate and hydrate forms of DRV have the same comparative bioavailability as shown by a comparative bioavailability study (Study TMC114-C148). The specifications for DRV particle size distribution have been previously established during the development of the original darunavir 300 mg tablet submission.

Cobicistat (COBI) is an amorphous solid with low glass transition temperature. For manufacturability and stability reasons, cobicistat is adsorbed on silicon dioxide. Cobicistat (non-adsorbed) is an amorphous solid which is dissolved in a solvent and loaded on silicon dioxide, thus the particle size of COBI is not relevant. Cobicistat on silicon dioxide has a pH dependent solubility (solubility increases as pH decreases). There is a pXRD test and acceptance criterion for the cobicistat drug substance as a control for solid state properties.

Emtricitabine (FTC) is a crystalline solid and form I is the thermodynamically stable form. FTC is soluble and solubility increases as pH decreases. The acceptance criteria for the FTC particle size distribution are approved for several emtricitabine-containing products. Due to the high solubility of emtricitabine across the physiological pH range, emtricitabine particle size is not expected to impact bioavailability.

Tenofovir alafenamide (TAF) is a prodrug of tenofovir. The form I (hemifumarate, referred as fumarate) is thermodynamically stable. TAF is soluble in water; solubility depends on pH (increases as pH decreases). The acceptance criterion for the TAF particle size is approved for other tenofovir alafenamide-containing products. Due to the solubility of tenofovir alafenamide across the physiological pH range, tenofovir alafenamide particle size is not expected to impact bioavailability. TAF is susceptible to hydrolysis therefore appropriate measures are employed to address TAF stability. The potential moisture contribution from the individual components of formulation was evaluated and as a result water content of COBI active substance and microcrystalline cellulose are considered critical material attributes. In addition water content of tablets is controlled at release and desiccant is added in the primary container.

The formulations used in phase I, II and III studies and their differences were presented in sufficient detail. The final formula has been used since phase II clinical studies and it has been demonstrated bio-equivalent to currently approved products containing the same active substances (see clinical part). The excipients used in Symtuza are well-known, common excipients including microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and film coating material. The quality of these excipients is compendial, except for film coating material for which internal specifications are applied.

The product is indicated for use in children from 12 years and older. The large tablet size may give rise to acceptability issues especially for children. It is noted that the rather large size of the Symtuza tablets (22 mm x 10 mm) is comparable to other antiretroviral products used in the same patient population. The company has acknowledged that the large tablet size may result in swallowing difficulties. Therefore, the possibility to crush or split the tablets has been further investigated in an ongoing relative bioavailability study. The results indicated that splitting does not result in differences versus intact tablets that are clinically relevant. However, the study is not considered sufficient to justify tablet splitting as it does not neither cover the variety in methods of tablet subdivision (hand, splitter, tool) nor the operator characteristics and does also not provide any data on loss of mass. Besides, there is no real evidence that patients who have difficulties swallowing the intact FDC tablet would be able to swallow the tablet following breaking and would also prefer this approach over the intake of the single component tablets. The acceptability of the intact tablets has been tested in another *in vivo* study. The swallowability of the intact FDC was found acceptable in the subjects who were enrolled in the later study but all subjects were treatment-experienced subjects. In view of the aforementioned, the CHMP recommended that a breakmark (scoreline) should be introduced, unless otherwise justified, to allow patients to easily break the tablet by hand without any relevant loss of mass prior to administration. In addition, the applicant is asked to investigate that the intake of a broken tablet eases swallowing in patients who cannot swallow the tablet intact. If not, alternative measures should be proposed.

For a fixed dose combination tablet, a single dissolution method would be preferred. However, in the case of Symtuza, the four active substances have different solubility profiles and a wide dosage strength range, making difficult to have a single dissolution method with adequate discriminatory power. DRV is practically insoluble in the physiological pH range and it is present at a high dose; sink conditions could not be reached without a surfactant in the medium. The starting point for method development was prior knowledge with the dissolution method for the approved combination Rezolsta. It was demonstrated that the method used for DRV is not suitable for the other active substances, while the method used for COBI is not suitable for DRV. The method used for DRV is the same as the one used for Rezolsta. The method used for COBI, FTC, and TAF is the same as the one used for COBI single agent.

DRV is practically insoluble in the physiological pH range therefore surfactant is used to achieve sink conditions. The selection of the dissolution method has been satisfactorily been justified.

COBI, FTC, and TAF have solubility depending on pH. A common dissolution method is used for the three substances. The selection of the dissolution method has been satisfactorily justified.

The discriminatory power of both methods has been discussed. The lack of the discriminative nature of the dissolution methods for some aspects (i.e. particle size, hardness, granulation parameters and composition) is considered acceptable, as those aspects are controlled at different stages.

The four drug substances combined contribute a significant amount (88%) of the total tablet weight. Given the relatively poor flowability and compressibility of the individual drug substance powders, a dry granulation process is used to produce granules that contain the four active substances to provide a final blend for tablet compression that has suitable flow and compressibility characteristics.

An overview of the manufacturing process equipment at the different scales has been presented. In vitro studies demonstrated that the process scale-up had no impact on the performance of the finished product.

A systematic Quality by Design (QbD) approach was applied, based on prior knowledge and development studies a risk (criticality) assessment was conducted on the potential impact of each stage of the manufacturing process on the finished product CQAs. These were defined to be product appearance, identification, assay, uniformity of dosage units, dissolution, purity/degradants, water content and microbiological purity. The risk

assessment has been described in sufficient detail in the dossier. The corresponding rationales have been given and the control strategy has been described. Design of experiments (DOE) studies have been performed for each step of the manufacturing process and all process parameters were designated as either critical process parameters (CPP) or non-CPP. Based on the results of the DOE studies (most studies were multivariate studies) PARs and/or target settings have been established for each of the process parameters (CPP as well as non-CPP) by demonstrating that operating within the tested ranges had no critical impact on the drug product CQAs. A design space is claimed for the roller compaction/milling, compression and film coating steps. The boundaries of the design space in terms of CPPs ranges have been explicitly laid down. The development studies have demonstrated the robustness of the manufacturing process and based on the results of the manufacturing process development studies, the finalized target settings and PARs for the manufacturing process are in general considered justified.

The container closure system of Symtuza film-coated tablets is a white, high-density polyethylene (HDPE), 120-mL bottle with child resistant (CR) polypropylene (PP) closure, with induction seal liner, containing a 3 g silica gel desiccant pouch. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The necessary ISO certificate has been submitted with regard to the child resistant feature.

Manufacture of the product and process controls

The manufacturing process comprises 8 main steps: initial blending without lubricant, initial blending with lubricant, roller compaction/milling, final blending, compression, preparation of the film-coating suspension, film-coating, packaging.

Design spaces have been proposed for the following steps of the manufacturing process of the medicinal product: roller compaction/milling, compression and film coating steps. The design spaces have been developed at commercial scale.

Holding times have been defined and justified.

The process is considered a non-standard process as tenofovir alafenamide covers approx. 0.72% of the total tablet core weight which is considered critical with regards to homogeneity according to “Annex II to note for guidance on process validation for finished products EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1”. Process validation data on three full production batches have been submitted according to an acceptable validation protocol. Based on the provided process validation data it is concluded that the proposed manufacturing process is satisfactorily validated and suitable for commercial manufacturing.

Product specification

The finished product release and shelf life specifications includes appropriate tests and limits for this kind of dosage form: appearance (visual), identification of the four active substances (UHPLC, UV), water content (Ph. Eur.), assay of the four active substances (HPLC), chromatographic purity of the four active substances (UHPLC), uniformity of dosage units (Ph. Eur.), dissolution, and microbiological purity (Ph. Eur.).

The specification is acceptable based on batch analysis results, stability results and in accordance with relevant European guidelines. Impurity levels are based on the active substance limits, development study results and toxicological studies.

The in-house analytical methods have in general been adequately described and validated. Sufficient information has been presented for the reference standards used.

A single dissolution test method was suitable during development, but a more discriminatory test method was required and the commercial test methods were developed for commercial batches. Comparison of the dissolution methods and the dissolution profiles generated using the development test method and the proposed commercial test methods were provided in the dossier.

A cross-over study was performed for the initial version of the assay/chromatographic purity test method used for batch release and for the updated method used as from the 12-month time point for the primary stability studies. The equivalence of the initial and updated versions of the test method was demonstrated.

Batch analytical data from two commercial scale batches and 9 other smaller scale batches have been presented. The data demonstrates compliance with the proposed release specification..

Stability of the product

Stability data on three pilot scale batches stored under long term conditions 25 °C/60% RH and 30 °C/75% RH for up to 21 months and under accelerated conditions 40 °C/75% RH for 6 months has been provided, according to the ICH Stability Guidelines; the use of the harsher 30 °C/75% RH condition for intermediate testing is acceptable. Samples were tested for appearance, water content, assay, chromatographic purity, dissolution and microbial purity. The stability test methods are the same as the release test methods with one exception: an updated version of the assay/chromatographic purity test method was implemented at the 12-month time point. A cross-over study was performed and the equivalence of the initial and updated versions of the test method has been demonstrated. No meaningful change is observed in any attribute studied at long-term and accelerated storage condition. All data reported comply with the proposed specifications and there are no trends observed.

A photostability study was conducted on one commercial scale batch the product, as per the ICH Q1B guideline. Despite a slight increase in some degradation products the change is considered not significant difference between protected and not protected samples. The finished product is therefore considered not sensitive to light.

Results of an in-use stability study on a commercial scale batch demonstrate that the finished product is stable up to 6 weeks at both 25 ºC and 30 ºC after opening of the container thus justifying the proposed in-use stability (SmPC section 6.3).

Based on the provided stability data, the proposed shelf life of 24 months in the original package with desiccant inside the bottle in order to protect the tablets from moisture as stated in the SmPC (section 6.3 and 6.4) is acceptable.

Adventitious agents

There are no materials of human or animal origin used in the manufacture of the finished product.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the four active substance and finished product has been presented in a satisfactory manner. The product development was based on prior knowledge with other already authorised products containing the same active substances. The results of tests carried out indicate

consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform performance in clinical use.

The applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the finished product. The design spaces have been adequately verified.

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 for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-To introduce a breakmark on the tablet to allow patients to easily break the tablet by hand without any relevant loss of mass prior to administration. The company should investigate if tablet breaking will ease swallowing in patients who are unable to swallow the tablet intact. Otherwise, an alternative administration strategy should be proposed.

2.3. Non-clinical aspects

2.3.1. Introduction

Symtuza is a fixed dose combination containing 800 mg of darunavir (as ethanolate), 150 mg of cobicistat, 200 mg of emtricitabine, and 10 mg of tenofovir alafenamide (as fumarate). All active substances are known medicinal products. The combination darunavir / cobicistat was authorised as Rezolsta while emtricitabine / tenofovir alafenamide as Descovy. Symtuza (D/C/F/TAF FDC) is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg). The recommended dose is one tablet once daily.

No new non-clinical data have been submitted. The nonclinical development program of the D/C/F/TAF FDC is entirely based on the individual development programs of the four components.

2.3.2. Pharmacology

Primary pharmacodynamic studies

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.

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.

Emtricitabine

Emtricitabine is a synthetic analogue of the naturally occurring pyrimidine nucleoside, 2′ -deoxycytidine. Intracellularly, emtricitabine is converted through 3 phosphorylation reactions to its active tri-phosphorylated anabolite emtricitabine triphosphate.

Emtricitabine triphosphate inhibits viral polymerases by direct binding competition with the natural deoxyribonucleotide substrate (deoxycytidine triphosphate), and after incorporation into DNA, by DNA chain termination. EC50 of emtricitabine against laboratory adapted strains of HIV-1 ranged from 0.001 to 0.62 µM depending on cell type and virus strain used in the assay. With clinical isolates of HIV-1, EC50 values ranged from 0.002 to 0.028 µM.

In vivo animal studies have been completed with emtricitabine or emtricitabine in combination to demonstrate its activity against immune deficiency in the macaque monkey. Macaques were infected with the simian immunodeficiency virus (SIV) and 50 days post-inoculation animals were treated subcutaneously with either tenofovir (20 mg/kg) and emtricitabine (50 mg/kg) or were not given any drugs. The treated macaques achieved SIV levels that were below the limit of detection (ie, < 100 copies/mL of viral RNA), whereas only 1 of the non-treated macaques showed a decrease in SIV RNA. SIV levels remained low in all treated animals for up to 6 months.

In another study, monkeys were exposed to 14 weekly doses of SHIV (SIV/HIV chimeric virus). Rhesus macaques were injected subcutaneously with tenofovir/emtricitabine daily, at 2 hours before and 24 hours after the first virus exposure or at 2 hours before first virus exposure only. Twenty of the 21 control animals became infected, however all 6 of animals treated with tenofovir/emtricitabine daily or before and 24 hours after the first challenge were fully protected after 14 challenges. In the single-dose group, 1 of 6 animals was infected, confirming that multiple dose therapy was highly effective at protecting these animals against rectal transmission of HIV.

Tenofovir alafenamide

Tenofovir alafenamide is hydrolysed to tenofovir by the lysosomal carboxypeptidase, cathepsin A and is then metabolised to the active metabolite, tenofovir diphosphate, which is an inhibitor of HIV-1, HIV-2 and HBV polymerases, and is an inhibitor of HIV-1 reverse transcriptase that competes with deoxyadenosine triphosphate (dATP) for incorporation into nascent DNA and terminates the elongation of the viral DNA chain during the process of retroviral reverse transcription, thereby effectively blocking the replication and spread of infectious HIV.

In vitro studies have shown that tenofovir alafenamide has anti-HIV activity in lymphoid T-cells, primary human PBMCs, and macrophages with EC50 values ranging from 3 to 14 nM. The in vitro activity of tenofovir alafenamide against HIV-1 is 100- to 600-fold greater than tenofovir and 4- to 6-fold greater than tenofovir diphosphate.

In MT-2 cells, tenofovir alafenamide shows low cytotoxicity with a selectivity index (SI) of > 10,000). Based on data generated with the parent nucleotide tenofovir, tenofovir alafenamide is expected to be active against a wide range of HIV-1 subtypes and also against HIV-2. In addition, tenofovir alafenamide is a potent inhibitor of hepatitis B virus (HBV) replication, exhibiting in vitro activity comparable to that of tenofovir diphosphate with an EC50 value of 18 nM.

No in vivo work with tenofovir alafenamide was conducted however this has been completed with the active component of tenofovir alafenamide , tenofovir. Monkeys received a single dose of 30 mg/kg radiolabelled tenofovir subcutaneously, and the extent of tenofovir in plasma and levels of intracellular tenofovir and tenofovir metabolite concentrations were determined. The tenofovir concentration in plasma reached a maximum of approximately 50 µM and declined with a t1/2 of 5 to 7 hours. As was seen in the in vitro studies, tenofovir is efficiently taken up by PBMCs and is metabolised to tenofovir diphosphate, with the intracellular concentrations of the active metabolite tenofovir diphosphate reaching 0.9 µM.

Secondary pharmacodynamic studies

Darunavir

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.

Cobicistat

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).

Emtricitabine

For emtricitabine, no cytotoxicity was observed in vitro in human PBMC, MT-2, HepG2, CEM, MOLT-4, and Vero cells at concentrations up to 100 µM. Emtricitabine was also found to be nontoxic to human bone marrow progenitor cells in vitro.

The potential for mitochondrial toxicity with emtricitabine was evaluated. Emtricitabine was incubated with HepG2 cells at concentrations ranging between 0.1 and 10 µM for 2 weeks, and MT-2 cells were incubated with emtricitabine at concentrations up to 100 µM for up to 8 weeks. Emtricitabine had no adverse effects on cell growth, mitochondrial DNA synthesis, or lactic acid production. Further studies confirmed this finding.

The inhibition of mitochondrial DNA synthesis was also assessed in an in vitro cell culture assay using Molt-4 cells (a T-lymphoblast cell line). Emtricitabine did not reduce the ratio of mitochondrial to cellular DNA when tested at concentrations of up to 100 µM after 7 days of continuous cell exposure.

Emtricitabine had no significant binding affinity at 19 different receptors, has shown little or no direct effect on various isolated muscle preparations (cholinergic, adrenergic, histaminergic, and serotonergic), and had no major inhibitory effects on the contractile responses to acetylcholine, norepinephrine, serotonin, isoproterenol, arachidonic acid, histamine, bradykinin, and angiotensin II.

Tenofovir alafenamide

CC50 values for tenofovir alafenamide ranged from 6.8 µM in dividing PBMCs to 25.1 µM in resting PBMCs. Tenofovir alafenamide showed low cytotoxicity in resting and in dividing PBMCs. Tenofovir alafenamide showed low cytotoxicity in T-lymphoblastoid cells providing ≥ 1997-fold increased selectivity relative to antiviral activity in T-lymphoblastoid cell lines. Similarly tenofovir alafenamide demonstrated low cytotoxicity to hepatic cells. Tenofovir alafenamide also showed little to no effect on erythroid and myeloid progenitor proliferation in vitro.

The cytotoxicity of tenofovir alafenamide and tenofovir was assessed in human HEK293T cells transiently expressing OAT1 and OAT3. Cells were incubated with serial dilutions of tenofovir or tenofovir alafenamide for 4 days. Tenofovir alafenamide did not interact with the renal organic anion transporters 1 or 3 (OAT1 or OAT3), and tenofovir alafenamide exhibited no OAT-dependent cytotoxicity in human epithelial kidney cells transiently expressing these transporters. In addition, the selectivity index (considering CC50 in renal HEK293 cells expressing OAT1 or OAT3 relative to EC50 in primary CD4+ T lymphocytes) for tenofovir alafenamide (29,000 and 4270, respectively) was much higher than for tenofovir (14 and 82, respectively). As a result tenofovir alafenamide is unlikely to accumulate in renal proximal tubules in an OAT-dependent manner, supporting the hypothesis that it has the potential for an improved renal safety profile.

The potential for tenofovir alafenamide to induce mitochondrial DNA depletion was evaluated in HepG2 cells. HepG2 cells treated with tenofovir alafenamide (0.1, 0.3, or 1.0 µM) for 10 days exhibited no significant reduction in mitochondrial DNA compared with untreated cells. No effect of tenofovir was seen on the synthesis of mitochondrial DNA or lactic acid production in HepG2 human liver cells or in normal human skeletal muscle cells. The results confirm the low potential for tenofovir to interfere with mitochondrial functions.

Safety pharmacology programme

Darunavir

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 Cmax 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.

Cobicistat

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.

Emtricitabine

In vitro the effects of emtricitabine on cardiac preparations was evaluated using isolated cardiac muscle from rat, guinea pigs and cats. Results from these in vitro studies suggested that emtricitabine was free of negative cardiac effects at 1 μM. No effects on the cardiovascular system were reported in anesthetised dogs administered a cumulative dose of 38.5 mg/kg of emtricitabine intravenously over a 1-hour period. Rats given oral doses of up to 250 mg/kg emtricitabine showed no effect on heart rate or blood pressure. In addition, there were no abnormalities reported on the ECG data obtained from the repeated-dose toxicity studies in monkeys, where AUC exposures were up to 26-fold higher than in humans at 200 mg.

A range of central nervous system effects were examined in a single study conducted with male ICR mice. Mice (10/dose) were given emtricitabine orally at 0 (distilled water), 10, 30, or 100 mg/kg as a single dose. Emtricitabine did not affect reflex, spontaneous locomotion, motor coordination, anticonvulsant activity, proconvulsant activity or analgesic activity at any dose tested. A further two studies in rats examined the effects of emtricitabine on reflexes, analgesic activity and conditioned avoidance. Emtricitabine had no effect on these parameters.

Effects of emtricitabine on the respiratory system have been examined in mice, rats and dogs. In mice and rats, animals were exposed to up to 1000 mg/kg of oral emtricitabine with no effect on respiratory rate at any dose. Male beagle dogs were intravenously administered emtricitabine at 1, 2.5, 5, 10, and 20 mg/kg (cumulative dose = 38.5 mg/kg) over an hour. No changes were observed on respiratory function at any dose.

Male ICR mice (10/dose) were given emtricitabine orally at 0 (distilled water), 10, 30, or 100 mg/kg, then given a charcoal suspension orally at 1 hour post-dose. Emtricitabine did not affect GI motility at any dose.

Male Long Evans-derived rats were given emtricitabine orally at 0 (distilled water), 10, 30, or 100 mg/kg and urine was collected for 6 hours post-dose. Emtricitabine did not affect urine output, pH, or electrolyte excretion at any dose.

Tenofovir alafenamide

Tenofovir alafenamide was evaluated at concentrations of 1 and 10 µM, and hERG inhibition was not significant. The IC50 for the inhibitory effect of tenofovir alafenamide on hERG was estimated to be greater than 10 µM. Oral administration of tenofovir alafenamide to conscious instrumented male beagle dogs at doses of 30 or 100 mg/kg (24 and 80 mg/kg free base equivalents) did not induce pharmacologic effects on heart rate, systemic blood pressure, or ECGs. However, in the 39-week repeated dose toxicity study in beagle dogs, a dose-related prolongation of the PR interval was observed at 6 and 18/12 mg/kg/day.

The effect of tenofovir alafenamide on the central nervous system has been examined in male SD rats. Animals were treated with single oral doses of tenofovir alafenamide (as the monofumarate form) with doses of 0, 100 or 1000 mg/kg (80 or 800 mg free base equivalents/kg). There was no evidence of any effect on the CNS at any dose tested up to 1000 mg/kg.

SD rats were administered tenofovir alafenamide by oral gavage at doses of 0, 100 or 1000 mg/kg (0, 80 or 800 mg free base equivalents/kg). At the highest dose the rate of gastric emptying was reduced, although this was not observed at 100 mg/kg. A dose of 100 mg/kg was considered to have had no effect on gastric emptying or intestinal motility..

The effect of tenofovir alafenamide on the renal system was evaluated in male SD rats following administration of single oral doses of 0, 100, or 1000 mg/kg (80 or 800 mg free base equivalents /kg). Urinary output of calcium was increased at 1000 mg/kg, however this was correlated with an increase in serum calcium concentration and indicated that the kidneys were functioning well in order to reduce the serum calcium load. The no-effect dose for a pharmacological effect on the renal system was 1000 mg/kg.

Pharmacodynamic drug interactions

Combinations of darunavir with current antiretrovirals were additive or modestly synergistic in an in vitro anti-HIV-1/IIIB MT4 cell-based assay. No significant changes were observed in the activity of selected antiretrovirals in the presence of cobicistat. PR interval prolongation by cobicistat in rabbit isolated heart appeared more pronounced in combination with atazanavir, but the differences were not considered clinically significant. Cathepsin A-mediated hydrolysis of tenofovir alafenamide was not inhibited by HIV protease inhibitors and several hepatitis C protease inhibitors. Telaprevir and boceprevir were identified as potent inhibitors of cathepsin A-mediated hydrolysis of tenofovir alafenamide.

Non-clinically, potential for PR interval prolongation has been reported for cobicistat and tenofovir alafenamide. The combination cobicistat / tenofovir alafenamide has already been approved for Genvoya, where it was concluded that no additional investigation of the combination was necessary, since clinically, no cardiovascular signals were observed from cobicistat or tenofovir alafenamide. Therefore, no additional studies are necessary.

2.3.3. Pharmacokinetics

Absorption

Darunavir absorption was rapid following oral administration in all species. The absolute oral bioavailability was 37% to 58% in adult rats and 60 to 122% in dogs. After repeated administration, a decrease in systemic exposure was observed in rats, mainly due to induction of CYP3A iso-enzymes, but not in dogs.

After oral dosing, bioavailability of cobicistat was low or low/moderate (33%, 11% and 7% in rat, dog and monkey resp.), likely due to high first-pass elimination. Auto-induction was observed in rats and mice, but not in dogs.

Emtricitabine was rapidly and well absorbed with oral bioavailability ranging from 58% to 97% in mice, rats and cynomolgus monkeys. There were no significant differences in pharmacokinetics following single and multiple dosing.

Tenofovir alafenamide was rapidly absorbed and rapidly converted into tenofovir in all investigated species (mice, rats, dogs and monkeys). PBMC concentrations were approximately 100-fold higher than corresponding plasma concentrations in dogs. Following repeated administration there was evidence of slight accumulation of tenofovir in rats and dogs, but not in monkeys.

Distribution

Plasma protein binding of darunavir was 63% in rabbits, 95% in rats and 75 – 94% in humans, with lower protein binding at higher concentrations. The tissue distribution in rats was extensive and rapid with the highest concentrations of radioactivity in liver and adrenal gland. No accumulation was observed except in the pigmented parts of the eye from which radioactivity decreased gradually. Darunavir crossed the placenta in pregnant rats. Darunavir exposure was much higher in juvenile rats (aged 12 or 26 days) than in adult rats.

Protein binding of cobicistat was moderately high (93 – 95% in non-clinical species and 94% in humans). After oral administration to rats, radioactivity was rapidly and widely distributed to most tissues. The tissues showing the highest concentrations of radioactivity, excluding the gastro intestinal tract, included liver, adrenal, kidney, and pituitary. In rats, cobicistat was reversibly associated with melanin.

The protein binding of emtricitabine was very low (< 5%) in mouse, rabbit, monkey, and human plasma. The tissue distribution in rats and monkeys was extensive and rapid. There was no sign of emtricitabine accumulation and elimination was rapid, no radioactivity was observed after 72 hours post-dose.

Protein binding of tenofovir alafenamide was 48% and 47% in vitro in dog and human plasma respectively. Ex vivo protein binding in humans was 14 – 23%. Protein binding of tenofovir was very low (<1% in human plasma). The highest concentrations were found in kidneys and liver in mice and rats, and in mice also in gall bladder, urinary bladder and diaphragm. Tenofovir passed the placenta in pregnant monkeys.

Metabolism

The metabolism of darunavir following single oral administration was extensive and qualitatively similar in all species, including 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. 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.

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 to weak inhibitor of CYP2C8, CYP2D6 and of human hepatic microsomal UGT1A1 activity and a modest inhibitor of CYP2B6.

Emtricitabine is not extensively metabolised and is eliminated primarily as unchanged drug by renal excretion in mice, rats, and cynomolgus monkeys. Emtricitabine is subject to Phase I metabolism (oxidation to a diastereomeric sulfoxide) and to some direct conjugation (glucuronidation of hydroxymethyl group) as minor metabolic routes.

Tenofovir alafenamide is subject to intracellular metabolism to tenofovir, which is further phosphorylated to tenofovir-monophosphate and tenofovir-diphosphate with tenofovir-diphosphate being the pharmacologically active form. Tenofovir alafenamide was not metabolised by CYP enzymes CYP1A2, CYP2C8, CYP2C9, CYP2C19

or CYP 2D6 and only slowly metabolised by CYP3A4. Intracellular metabolic activation of tenofovir alafenamide in PBMCs or other lymphatic tissues involves conversion to tenofovir by cathepsin A. In contrast to PBMCs, tenofovir alafenamide was primarily hydrolysed by carboxylesterase 1 in primary hepatocytes.

Excretion

Darunavir was excreted primarily via the feces with fecal excretion of 82 – 94% in rats, dogs and humans and urinary excretion of 4% in rats and dogs and 12% in humans. Darunavir was excreted in milk of rats.

Cobicistat was excreted primarily in feces in mice, rats and dogs. In bile duct-cannulated rats and dogs respectively 69% and 64% of dosed radioactivity was found in bile. Cobicistat was excreted in milk of rats.

Emtricitabine was excreted primarily via renal excretion and primarily as parent drug, in mice, rats and monkeys.

Radio-labelled tenofovir alafenamide was excreted for 22 – 36% in urine and 37 – 72% in feces of mice, rats and dogs. After IV administration of radiolabelled tenofovir to bile duct-cannulated animals, in rats, excretion was 93% in urine, 4% in feces and 2% in bile and in dogs, excretion was 27% in urine, 43% in feces and 14% in bile. Tenofovir was excreted in milk of monkeys.

2.3.4. Toxicology

Single dose toxicity

Single oral doses of ≤ 100 mg/kg darunavir in mice and ≤ 500 mg/kg in rats produced no mortality and were well tolerated. In dogs, the maximum tolerated dose was 75 mg/kg, with vomiting being the limiting adverse effect.

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

Single dose toxicity studies with emtricitabine were conducted in mice and rats, using oral dose levels ranging from 1050 to 4000 mg/kg and i.v. dose levels ranging from 200 to 700 mg/kg. There were neither deaths nor any overt signs of toxicity observed at any of the doses tested.

In rats, oral doses up to 1000 mg/kg tenofovir alafenamide were well tolerated. In dogs, the NOAEL was 30 mg/kg p.o. Renal tubular changes and thymic atrophy were observed from 90 mg/kg and salivation, vomiting, reduced activity, tremors, and incoordination at 270 mg/kg.

Repeat dose toxicity

Darunavir induced an increase in the red blood cell turnover, prolonged APTT and liver and thyroid changes which were associated with liver enzyme induction and an enhanced metabolism of thyroid hormones in rats. Increases in liver transaminases and single cell necrosis in combination studies with ritonavir in rats were attributed to ritonavir toxicity. In dogs, a limited increase in alkaline phosphatase (up to 45%) was observed. The maximum achieved exposure to darunavir in animal studies was low.

In repeated dose studies with cobicistat, liver changes were observed in rats and mice which were associated with enzyme induction. In rats, slightly decreased red blood cell parameters were observed. In dogs, emesis, decreases in body weight and food consumption and up to 2-fold increases in ALT and ALP were observed.

In repeated dose studies with emtricitabine in mice, rats and monkeys, changes in the red blood cell parameters were observed which were interpreted as mild, reversible anaemia.

Target organs of tenofovir alafenamide were kidneys and bone, which are the known target organs of tenofovir. Effects on kidneys consisted of karyomegaly in rats and dogs and tubular degeneration / regeneration in dogs. Atrophy of metaphyseal cancellous bone was observed in rats and increased biochemical markers of bone turnover and decrease serum 1, 25-dihydroxy- and 25-hydroxyvitamin D3 in rats and dogs. In the 39-week study in dogs, minimal infiltration of histiocytes was present in some animals in eye, with posterior uveitis, lung and spleen. In-life ophthalmologic examinations were normal in this study and in other studies and other species. No microscopic changes were observed in ocular tissue in other animal species and in a 4-week dog study.

Combination darunavir/cobicistat/emtricitabine/tenofovir alafenamide

Non-clinically, effects on red blood cell parameters were seen for darunavir, cobicistat and emtricitabine. For all three compounds these effects were mild or limited. Anaemia is included as adverse effect in the SmPC. There are no relevant other overlapping toxicities. Additional non-clinical studies to study potential interactions are considered not necessary.

Genotoxicity and carcinogenicity

Darunavir, cobicistat, emtricitabine and tenofovir alafenamide tested negative in standard packages of genotoxicity studies.

In carcinogenicity studies with darunavir in rats and mice and with cobicistat in rats, increased tumours were found in liver and/or thyroid, which were considered associated with liver enzyme induction and not relevant for humans. No increased tumour incidence was observed in a carcinogenicity study with cobicistat in mice. In long-term carcinogenicity studies with emtricitabine, no drug-related increases in tumour incidence were found in rats and mice. No carcinogenicity studies were performed with tenofovir alafenamide. In a carcinogenicity study with tenofovir disoproxil in mice, duodenal neoplasms were observed at low incidence at 15 times the human therapeutic AUCss. A rat carcinogenicity study with tenofovir disoproxil was negative.

Reproductive and developmental toxicity

No effects on fertility and early embryonic development were observed for darunavir, cobicistat and tenofovir alafenamide in rats and for emtricitabine in mice and rats.

No embryo-foetal toxicity was observed for darunavir in rats, rabbits and mice, but exposure was low. Cobicistat did not cause teratogenicity in rats and rabbits. In rats, cobicistat caused increases in post-implantation loss, skeletal variations and decreased fetal weights, which were associated with significant maternal toxicity. Emtricitabine did not cause embryo-foetal toxicity in mice and rabbits, despite the presence of maternal toxicity in rabbits. Tenofovir alafenamide did not cause teratogenicity in rats and rabbits. In rats, tenofovir alafenamide caused decreased foetal body weight and skeletal variations.

No effects on the pre- and postnatal development were observed for cobicistat and emtricitabine in rats and mice respectively. Darunavir caused a reduction in pup body weight gain and a slight delay in the opening of eyes and ears in rats. No pre- and postnatal development study was performed with tenofovir alafenamide.

Tenofovir disoproxil caused reduced pup survival and animal weights and a slight delay in sexual maturation in rats.

Juvenile toxicity studies were performed with darunavir and cobicistat in rats. Darunavir caused higher systemic exposure and toxicity (mortality, central nervous system effects) in pups younger than 23 days than in pups older than 23 days or in adults, probably due to immature metabolism and blood brain barrier. In young rats dosed from post-natal day 22 to 49 with cobicistat, no increased toxicity compared to adults was observed.

Local tolerance and antigenicity

Darunavir was not irritating to skin or eyes. Cobicistat was mildly irritating to skin and a non-severe irritant to eyes. Tenofovir alafenamide was not irritating to skin and a noncorrosive/non-severe irritant to eyes. No local tolerance studies were performed with emtricitabine.

Darunavir, cobicistat and tenofovir alafenamide showed no potential for sensitization in the local lymph node assay in mice. No antigenicity studies were performed with emtricitabine.

Immunotoxicity

No immunotoxicity was observed in a T-cell dependent antibody assay with darunavir in rats. In a T-cell dependent antibody assay with cobicistat in rats, anti-KLH IgG titer was decreased in females. No significant effects were observed on anti-KLH IgG titer in males or on IgM titer. Emtricitabine did not affect the IgM antibody response in the rat to sheep red blood cells. No immunotoxicity studies were performed with tenofovir alafenamide or with tenofovir disoproxil.

2.3.5. Ecotoxicity / environmental risk assessment

Darunavir

Substance (INN / Invented Name): darunavir			
CAS-number (if available): 206361-99-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} 2.41	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	2.41	not B
Persistence	ready biodegradability	not readily biodegradable	
	DegT50	$DT_{50,\ water}$ = 15/51 d (r/r) $DT_{50,\ sediment}$ = 141/267 d (r/r) $DT_{50,\ system}$ = 50/86 d (r/r)	r=river; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	NOEC ≥43 mg/L NOEC 19 mg/L NOEC ≥9.4 mg/L	ecotoxicity: does not meet T criterion
	CMR	not investigated	potentially T
PBT-statement :	darunavir is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default F_{pen}	4	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)	not investigated		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Water solubility	OECD 105	0.192 g/L at pH 4 and 20°C	

		0.163 g/L at pH 7 and 20°C 0.179 g/L at pH 9 and 20°C			
Hydrolysis	OECD 111	t½ = 316 d at pH 4 and at 30°C and 40°C			
Adsorption-Desorption	OECD 106	K_d = 75.3 L/kg; K_{oc} = 345 L/kg			activated sludge
		K_d = 42 L/kg; K_{oc} = 993 L/kg			sandy loam
		K_d = 4.12 L/kg; K_{oc} = 389 L/kg			loam
		K_d = 18.1 L/kg; K_{oc} = 933 L/kg			loamy sand
		K_d = 9.5 L/kg; K_{oc} = 265 L/kg			sandy clay loam
		K_d = 8.18 L/kg; K_{oc} = 732 L/kg			clay
Ready Biodegradability Test	OECD 301	not readily biodegradable			no primary degradation
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 8.1/27 d (r/r) $DT_{50, sediment}$ = 75/142 d (r/r) $DT_{50, system}$ = 26/46 d (r/r) % shifting to sediment = 30.9 and 22.9			Values determined at 20°C; Significant shifting to sediment
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	≥43	mg/L	growth rate
D. magna, Acute toxicity test	OECD 202	EC50	>44	mg/L	immobility
Daphnia sp. Reproduction Test	OECD 211	NOEC	19	mg/L	reproduction
FIsh, Acute toxicity test	OECD 203	LC50	>38	mg/L	mortality
Fish, Early Life Stage Toxicity Test/ *P. promelas*	OECD 210	NOEC	≥9.4	mg/L	survival, growth
Activated Sludge, Respiration Inhibition Test /*P. promelas*	OECD 209	NOEC	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/ *C. riparius*	OECD 218	NOEC	≥80	mg/kg_{dw}	development rate 1.8% o.c.

Conclusions on studies for darunavir

Darunavir is not PBT, nor vPvB.

Considering the above data, darunavir is not expected to pose a risk to the environment.

Cobicistat

Substance (INN / Invented Name): cobicistat			
CAS-number (if available): 1004316-88-4			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	log D_{ow} = 3.05, 4.00, 4.10 at pH 5, 7, 9	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log D_{ow} = 3.05, 4.00, 4.10 at pH 5, 7, 9. Log K_{ow} = 4.10	
	BCF	1.67 and 1.37 L/kg	not B
Persistence	ready biodegradability	not readily biodegradable	
	DegT50	$DT_{50\ water}$ = 12/25 d $DT_{50\ system}$ = 1076/866 d	corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥29.3 mg/L ≥17.5 mg/L 4.9 mg/L	ecotoxicity: does not meet T criterion
	CMR	not investigated	potentially T
PBT-statement :	cobicistat is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default F_{pen}	0.75	µg/L	> 0.01 threshold

Other concerns (e.g. chemical class)	not investigated				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 1654, 2664 L/kg $K_{oc\ soil}$ = 3624, 3246, 9012 L/kg			
Ready Biodegradability Test	OECD 301B	note readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 5.6, 12d (l/l) $DT_{50,\ system}$ = 507, 408 d (l/l) shifting to sediment: 51-69%			l=lake; DT_{50} values at 20°C; significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*P. subcapitata*	OECD 201	NOEC	≥29.3	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥17.5	mg/L	survival, reproduction
Fish, Early Life Stage Toxicity Test/ *P. promelas*	OECD 210	NOEC	4.9	mg/L	fry survival
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥60	mg/L	respiration; NOEC set equal to water solubility
Phase IIb Studies					
Bioaccumulation/ *O. mykiss*	OECD 305	BCF_K	1.67 1.39	L/kg	%lipids:4.9%; kinetic BCF
Sediment dwelling organism/*C. riparius*	OECD 218	NOEC	1250	mg/kg_{dw}	emergence, normalised to 10% o.c.

Conclusions on studies for cobicistat

Cobicistat is not PBT, nor vPvB.

Considering the above data, cobicistat is not expected to pose a risk to the environment.

Emtricitabine

Substance (INN/Invented Name): emtricitabine			
CAS-number (if available): 143491-57-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} -0.7	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.7	not B
Persistence	ready biodegradability	not readily biodegradable	
	DegT50	DT50 aerobic = > 100 d DT50 anaerobic = > 100 d	Values at 20°C Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	≥110 mg/L ≥110 mg/L 6.1 mg/L	ecotoxicity: does not meet T criterion
	CMR	not investigated	potentially T
PBT-statement :	emtricitabine is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	1.0	µg/L	> 0.01 threshold
Other concerns (e.g. chemical class)	not investigated		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc,\ sludge}$ 21.1-45.6 L/kg	
Ready Biodegradability Test	OECD 301D	not readily biodegradable	

Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 aerobic = > 100 d DT50 anaerobic = > 100 d % shifting to sediment: 12-54%			DT_{50} values at 20°C; significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	≥110	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥110	mg/L	survival, growth, reproduction
Fish, Early Life Stage Toxicity Test/ *P. promelas*	OECD 210	NOEC	6.1	mg/L	growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism/ *C. riparius*	OECD 218	NOEC	≥38	mg/kg_{dw}	emergence, development rate 1.9% o.c.

Conclusions on studies for emtricitabine

Emtricitabine is not PBT, nor vPvB.

Considering the above data, emtricitabine is not expected to pose a risk to the environment.

Tenofovir alafenamide

Substance (INN / Invented Name): tenofovir					
CAS-number (if available): 147127-20-6					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} -3.8 - -4.3			not B
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log D_{ow}	-3.8 - -4.3			not B
Persistence	ready biodegradability	not readily biodegradable			
	DT50	DT_{50} sediment (20°C): 142.0 d DT_{50} sediment (12°C): 303.0 d			vP
	NOEC algae NOEC crustacea NOEC fish	32 mg/L 100 mg/L ≥10 mg/L			ecotoxicity: does not meet T criterion
Toxicity	CMR	not investigated			potentially T
PBT-statement :	tenofovir is considered to be not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default F_{pen}	0.134	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)	not investigated				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ soil}$ 351 - 1091 L/kg $K_{F\ sludge}$ 6.0 - 21 L/kg			
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT_{50_water} = 2.0 - 3.5 d $DT_{50\_sediment}$ = 28.9 – 142.0 d $DT_{50\_total\ system}$ = 10.4 – 32.7 d >10% parent associated with sediment from Day 7; 3 significant metabolites in water and/or sediment out of which two are considered persistent.			Tenofovir is considered very persistent in sediments
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**

Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	NOEC	32	mg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	100	mg/L	reproduction
Fish, Early Life Stage Toxicity Test/ *P. promelas*	OECD 210	NOEC	≥10	mg/L	survival, growth
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥1000	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism / *C. riparius*	OECD 218	NOEC	290	mg/kg_{dw}	emergence, dev. rate; normalised to 10% o.c.: 1706 mg/kg_{dw}

Conclusions on studies for tenofovir

Tenofovir is not PBT, nor vPvB. Considering the above data, tenofovir is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The data supporting this application was generated for the single components of the fixed dose combination (darunavir, cobicistat, emtricitabine and tenofovir alafenamide) and as a consequence no new non-clinical studies were provided.

Potential for PR interval prolongation has been reported for cobicistat and tenofovir alafenamide in non-clinical studies; however clinically,no cardiovascular signals were observed from cobicistat or tenofovir alafenamide. No additional investigation of the combination was considered necessary.

Effects on red blood cell parameters were observed for darunavir, cobicistat and emtricitabine in non-clincial studies. For all three compounds these effects were mild or limited. Of note, anaemia is listed in the SmPC. There are no relevant other overlapping toxicities.

Additional non-clinical studies to study potential interactions are not considered necessary.

2.3.7. Conclusion on the non-clinical aspects

There are no objections for the approval of the darunavir / cobicistat / emtricitabine / tenofovir alafenamide fixed dose combination from a non-clinical point of view.

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.

Table 1. Overview of clinical studies

Study	Study Design	Numbers by Treatment Regimen	Data
DRV/COBI/F/TAF			
TMC114FD2HTX1002 Healthy subjects	Phase 1, randomized, 3-panel, open-label, 2-way crossover study in healthy subjects. In each panel, during 2 subsequent sessions, each subject received 2 treatments as a single dose, randomized (within panel) according to a classical 2-sequence, 2-period Williams design.	72 healthy volunteers (24 subjects in each panel).	4 Days PK per panel
TMC114FD2HTX1001 Healthy subjects	Phase 1, single-dose PK and pivotal bioequivalence of the D/C/F/TAF FDC relative to the separate agents (DRV 800 mg tablet formulation and F/TAF 200/10 mg FDC in the presence of 150 mg COBI), under fed conditions (standardized regular-fat breakfast, in healthy subjects.	96 healthy adult subjects	1 Day – single dose PK.
GS-US-299-0102 ART-naïve	Phase 2, randomized, double-blind, multicenter, active controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD	D/C/F/TAF FDC (N = 103) DRV+COBI+TVD (N = 50)	Week 48 efficacy, PK, and safety
DRV/COBI			
GS-US-299-0101 Healthy subjects	Phase 1, adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple cohort, single-center study.	102 subjects were enrolled (N=30 in Part 1, N=36 in Part 2, and N=36 in Part 3).	Full PK - Part 1, 21 days; Part 2, 20 days; Part 3, 24 days
GS-US-216-0130 ART-naïve	Phase 3, open-label, multicenter study to evaluate the safety, efficacy, and tolerability of DRV/COBI administered as single agents	DRV/COBI (N=313)	Week 48 efficacy, Week 48 and roll-over phase safety
GS-US-236-0118 ART-naïve or virologically suppressed Renal impairment (mild/moderate)	Phase 3, open-label, multicenter study to evaluate the safety, of COBI-containing HAART in HIV-1 infected patients with mild to moderate renal impairment	DRV/COBI (N=22, Cohort 2 PI, DRV/COBI subgroup)	Week 96 efficacy and safety
F/TAF (as either E/C/F/TAF FDC or as F/TAF FDC + 3rd Agent			
GS-US-292-0104 ART-naïve	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + PBO-to-match STB (N = 435) STB + PBO-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety
GS-US-292-0111 ART-naïve	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + PBO-to-match STB (N = 431) STB + PBO-to-match E/C/F/TAF FDC (N = 435)	Week 48 efficacy, PK, and safety

GS-US-292-0102 ART-naïve	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in Study GS-US-299-0102	Randomized phase: E/C/F/TAF FDC + placebo-to-match STB (N = 112) STB + placebo-to-match E/C/F/TAF FDC (N = 58) Open-label extension phase: Continued on E/C/F/TAF FDC (N = 105) Switch to E/C/F/TAF FDC (N = 161) from STB to E/C/F/TAF FDC (N = 53) from D/C/F/TAF to E/C/F/TAF FDC (N = 70) from DRV+COBI+TVD to E/C/F/TAF FDC (N = 38)	Week 48[b] efficacy, PK, and safety
GS-US-311-1089 Virologically suppressed	Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to F/TAF FDC- containing combination regimen	Switch to F/TAF FDC (N=333) Stay on F/TDF +3rd Agent (N=330)	Week 48 efficacy and safety
GS-US-292-0112 ART-naïve or virologically suppressed Renal impairment (mild/moderate)	Phase 3, open-label, multicenter, multiple cohort study to evaluate the safety, efficacy, and tolerability of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 248)	Week 24 (and partial Week 48) efficacy and safety
GS-US-292-1249 ART-naïve or virologically suppressed HIV-1/HBV co-infected	Phase 3b, open-label study to evaluate the efficacy and safety of E/C/F/TAF FDC in HIV-1/hepatitis B coinfected adults	E/C/F/TAF FDC (N = 77) HIV-suppressed (N=74) HIV and HBV treatment-naive (N=3)	Week 48 efficacy, PK, and safety
GS-US-292-0106 ART-naïve Adolescents	Phase 2/3, open-label, multicenter, 2-part, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 50) PK sub-study: N = 24	Week 48 efficacy, PK, and safety

2.4.2. Pharmacokinetics

Darunavir (DRV; Prezista) is a human immunodeficiency virus type 1 (HIV-1) protease inhibitor (PI) currently indicated as a single agent for the treatment of HIV 1 infection. Darunavir needs to be administered with a pharmacokinetic (PK) enhancer to increase its bioavailability, via cytochrome P450 (CYP) 3A inhibition.

Cobicistat (COBI) is a structural analogue of (low-dose) ritonavir and is a potent mechanism-based CYP3A inhibitor. Cobicistat has no anti-HIV-1 activity but is licensed as a PK enhancer of DRV 800 mg once daily. Cobicistat increases the systemic exposure of other co-administered drugs metabolized by CYP3A, including the HIV-1 integrase strand transfer inhibitor elvitegravir (EVG) as well as the HIV-1 PI DRV. Darunavir and COBI (DRV/COBI; Rezolsta) as a FDC tablet (800 mg/150 mg) is indicated in combination with other antiretroviral medicinal products for the treatment of HIV 1 infection. Cobicistat 150 mg once daily is also approved as part of a fixed-dose combination (FDC) drug containing elvitegravir (EVG), emtricitabine (FTC, Emtriva), tenofovir disoproxil fumarate (TDF, Viread) or tenofovir alafenamide (TAF), and COBI (Stribild/Genvoya) for the treatment of HIV 1 infection in adults and adolescents aged 12 years and older.

Emtricitabine is an approved nucleoside reverse transcriptase inhibitor (NRTI), indicated in combination with other antiretroviral medicinal products for the treatment of HIV-1 infected adults and children aged at least 4 months.

Tenofovir (TFV) is a nucleotide analogue that inhibits HIV-1 reverse transcription. The active form of TFV is intracellular tenofovir-diphosphate (TFV-DP). Tenofovir needs to be administered as a prodrug to improve its oral absorption. Tenofovir disoproxil fumarate is an oral prodrug of TFV and remains the preferred nucleotide analogue reverse transcriptase inhibitor. However, nephrotoxicity and reduced bone mineral density may occur, including elevated risks of reduced kidney function, proteinuria and proximal tubular dysfunction in some patients.

Tenofovir alafenamide (TAF) is an oral prodrug of TFV that is more stable in plasma than TDF and is predominantly hydrolyzed to TFV intracellularly by cathepsin A, resulting in higher intracellular levels of the active phosphorylated metabolite TFV-DP and much lower circulating plasma levels of TFV relative to TDF. This distinct metabolism of TAF is intended to both maximize antiviral potency and improve clinical safety compared with TDF.

The combination of FTC and TAF (F/TAF, Descovy) is licensed as a combination tablet indicated for the treatment of HIV-1 in combination with other antiretroviral agents in adults and adolescents 12 years and older. When used in combination with an antiretroviral therapy (ART) requiring a PK enhancer, including boosted DRV, the recommended dose of F/TAF is 200/10 mg.

Once daily combined ART regimens are aimed at reducing the pill burden for patients with HIV 1. There remains a need for simplified PI-based ART that combines potent and sustained efficacy, favourable tolerability, and minimal long-term toxicity, with practical, convenient dosing. To reduce the pill burden for DRV-containing antiretroviral regimens, the Applicant and Gilead Sciences have co-formulated TAF with DRV, COBI, and FTC to form the first PI based FDC single-tablet option. The D/C/F/TAF FDC is intended to be marketed for use in the same populations of HIV-1 infected subjects for which DRV/COBI 800/150 mg in combination with other antiretrovirals once daily is authorised and extended to the adolescent population.

The development program for the D/C/F/TAF FDC tablet combining four components into a single tablet focused on bridging the PK for each of the components in their approved dose for co-administration between the FDC tablet and combination of formulations of the separate agents. Three biopharmaceutics studies evaluated the relative bioavailability or bioequivalence of DRV, COBI, FTC, and TAF co-administered as single agents, or as the D/C/F/TAF FDC tablet, in healthy subjects. This PK bridging also allows the extrapolation of historical safety and efficacy data for DRV, COBI and FTC/TAF to the D/C/F/TAF FDC. In addition, one study evaluated the PK, efficacy and safety of the D/C/F/TAF FDC in HIV-1 infected ART-naïve subjects. The PK and/or PD properties of D/C/F/TAF as a fixed dose combination were studied in 423 subjects (72 subjects in TMC114FD2HTX1002, 96 subjects in TMC114FD2HTX1001, 102 subjects in GS-US-299-0101 and 153 subjects in GS-US-299-0102).

Overview of the development of the single components

The development program of the D/C/F/TAF FDC tablet has additionally been built on the information accrued from the development program for DRV/COBI and on the development program for F/TAF.

DRV/COBI

The data that supported the registration of the DRV/COBI 800/150 mg FDC were two relative oral bioavailability studies (bridging DRV/COBI with established data from single agent DRV boosted with low-dose ritonavir), one bioequivalence study, and one Phase 3b, open-label study:

Study GS-US-216-0115 compared darunavir/low-dose ritonavir (DRV/rtv) 800/100 mg co-administered as single agents to DRV/COBI 800/150 mg co-administered as single agents in healthy subjects following repeated once daily dosing under fed conditions.

Study TMC114IFD1001 compared DRV/COBI 800/150 mg FDC tablet formulations to DRV/rtv 800/100 mg co-administered as single agents in healthy subjects following repeated once daily dosing under fed conditions.

Study TMC114IFD1003 established bioequivalence of the DRV/COBI FDC to combined administration of formulations of the separate agents, and evaluated the food effect for the DRV/COBI FDC.

Study GS-US-216-0130 assessed the safety and efficacy of the combined use of DRV and COBI, co-administered as separate agents in HIV-1 infected subjects and contained an intensive PK substudy (N=60) and sparse PK sampling for population PK purposes.

The full list of PK studies supporting the DRV/COBI dossier is displayed in Table 2.

Table 2. Number of Studies and Subjects – DRV/COBI

Type of Study	Number of Studies	Population	Number of Subjects
Phase 1:			
Single dose PK	2 (TMC114IFD1003, GS-US-236-0105)	Healthy subjects	157 (133+24)
Multiple dose PK	2 (TMC114IFD1001, GS-US-216-0115)		69 (36+33)
Mass-balance	2 (TMC114-C109, GS-US-216-0111)	Healthy subjects	16 (8+8)
Renal impairment	2 (GS-US-216-0121, GS-US-216-0124)	Healthy subjects and subjects with renal-impairment	78 (54+24)
Hepatic impairment	2 (TMC114-C134, GS-US-183-0133)	Healthy subjects and subjects with hepatic-impairment	52 (32+20)
Drug-drug interaction	24 (DRV) (TMC114-C123, TMC114-C124, TMC114-C111, TMC114-C119, TMC125-C176, TMC278-C112, TMC114-MK0518, TMC114-A4001052, TMC114-C122, TMC114-C150, TMC114-C142, TMC114-C172, TMC114-C121, TMC114-C129, TMC125VIR1001, TMC114-C107, TMC114-C163, TMC114-C131, VX950-C124 TMC114-C133, TMC114-C120, TMC114-C171, TMC114-C127, TMC114-C128) 6 (COBI) (GS-US-216-0112, GS-US-201-0104, GS-US-216-0120, GS-US-216-0122, GS-US-216-0123, GS-US-236-0106)	Healthy subjects, HIV-negative subjects on stable methadone therapy (C127), HIV-negative subjects on buprenorphine/ naloxone maintenance therapy (C171), HIV-1 infected subjects on stable nevirapine (C119)	485 (18+13+12+19+32+16+18+16+18+17+18+32+36+26+33+16+27+19+20+16+14+17+16+16) 175 (53+18+33+16+34+21)
QT/QTc	2 (TMC114-C153, GS-US-216-0107)	Healthy subjects	88 (40+48)
Phase 3:			
Safety/Efficacy	1 (GS-US-216-0130)	HIV-1 infected subjects	313
Total	43		1433

Number of subjects includes all subjects that were treated in studies.

The marketing application for DRV/COBI was also based on two Phase 3 DRV/rtv studies including 1,279 HIV-1 infected subjects, as well as integrated PK analyses from Phase 2 DRV/rtv studies including 596 HIV-1 infected subjects.

F/TAF

A comprehensive clinical program characterized the PK of F/TAF and its components, including a proof-of-concept study, several Phase 3 studies with components of F/TAF as part of the ARV regimen, comparative bioavailability and bioequivalence studies, 2 mass-balance studies, 1 thorough QT/QTc study, 6 drug-drug interaction studies, 1 hepatic impairment study and 1 renal impairment study (Table 3).

Table 3. Number of Studies and Subjects – F/TAF

Type of Study[b]	Number of Studies[b]	Population	Number of Subjects
Phase 1			
Mass-balance	2 (GS-US-120-0109, FTC-106)	Healthy Subjects	14 (8+6)
Renal Impairment	2 (GS-US-120-0108, FTC-107)	Subjects with renal impairment	57 (27+30)
Hepatic Impairment	1 (GS-US-120-0114)	Healthy subjects and subjects with hepatic-impairment	40
Single-dose PK	2 (GS-US-311-1472, GS-US-292-0103)[a]	Healthy subjects	120 (100+20)
Extrinsic factor PK	8 (GS-US-311-1386, GS-US-311-0101, GS-US-120-0117, GS-US-120-0118, GS-US-120-1538, GS-US-120-1554, GS-US-292-0110, GS-US-292-1316)	Healthy subjects and HIV-1 infected subjects	281 (40+50+36+40+18+34+43+20)
Thorough QT	1 (GS-US-120-0107)	Healthy subjects	59
Phase 2/3			
Patient PK and PD	6 (GS-US-120-0104, GS-US-292-0104, GS-US-292-0111, GS-US-311-1089, GS-US-292-0106, GS-US-292-0112)	HIV-infected HIV-infected with renal impairment	1,287 (40+435+431+333+48) 248
Total	22		2,106

a In Study GS-US-292-0103, subjects may have received TAF 25 mg or both TAF 25 mg and E/C/F/TAF. Subjects were counted once for each study treatment received; in Study GS-US-311-1472, subjects received F/TAF (200/10 mg) + COBI and E/C/F/TAF. Subjects were counted only once.

b Only studies for which pharmacokinetic data are used in this application are listed.

Number of subjects includes all subjects that were treated in studies.

Bioanalytical methods

All analytes were measured using LC-MS/MS assays for unchanged drug in plasma, which were validated according to the applicable guidelines and all acceptance criteria as specified in the guidelines were met.

Pharmacokinetic data analysis

All PK parameters were calculated using conventional non-compartmental methods using actual times of blood sampling via Phoenix WinNonlin. In addition, the population PK analysis for the supportive studies and GS-US-299-0102 used a non-linear mixed effects modelling approach to generate the PK parameters.

Extensive population PK analyses were not performed as part of the clinical program for the D/C/F/TAF FDC. Population PK data for TAF are available for a limited number of subjects in the GS-US-299-0102 study and is discussed under pharmacokinetics in the target population.

Statistical methods

PK parameters were summarized by descriptive statistics. Pairwise comparisons between two treatments for maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) values were based on log-transformed data. Ratios and 90% confidence intervals (CI) represent the ratio of point estimates of the geometric mean or least square (LS) mean and associated CIs, except for study TMC114FD2HTX1001 where 90.14% CIs were derived because of the intermediate sample size re-estimation.

Bioequivalence between treatments or absence of food effect or absence of drug-drug interaction was concluded if the 90% CI of area under the plasma concentration-time curve measured from time zero and extrapolated to infinity (AUC_{∞}) and C_{max} treatment ratios were within established limits of 80.00% to 125.00%. For TAF PK, given its higher within-subject variability, broader limits of 70.00% to 143.00% were sometimes used, as indicated in the clinical study report provided.

Overview of the development of the fixed dose combination

Formulation development

The target product profile was a once daily immediate release oral solid dosage form incorporating 800 mg equivalent (eq.) of DRV (free form), 150 mg eq. of COBI (non-adsorbed form), 200 mg of FTC, and 10 mg eq. of TAF (free form), while maintaining a maximum core tablet weight of approximately 1,600 mg. The formulation development was based on prior formulation experience with DRV in the Prezista product line and with DRV/COBI in the Rezolsta product line, the inclusion of FTC and TAF and the need to minimize tablet size while combining four drug substances in a FDC product.

Both monolayer and bilayer tablet formulation concepts were evaluated. The bilayer tablet was evaluated to mitigate potential chemical instability of TAF. For all formulations, DRV, COBI, and FTC were used at 800, 150, and 200 mg eq., respectively. For TAF, a dose range of the drug product was initially based on relevant clinical data with the separate agent (8 to 40 mg). D/C/F/TAF concept formulations containing TAF 25 mg or TAF 10 mg were evaluated clinically. Each formulation concept required different formulation and processing approaches.

Two different monolayer tablet formulations (A and B) were developed using a co-dry granulation formulation concept and used for further clinical evaluation, that are only differentiated by the quantity of TAF present in each formulation (25 mg eq. and 10 mg eq., respectively, tablet weight 1597 mg).

In the bilayer formulation, layer 1 contained DRV and layer 2 contained COBI, FTC and TAF, according to a concept with a fluid bed/dry granulation process using HPC as a binder for DRV.

The monolayer and bilayer tablet formulations described above were evaluated in a relative bioavailability study GS-US-299-0101, which is described below. The monolayer formulation containing 10 mg TAF (monolayer A [denoted as Formulation 3 in the GS-US-299-0101 study]) was selected as the Phase 2 formulation.

The Phase 2 formulation was used in study GS-US-299-0102 in HIV-1 infected subjects. The manufactured Phase 2 drug product batches all met the proposed release specifications. During the manufacture of Phase 2 formulation batches, minor processing issues related to poor powder flow during tablet compression were encountered. To facilitate processing, the extragranular quantity of croscarmellose sodium and microcrystalline cellulose were moved to the intragranular phase and the formulation was designated G001 (intended

commercial formulation). The overall quantity of each component in the core tablets is identical between the Phase 2 and G001 formulations.

In the manufacture of the commercial G001 formulation, the non-functional film coating agent was changed from Opadry II White 85F18422 to Opadry II Yellow 85F120020. This is not expected to alter the relative bioavailability of the D/C/F/TAF FDC G001 formulation.

The intended commercial formulation (G001) of the D/C/F/TAF FDC was used in the pivotal bioequivalence study (TMC114FD2HTX1001) as well as in study TMC114FD2HTX1002. An overview of the biopharmaceutics studies, including the used formulations, is provided in Table 11. The PK and/or PD properties of D/C/F/TAF as a fixed dose combination were studied in 423 subjects.

Table 4. Clinical Biopharmaceutics Studies With D/C/F/TAF

Study Type Clinical Study Number	**Dosage Form**	**Formulation Number**	**Dose (mg)**
Relative Oral Bioavailability:			
TMC114FD2HTX1002 (Panel 1 and Panel 2)	1 x D/C/F/TAF FDC tablet	G001	800/150/200/10
	1 x DRV 1 x COBI and 1 x F/TAF tablet	Commercial	800, 150 and 200/10
	1 x E/C/F/TAF FDC tablet	Commercial	150/150/200/10
GS-US-299-0101	1 x D/C/F/TAF FDC tablet	Formulation 1 (monolayer)	800/150/200/25
	1 x D/C/F/TAF FDC tablet	Formulation 2 (bilayer)	800/150/200/25
	1 x D/C/F/TAF FDC tablet	Formulation 3[a] (monolayer)	800/150/200/10
	1 x DRV and 1 x COBI	Commercial	800 and 150
	1 x FTC and 1 x TAF	Commercial (FTC) and TAF tablet	200 and 25
Pivotal Bioequivalence:			
TMC114FD2HTX1001	1 x D/C/F/TAF FDC tablet	G001	800/150/200/10
	1 x DRV, 1 x COBI and 1 x F/TAF tablet	Commercial	800, 150 and 200/10
Food Effect:			
TMC114FD2HTX1002 (Panel 3)	1 x D/C/F/TAF FDC tablet	G001	800/150/200/10

a Formulation 3 was subsequently denoted as G001.

Relative bioavailability study GS-US-299-0101

This was a Phase 1, adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study. 102 subjects were enrolled (N=30 in Part 1, N=36 in Part 2, and N=36 in Part 3). Clinical study report was dated November 30, 2012.

Study GS-US-299-0101 compared three candidate D/C/F/TAF FDC tablet formulations after repeated dosing in order to select a formulation for Phase 2; and subsequently the PK and bioavailability of DRV, COBI, FTC, TAF, and TFV when administered as the selected Phase 2 D/C/F/TAF FDC relative to the administration of the individual components: DRV plus COBI or FTC plus TAF.

Part 1 evaluated the PK of DRV, COBI, FTC, TAF, and TFV when administered as 3 FDC formulations of D/C/F/TAF (including 2 TAF doses) in order to select the Phase 2 TAF dose and formulation. The treatments were given

according to a parallel design once daily in the morning for 21 days with food. PK of TAF and TFV was compared on Days 1, 6, 12 and 21; PK of DRV, COBI and FTC was compared on Day 12. The following treatments were compared: treatment A FDC Formulation 1 monolayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF **25** mg), treatment B FDC Formulation 2 bilayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF **25** mg) and treatment C FDC Formulation 3 monolayer (DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF **10** mg).

Tenofovir alafenamide and TFV single- and multiple-dose exposures were comparable between the higher TAF dose formulations (Formulations 1 and 2; 25 mg TAF), while administration of lower TAF dose formulation (Formulation 3; 10 mg TAF) led to proportionally lower exposures of TAF and TFV. The resulting TFV plasma levels from the FDC with 10 mg TAF were approximately 90% lower than levels following administration of a FDC containing E/C/F/TDF or following administration of TDF with boosted PIs.

Tenofovir exposures from each formulation were consistent across Day 12 and Day 21, indicating achievement of steady state. Following multiple doses of each FDC formulation, the TAF exposure parameters AUC_{last} and C_{max} were lower (approximately 30% to 50%), as compared with exposures following a single dose, consistent with a mixed inhibitory/inductive effect on TAF absorption. The TAF exposures were in a range associated with antiviral activity, for all formulations (i.e. similar to those observed in a previous proof-of-concept study [GS-US-120-0104]).

Darunavir, COBI and FTC exposures were comparable across formulations; formal statistical testing showed that 90% CIs for LS mean ratio of C_{max} and AUC were generally within the 80% to 125% bounds. Systemic exposures of DRV, COBI, and FTC were consistent with historical data, for all formulations.

Subsequently, Formulation 3 was chosen for Part 3 of this study and for further development.

Part 3 evaluated the PK and bioavailability of DRV, COBI, FTC, TAF, and TFV when administered as the proposed Phase 2 D/C/F/TAF FDC relative to the administration of DRV 800 mg + COBI 150 mg alone (in cohort 1, N=19) or to FTC 200 mg + TAF 25 mg alone (in cohort 2, N=16). This part of the study confirmed that no major drug-drug interaction occurs between DRV/COBI and FTC, when administered as D/C/F/TAF(10 mg) FDC relative to either the administration of DRV/COBI or F/TAF(25 mg) alone. Based on Cmax and AUC, single-dose TAF exposures were lower and TFV exposures were similar following administration of D/C/F/TAF FDC (TAF 10 mg) compared with FTC + TAF (25 mg).

Part 2 of study GS-US-299-0101 study confirmed that no major drug-drug interaction occurs between DRV/COBI, FTC and TDF (i.e. TFV), when administered as COBI-boosted DRV (DRV 800 mg + COBI 150 mg) plus F/TDF (FTC 200 mg/TDF 300 mg) FDC relative to either the administration of DRV/COBI or F/TDF FDC alone.

The monolayer formulation containing 10 mg TAF (monolayer A [denoted as Formulation 3 in the GS-US-299-0101 study]) was selected as the Phase 2 formulation. The Phase 2 formulation was subsequently used in study GS-US-299-0102 in HIV-1 infected subjects. During the manufacture of Phase 2 formulation batches, minor changes were made to the formulation and the new formulation was designated G001 (intended commercial formulation). The overall quantity of each component in the core tablets is identical between the Phase 2 and G001 formulations. The intended commercial formulation (G001) of the D/C/F/TAF FDC was used in the pivotal bioequivalence study TMC114FD2HTX1001 as well as in the food effect study TMC114FD2HTX1002.

As the overall quantity of each component in the core tablets and each excipient is identical between the Phase 2 and G001 formulations, no major differences in absorption and thus PK exposures between both formulations are expected. However this cannot be confirmed by clinical PK data as the available PK data from studies

TMC114FD2HTX1001/1002 refer to single-dose data and the available PK data from studies GS-US-299-0101/0102 refer to multiple-dose data and therefore PK data cannot be compared directly.

Pivotal bioequivalence study TMC114FD2HTX1001

The objective of this study was to evaluate the single-dose PK and pivotal bioequivalence of the D/C/F/TAF FDC relative to the separate agents (DRV 800 mg tablet formulation and F/TAF 200/10 mg FDC in the presence of 150 mg COBI), under fed conditions (standardized regular-fat breakfast, in healthy subjects).

The study population comprised 96 healthy adult subjects, with a blinded (for treatment) sample size re-estimation when 96 subjects had been dosed (because of uncertainty around the within-subject variability in TAF PK. The results of this sample size re-estimation indicated no additional subjects were to be recruited, and recruitment was halted at 96 subjects.

A summary of the PK parameters is presented in Table 5. The D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration of the separate agents DRV, the F/TAF FDC, and COBI, with respect to both rate and extent of absorption of the four components involved. The 90% CIs of the LS mean ratios of all main PK parameters for all four compounds (DRV, COBI, FTC, TAF) were within the 80.00% to 125.00% acceptance range.

The comparison of the D/C/F/TAF 800/150/200/10-mg FDC tablet to the separate agents DRV, the F/TAF FDC, and COBI is acceptable for assessment of bioequivalence, as all of these agents are authorised separately, in various combination products and based on full dossiers. Furthermore, fixed dose combinations of the components (DRV/COBI and F/TAF) are already approved, respectively as REZOLSTA and DESCOVY, and can be used in combination.

Table 5. Single-dose PK Parameters Including Statistical Analysis of DRV, COBI, FTC and TAF (Study TMC114FD2HTX1001)

	Mean (SD); t_{max}: Median (Range)		
Parameter	D/C/F/TAF (Test) N=94[a]	DRV, F/TAF, COBI (Reference) N=96[a]	Test versus Reference LS Mean Ratio, % (90.14 % CI)[b]
DRV			
C_{max}, ng/mL	7042 (1481)	6620 (1429)	106.73 (103.50; 110.06)
t_{max}, h	4.00 (1.50; 8.00)	4.00 (2.00; 12.00)	-
AUC_{last}, ng.h/mL	87,200 (27385)	84,406 (29481)	104.84 (100.87; 108.97)
AUC_{∞}, ng.h/mL	87,280 (28097)	85,210 (29561)	103.74 (99.62; 108.02)
$t_{1/2,}$ h	5.9 (2.1)	6.2 (2.7)	-
COBI			
C_{max}, ng/mL	894 (254)	881 (207)	100.69 (96.80; 104.73)
t_{max}, h	4.00 (1.50; 6.00)	4.00 (1.50; 5.05)	-
AUC_{last}, ng.h/mL	6,681 (2486)	6763 (2436)	98.77 (95.14; 102.52)
AUC_{∞}, ng.h/mL	6,785 (2518)	6868 (2459)	98.76 (95.15; 102.52)
$t_{1/2,}$ h	3.7 (0.7)	3.7 (0.7)	-
FTC			
C_{max}, ng/mL	2041 (481)	2053 (469)	99.32 (95.61; 103.17)
t_{max}, h	2.00 (0.60; 5.00)	2.00 (0.50; 5.00)	-

AUC_{last}, ng.h/mL	11,722 (1959)	11,746 (1868)	100.04 (98.46; 101.66)
AUC_{∞}, ng.h/mL	11,882 (2002)	11,927 (1935)	100.13 (98.36; 101.93)
$t_{1/2,}$ h	16.5 (3.3)	17.0 (3.4)	-
TAF			
C_{max}, ng/mL	110 (54.1)	120 (74.0)	96.87 (88.95; 105.50)
t_{max}, h	1.50 (0.25; 3.50)	1.01 (0.25; 4.00)	-
AUC_{last}, ng.h/mL	123 (42.0)	132 (58.1)	96.59 (91.72; 101.73)
AUC_{∞}, ng.h/mL	127 (39.4)	141 (59.7)	95.42 (90.62; 100.48)
$t_{1/2,}$ h	0.3 (0.1)	0.3 (0.1)	-

a N=maximum number of subjects with data

b As a result of the blinded sample size re-estimation, to control the nominal type I error rate, an adjusted CI of 90.14% was used for the statistical analysis.

Food effect study TMC114FD2HTX1002

In study TMC114FD2HTX1002, the effect of concomitant food intake (standardized high calorie/high-fat breakfast, 56 g fat) on the oral bioavailability of DRV, COBI, FTC and TAF following oral administration of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet was investigated.

This was a Phase 1, randomized, 3-panel, open-label, 2-way crossover study in healthy subjects. In each panel, during 2 subsequent sessions, each subject received 2 treatments as a single dose, randomized (within panel) according to a classical 2-sequence, 2-period Williams design. The study population comprised 72 healthy volunteers (24 subjects in each panel).

The results of panel 3 of the food-effect FDC study show that mean C_{max} of FTC and TAF were 1.26- and 1.82-fold higher, respectively, after administration of the D/C/F/TAF FDC under fasted compared to fed conditions, and mean AUC_{last} for both FTC and TAF were comparable for both conditions. Mean C_{max} and AUC values were lower under fasted compared to fed condition for both DRV (30% to 45% lower) and COBI (16% to 29% lower).

The impact of food on the PK of COBI, FTC and TAF is not considered to be clinically relevant by the applicant, which can be agreed to. Based on the improved absorption of DRV in fed condition and in line with other DRV containing formulations, it is recommended that the D/C/F/TAF FDC tablet be taken with food. The type of food does not affect the exposure of DRV. Intake with food was also recommended for subjects in studies with the D/C/F/TAF FDC (except when evaluating the food effect) or studies with other DRV-containing regimens. This advice is also in agreement with the advice in the Rezolsta (DRV/COBI) SmPC, which states that the FDC tablet should be taken with food and the Descovy (F/TAF) SmPC, which states that the FDC tablet may be taken with or without food.

In summary, the CHMP agreed with the strict intake with food and is reflected in the SmPC.

Panel 1 of study TMC114FD2HTX1002 evaluated the relative oral bioavailability of TAF and FTC after single-dose administration of D/C/F/TAF 800/150/200/10 mg FDC compared to E/C/F/TAF 150/150/200/10 mg FDC under fed (regular-fat standard breakfast, 21 g fat) conditions. The results of this panel show that no major differences were observed regarding the PK of FTC for both FDC tablets and exposure to TAF was 30% lower for D/C/F/TAF versus E/C/F/TAF, but these results are less relevant for this application.

Panel 2 of study TMC114FD2HTX1002evaluated the relative oral bioavailability of DRV, COBI, FTC, and TAF after single-dose administration of D/C/F/TAF 800/150/200/10 mg FDC compared to the separate agents (DRV as 1

x 800 mg tablet, F/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet) under fed (regular-fat standard breakfast, 21 g fat) conditions. The design of this panel of the study was similar to the design of the pivotal bioequivalence study TMC114FD2HTX1001, but this panel preceded the pivotal bioequivalence study and used a smaller sample size (24 subjects versus 96 subjects). The PK parameters for DRV, COBI and FTC all showed bioequivalence with respect to the usual 80 to 125% acceptance interval. For TAF AUC bioequivalence was also demonstrated, but for TAF C_{max} the lower confidence limit (72%) was below the 80 to 125% acceptance interval. The point estimate of 91% does not exclude bioequivalence however and the smaller size of this study and the large variation in TAF plasma exposures need to be taken into account. The median t_{max} and terminal half-life ($t_{1/2}$) were comparable between treatments for all components. In general, it can be concluded that the results of this panel are in agreement with the results of the fully powered pivotal bioequivalence study.

Phase 2 Study GS-US-299-0101 in HIV-1 infected subjects

The non-compartmental PK of DRV, COBI, FTC, TAF and TFV following multiple-dose administration of the D/C/F/TAF FDC in HIV-1 infected subjects were assessed in a PK substudy of Phase 2 study GS-US-299-0102 and compared to those for DRV+COBI+F/TDF, which has been assessed previously as part of the Descovy dossier. Overall, the plasma exposures of TAF, DRV, COBI, and FTC in this study were consistent with historical data for these agents, both in healthy and HIV-1 infected subjects.

Multiple-dose DRV, COBI and FTC PK parameters in study GS US 299 0102 (target population) were consistent with those observed in GS-US-299-0101 (healthy population), when D/C/F/TAF was administered as the FDC.

For TAF, the median (Q1, Q3) plasma half-life was 0.45 (0.38, 0.66) hours, no drug was detectable 8 hours after administration, and the mean AUC_{last} (130.5 ng.h/mL) was consistent with historical data for subjects receiving the D/C/F/TAF FDC or TAF 25 mg single agent in the TAF proof-of-concept study (mean AUC_{last} 115.2 ng.h/mL, study GS-US-120-0104).

The TFV plasma concentrations following the D/C/F/TAF FDC were markedly lower, as anticipated, compared with those following DRV + COBI + F/TDF. Administration of the D/C/F/TAF FDC led to substantially lower (~90%) mean [%CV] systemic exposure (AUC_{tau}, 339 [37.1%] ng.h/mL) versus administration of DRV plus COBI plus F/TDF (3737 [26.8%] ng.h/mL).

These data showed that there no major differences in pharmacokinetics of DRV, COBI, FTC and TAF (TFV) between healthy subjects and HIV-1 infected subjects. This was confirmed for TAF and TFV by additional population PK modelling.

Key pharmacokinetics aspects

Absorption

Darunavir, COBI, FTC and TAF are all orally available when co-administered as the D/C/F/TAF FDC tablet. Darunavir has an absolute bioavailability of 82% when co-administered with the PK enhancer rtv, and 37% when administered without rtv. The absolute bioavailability of DRV when administered with COBI is unknown. The mean absolute bioavailability of FTC (administered as 200 mg capsule) is estimated to be 93%. The absolute bioavailability of TAF is unknown.

Darunavir exposure is enhanced by co-administration with COBI, such that DRV exposures (AUC_{24h} and C_{max}) comparable to DRV co-administered with rtv are achieved.

The D/C/F/TAF FDC is bioequivalent to co-administration of formulations of the separate agents DRV, COBI, and F/TAF.

The D/C/F/TAF FDC should be taken with food, in line with the advice in the Rezolsta (DRV/COBI) SmPC, which states that the FDC tablet should be taken with food and the Descovy (F/TAF) SmPC, which states that the FDC tablet may be taken with or without food. The food-effect study with the FDC showed that mean C_{max} of FTC and TAF were 1.26- and 1.82-fold higher, respectively, after administration of the D/C/F/TAF FDC under fasted compared to fed conditions, and mean AUC_{last} for both FTC and TAF were comparable for both conditions. Mean C_{max} and AUC values were lower under fasted compared to fed condition for both DRV (30% to 45% lower) and COBI (16% to 29% lower). The impact of food on the PK of COBI, FTC and TAF is agreed to be not clinically relevant. Based on the improved absorption of DRV in fed condition and in line with other DRV containing formulations, it is recommended that the D/C/F/TAF FDC tablet be taken with food. The type of food does not affect the exposure of DRV.

The mean DRV, COBI, FTC, and TAF exposures following multiple-dose administration of D/C/F/TAF 800/150/200/10 mg once daily in healthy subjects were generally comparable to the exposures following administration of the D/C/F/TAF 800/150/200/10 mg FDC once daily in HIV-1 infected subjects.

In an additional relative bioavailability study (TMC114FD2HTX1004), the administration of the whole D/C/F/TAF FDC tablet was compared to administration of a split tablet and of a crushed tablet (mixed in applesauce), under fed conditions in healthy adult subjects. Intake of the D/C/F/TAF FDC as a split tablet compared to as a whole tablet did not impact the relative bioavailability (AUC and C_{max}) of the different components (DRV, COBI, FTC and TAF), except for an 11% decrease in TAF C_{max}. The latter is not considered clinically relevant. Intake of the D/C/F/TAF FDC as a crushed tablet compared to as a whole tablet decreased the relative bioavailability of TAF by 29% for C_{max} and 19% for AUC and did not impact the relative bioavailability of DRV, COBI and FTC (except for a 17% decrease in FTC C_{max}). These results show that the D/C/F/TAF tablet can be split prior to intake without impact on the bioavailability of the components.

Distribution

Darunavir is approximately 95% bound to plasma protein. Darunavir binds primarily to plasma α1-acid glycoprotein.

Cobicistat is 97% to 98% bound to human plasma proteins and the mean plasma to blood-drug concentration ratio was approximately 2.

In vitro binding of emtricitabine to human plasma proteins was < 4%, independent of concentration (over the range of 0.02-200 mcg/mL). At peak plasma concentration, the mean plasma to blood drug concentration ratio was approximately 1.0.

Ex vivo binding of tenofovir alafenamide to human plasma proteins in samples collected during clinical studies was approximately 80%. In vitro binding of tenofovir to human plasma proteins is < 0.7%, independent of concentration (over the range of 0.01-25 mcg/mL).

Elimination

Darunavir and COBI are primarily metabolized by CYP3A. Cobicistat is a mechanism-based inhibitor of CYP3A and increases the DRV exposure such that DRV exposures (AUC24h and Cmax) comparable to DRV co-administered with rtv are achieved. Darunavir is predominantly excreted in feces, with minimal renal excretion. The renal excretion of COBI is also low.

Emtricitabine is primarily eliminated from the plasma via renal excretion as unchanged drug (approximately 65% of an oral dose and approximately 73% of an intravenous dose). Emtricitabine undergoes little metabolism; therefore, metabolism is a minor route of FTC elimination.

Inside cells, tenofovir alafenamide is converted by intracellular enzymes to TFV and subsequently phosphorylated to the pharmacologically active TFV-DP. Due to increased plasma stability and activation by cathepsin A, as compared with TDF, TAF is more efficiently loaded into peripheral blood mononuclear cells (PBMCs) (including lymphocytes and other HIV target cells) and macro¬phages, which results in greater concentrations of TFV-DP in PBMCs and lower exposure of TFV in the systemic circulation (approximately 90% lower). Tenofovir alafenamide is thus extensively metabolized, and predominantly excreted as TFV. There is very minimal renal excretion for TAF.

Dose proportionality and time dependencies

Dose proportionality

Based on the clinical studies with individual components, it is concluded that DRV administered with booster rtv increased somewhat less than dose proportionally, COBI increased supra-proportionally and both FTC and TAF behaved dose proportionally across the range of doses studied.

DRV in plasma in combination with COBI tends to exhibit time dependent pharmacokinetics and despite a mean elimination half-life of 6 hours does accumulate over time upon once daily dosing, approximately 30% increased based on a cross-study comparison. This is probably related to the non-linear boosting effect of COBI.

COBI in plasma shows time (and dose) dependent pharmacokinetics and exhibits a 1.5- to 1.7-fold increase in exposure following once daily dosing relative to single-dose administration (mean elimination half-life 3-4 hours). Being a mechanism based inhibitor of CYP3A, COBI exhibits both dose/concentration- and time-dependent inhibition of CYP3A. Its ability to effectively DRV as a CYP3A substrate is dependent on the concentrations that are achieved pre-systemically and/or systemically.

FTC in plasma tends to follow linear, first-order pharmacokinetics, with steady-state plasma FTC concentration-time profiles (upon once daily dosing) predictable from single dose data with approximately 20% accumulation (mean elimination half-life 17 hours).

Following once daily dosing of each FDC formulation, the TAF exposure parameters AUCtau and Cmax were lower (approx. 30% and 25%), as compared with exposures following a single dose, consistent with a mixed inhibitory/inductive effect on TAF absorption, indicative of non-linear pharmacokinetics of TAF in time. The decrease in TAF levels following multiple doses of the FDC formulation containing 10 mg TAF, relative to single-dose administration, may be due to an inductive effect of DRV on P-gp.

In contrast, there was a 2- to 3-fold increase in plasma TFV after once daily dosing compared to single dose administration (in line with a mean elimination half-life around 30 hours).

Intra- and inter-individual variability

Based on the data from the clinical studies with the new FDC combination administered after multiple dosing under fed conditions, the between-subject variability in DRV exposure and in COBI exposure was in the range of 25-45%, in FTC exposure in the range of 15-35% and in TAF exposure in the range of 25-35%. The between-subject variability in exposure tended to be higher for HIV-1 infected subjects as compared to healthy subjects for all analytes.

Specifically for TAF, the between-subject variability in the absorption phase of the first single dose was significantly higher, but variability of Cmax after multiple dosing was also in the range of 25-50%.

Furthermore, for DRV and COBI between-subject variability in exposure under fasted conditions tended to be higher than under fed conditions.

Within-subject variability estimates as derived from the pivotal bioequivalence trial were all ≤ 16% for AUC and Cmax of DRV, COBI and FTC; for TAF Cmax and TAF AUC within-subject variability was 36% and 21%, respectively.

Pharmacokinetics in target population

The non-compartmental PK of DRV, COBI, FTC, TAF and TFV following multiple-dose administration of the D/C/F/TAF FDC in HIV-1 infected subjects were assessed in a PK substudy of Phase 2 study GS-US-299-0102 and compared to those for DRV+COBI+F/TDF.

Study GS-US-299-0102

Study GS-US-299-0102 was a Phase 2, randomized, double-blind study to evaluate the safety and efficacy of a D/C/F/TAF 800/150/200/10 mg FDC versus COBI-boosted DRV (DRV 800 mg plus COBI 150 mg) plus F/TDF 200/300 mg (Truvada) in HIV-1 infected ART-naïve adult subjects. The PK of the components was also assessed. Subjects were randomized 2:1 (D/C/F/TAF FDC: DRV plus COBI plus F/TDF). Both treatments were administered once daily for 48 weeks. Overall, 153 subjects (103 subjects in the D/C/F/TAF FDC group and 50 subjects in the DRV plus COBI plus F/TDF group) were enrolled, of which 21 and 11, respectively, participated in the PK substudy: on or between the Week 4 and 8 visit, blood sampling for intensive PK profiling in plasma and/or PBMCs was conducted at selected study sites (blood samples collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post-dose). At Week 8, 24, and 48 visits, for all subjects PK trough samples were taken.

Steady-state PK parameters for DRV, COBI, FTC, TAF, TFV and TFV-DP (PBMCs) were determined under fed conditions following administration of the D/C/F/TAF FDC for subjects who participated in the intensive PK substudy (n=21, visit at Week 4 or 8); 14 subjects were included in the PBMC substudy analysis set. Steady-state plasma PK parameters for TFV and TFV-DP (PBMCs) were determined under fed conditions following administration of DRV plus COBI plus F/TDF for subjects who participated in the intensive PK substudy (n=11); 8 subjects were included in the PBMC substudy analysis set. In addition, TAF population PK parameters (sparse sampling) are available for 52 subjects in the D/C/F/TAF treatment arm.

The plasma PK parameters for DRV, COBI, FTC and TAF are shown in Table 6. The plasma exposures of DRV, COBI, and FTC were consistent with historical data for these agents. For TAF, the median (Q1, Q3) plasma half-life was 0.45 (0.38, 0.66) hours, no drug was detectable 8 hours after administration, and the mean AUC_{last} (130.5 ng.h/mL) was consistent with historical data for subjects receiving the D/C/F/TAF FDC or TAF 25 mg single agent in the TAF proof-of-concept study (mean AUC_{last} 115.2 ng.h/mL, study GS-US-120-0104).

The TFV plasma concentrations following the D/C/F/TAF FDC were markedly lower, as anticipated, compared with those following DRV + COBI + F/TDF (Figure 5 and Table 7). Administration of the D/C/F/TAF FDC led to substantially lower (~90%) mean [%CV] systemic exposure (AUC_{tau}, 339 [37.1%] ng.h/mL) versus administration of DRV plus COBI plus F/TDF (3737 [26.8%] ng.h/mL).

The PBMC intracellular TFV-DP AUC_{tau} was markedly higher in the D/C/F/TAF FDC group than in the DRV plus COBI plus F/TDF group. The TFV-DP AUC_{tau} LS mean ratio (TAF vs TDF) of 652% was consistent with the approximate 5- to 7-fold increase in TFV-DP exposure observed following administration of TAF 25 mg versus TDF 300 mg in study GS-US-120-0104.

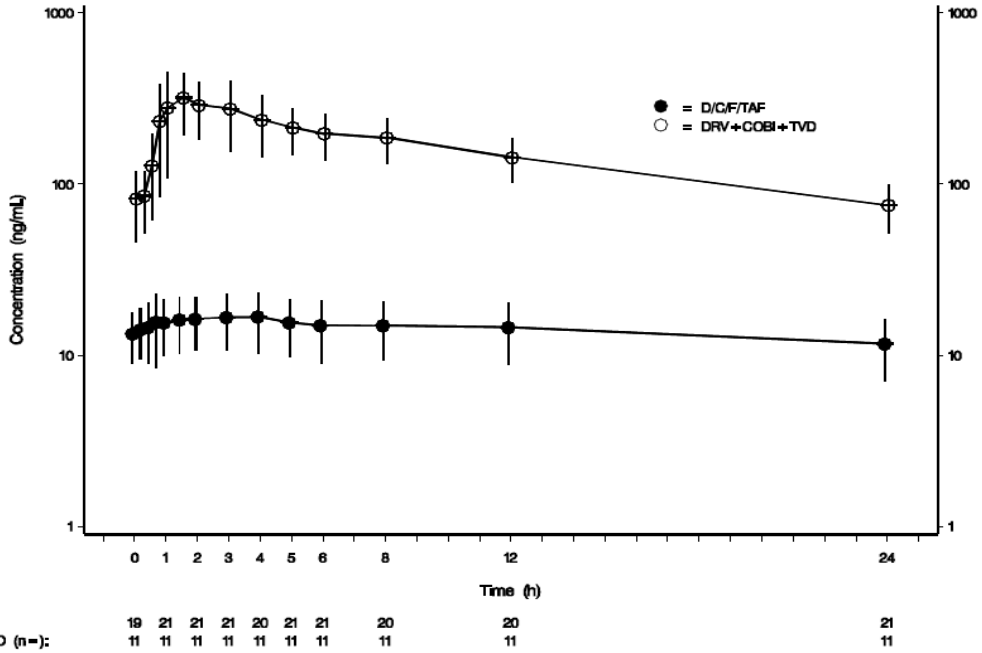


Figure 5. Mean Plasma Concentration-time Curves of TFV in plasma (including SD bars) on visit at Week 4 or 8 or in-between (PK Substudy, Study GS-US-299-0102)

Table 6. PK Parameters of DRV, COBI, TAF and FTC on visit at Week 4 or 8 or in-between (PK Substudy; D/C/F/TAF treatment arm; Study GS-US-299-0102)

	Mean (SD); t_{max}, $t_{1/2}$: Median (Range)			
Parameter	DRV N=21	COBI N=21	TAF N=21	FTC N=21
C_{max}, ng/mL	8826.2 (33.3)	1128.7 (35.3)	163.0 (51.9)	2056.4 (25.3)
t_{max}, h	3.00 (2.00, 4.00)	3.03 (3.00, 4.00)	0.53 (0.50, 1.00)	1.52 (1.50, 2.00)
AUC_{last}, ng.h/mL	-	-	130.5 (34.1)	-
AUC_{tau}, ng.h/mL	99301.8 (45.3)	8744.5 (43.9)	-	11918.0 (35.9)
C_{tau}, ng/mL	1651.0 (108.0)	30.5 (135.1)	-	93.1 (58.3)
$t_{1/2}$, h	9.42 (6.31, 13.87)	3.16 (2.77, 3.70)	0.45 (0.38, 0.66)	7.51 (6.40, 8.79)

Table 7. Statistical Comparison of plasma TFV PK Parameters on visit at Week 4 or 8 or in-between (PK Substudy, GS-US-299-0102)

Parameter	Mean (SD)		Test/ Reference LS Mean Ratio % (90% CI)
	D/C/F/TAF FDC (Test) N=21	DRV+COBI+F/TDF (Reference) N=11	
AUC_{tau}, ng.h/mL	339.0 (37.1)	3737.0 (26.8)	8.64 (6.99, 10.68)
C_{tau}, ng/mL	11.7 (39.3)	75.4 (30.9)	14.79 (11.67, 18.75)
C_{max}, ng/mL	18.8 (37.6)	413.2 (28.3)	4.39 (3.53, 5.45)

Table 8. Statistical Comparison of AUCtau for Intracellular TFV-DP on visit at Week 4 or 8 or in-between (PK Substudy, GS-US-299-0102)

	LS Mean by Treatment			
TFV-DP PK Parameter	**D/C/F/TAF (N=14)**	**DRV+COBI+F/TDF (N=8)**	**LS Mean Ratio (%)**	**90% CI (%)**
AUC_{tau} (µM.h)	17.12	2.62	652.09	(268.28, 1585.00)

Population PK model

Only for TAF, an additional population PK model was used to estimate individual TAF AUCtau based on sparse sampling in Study GS-US-299-0102. TAF exposures were estimable for 52 subjects in the D/C/F/TAF treatment arm. The mean (%CV) TAF AUCtau was 101.7 ng.h/mL (49.8%) and the mean (%CV) TAF Cmax was 94.1 ng/mL (53.3%) based on the population PK model.

There are no data from population PK analyses for the other FDC components from studies with the D/C/F/TAF FDC.

Comparison of healthy subjects and patients

Overall, the plasma exposures of TAF, DRV, COBI, and FTC in the D/C/F/TAF FDC study in HIV-1 infected subjects (study GS-US-299-0102) were consistent with historical data for these agents, both in healthy and HIV-1 infected subjects.

Multiple-dose DRV, COBI and FTC PK parameters in study GS US 299 0102 (target population) were consistent with those observed in GS-US-299-0101 (healthy population), when D/C/F/TAF was administered as the FDC.

In the D/C/F/TAF Phase 2 study GS-US-299-0102, the median (Q1, Q3) plasma half-life for TAF was 0.45 (0.38, 0.66) hours, no drug was detectable 8 hours after administration, and the mean (%CV) AUC_{last} was 130.5 (34.1) ng.h/mL, which is consistent with historical data for TAF in healthy subjects receiving D/C/F/TAF or HIV-1 infected subjects receiving TAF 25 mg single agent in the proof-of-concept study GS-US-120-0104 (mean AUC_{tau} 115.2 ng.h/mL). The TAF PK parameters for D/C/F/TAF (TAF 10 mg) from study GS-US-299-0101 were also consistent with these historical data from study GS-US-120-0104 with TAF 25 mg single agent.

Table 9. Across-Study Comparison of PK Parameters of DRV, COBI, FTC and TAF After Multiple-Dose Administration of D/C/F/TAF 800/150/200/10 mg Once Daily as FDC Tablet or as Separate Agents in Healthy Subjects or in HIV 1 Infected Subjects (Fed Conditions)

	Mean (SD); t_{max}: Median (Range)			
	Healthy **D/C/F/TAF FDC 800/150/200/10 mg qd N=19[a]**	**Healthy** **D/C/F/TAF FDC 800/150/200/10 mg qd N==19**	**Healthy Single Agents DRV + COBI (800/150 mg) or F/TAF (200/25 mg) qd N=19/N=16[c]**	**HIV-1 Infected ART Naïve** **D/C/F/TAF FDC 800/150/200/10 mg qd N=21**
	Day 12	**Day 12**	**Day 12**	**Weeks 4-8**
Parameter	GS-US-299-0101 (part 1; formulation 3)	GS-US-299-0101 (part 3)	GS-US-299-0101 (part 3)	GS-US-299-0102
DRV C_{max}, ng/mL	9,743 (14.3)	9,233 (20.2)	9,320 (13.5)	8,826 (33.3)
t_{max}, h	3.00 (3.00, 4.00)	3.00 (3.00, 4.00)	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)
AUC_{tau}, ng.h/mL	113,654 (23.8)	102,289 (26.3)	102,149 (28.5)	99,302 (45.3)
$t_{1/2}$, h	7.13 (6.53, 9.01)	6.84 (6.05, 8.66)	6.48 (5.41, 7.92)	9.42 (6.31, 13.87)
COBI C_{max}, ng/mL	1,305 (13.8)	1,237 (15.4)	1,249 (16.9)	1,129 (35.3)
t_{max}, h	3.00 (2.00, 4.00)	3.00 (3.00, 4.00)	3.00 (2.00, 4.00)	3.03 (3.00, 4.00)
AUC_{tau}, ng.h/mL	10,097 (23.7)	9,230 (18.9)	9,229 (18.9)	8,745 (43.9)
$t_{1/2}$, h	2.90 (2.81, 3.42)	3.11 (2.79, 3.31)	2.92 (2.73, 3.44)	3.16 (2.77, 3.70)
FTC C_{max}, ng/mL	2,199 (20.7)	2,363 (17.4)	2,207 (23.1)	2,056 (25.3)
t_{max}, h	1.75 (1.50, 2.00)	1.50 (1.50, 2.00)	2.00 (1.50, 2.00)	1.52 (1.50, 2.00)
AUC_{tau}, ng.h/mL	12,602 (16.4)	13,444 (20.6)	11,557 (18.6)	11,918 (35.9)
$t_{1/2}$, h	5.48 (4.74, 6.96)	13.22 (6.87, 21.81)	15.90 (8.48, 22.88)	7.51 (6.40, 8.79)
TAF C_{max}, ng/mL	130.7 (39.2)	184.0 (35.8)	-	163.0 (51.9)
t_{max}, h	0.50 (0.50, 1.00)	0.75 (0.50, 1.00)	-	0.53 (0.50, 1.00)
AUC_{tau}, ng.h/mL	116.4 (26.0)[b]	166.7 (30.0)	-	130.5 (34.1)[b]
$t_{1/2}$, h	0.41 (0.33, 0.51)	0.37 (0.32, 0.44)	-	0.45 (0.38, 0.66)

a N=maximum number of subjects with data

b AUClast presented

c TAF data not presented from the administration of single components as the higher dose of TAF 25 mg administered does not allow for direct comparison to the 10 mg dose in the D/C/F/TAF FDC.

AUClast=AUC from 0h up to the time of the last measurable (non- below quantification limit) concentration after dosing; AUCtau=AUC from time of administration up to the end of the dosing interval; CI=confidence interval; Cmax=maximum observed analyte concentration; Ctau=trough concentration; LS=least square; N=number of subjects; qd=once daily; SD=standard deviation; t1/2=apparent elimination half-life; tmax=actual sampling time to reach the maximum observed analyte concentration; vs=versus.

Special populations

The information and guidance for special populations for the D/C/F/TAF FDC is derived from that for the separate agents, DRV, COBI, and F/TAF.

Elderly

Age was not a significant covariate for the PK of any of the components of the D/C/F/TAF FDC in the age range ≤65 years. Limited PK information is available in the population of elderly (age ≥65 years) for the D/C/F/TAF FDC as well as its individual components.

Paediatric population

Adult doses for DRV, COBI, and F/TAF have shown to provide systemic exposures in paediatric subjects aged ≥12 and <18 years that is comparable to that in adults.

Gender and race

Sex was not a significant covariate for the PK of any of the components of the D/C/F/TAF FDC.

No clinically relevant differences due to race or ethnicity were identified for the PK of any of the components of the D/C/F/TAF FDC.

Hepatic impairment

Pharmacokinetic data and relevant safety data support administration of the D/C/F/TAF FDC once daily without dose adjustment in subjects with mild or moderate hepatic impairment. The effect of severe hepatic impairment has not been evaluated.

Renal impairment

Pharmacokinetic data and relevant safety data support administration of the D/C/F/TAF FDC once daily without dose adjustment in subjects with mild to moderate renal impairment (estimated glomerular filtration rate calculated using Cockcroft Gault equation [eGFR] ≥ 30 mL/min). The D/C/F/TAF FDC should not be initiated in patients who have an eGFR <30 ml/min.

Hepatitis B and/or Hepatitis C Virus Coinfection

There were insufficient pharmacokinetic data in the clinical trials to determine the effect of hepatitis B and/or C virus infection on the pharmacokinetics of darunavir, cobicistat, emtricitabine, or tenofovir alafenamide.

Pharmacokinetic interaction studies

The drug interaction profile of the D/C/F/TAF FDC is primarily driven by the drug interaction profile of DRV/COBI.

Darunavir and COBI are both mainly inhibitors of CYP3A, CYP2D6 and P-glycoprotein (P-gp). Co-administration with drugs primarily metabolized by CYP3A, CYP2D6 and/or P-gp may result in increased plasma concentrations of those drugs.

Because DRV and COBI are metabolized by CYP3A, drugs that induce CYP3A activity are expected to increase the apparent clearance (CL/F) of DRV and COBI, resulting in decreased plasma concentrations of DRV and/or COBI. Co-administration with other drugs that inhibit CYP3A may decrease the CL/F of DRV and COBI and may result in increased plasma concentrations of DRV and/or COBI.

Emtricitabine has a low potential for drug interactions, both as a substrate or as a perpetrator. Emtricitabine is not an inhibitor of CYP450 enzymes and the potential for CYP mediated interactions involving FTC with other medicinal products is low.

Emtricitabine is primarily excreted by the kidneys by a combination of glomerular filtration and active tubular secretion. No drug interactions due to competition for renal excretion have been observed.

Tenofovir alafenamide has a low potential for drug interactions as a perpetrator. Tenofovir alafenamide is not an inhibitor of CYP450 enzymes.

Tenofovir alafenamide is a substrate of the efflux transporter P-gp. Drugs that induce P-gp activity are expected to decrease the absorption of TAF, resulting in decreased plasma concentrations of TAF. Co-administration of TAF with drugs that inhibit P-gp may increase the absorption and plasma concentrations of TAF.

No drug-drug interaction studies have been performed using the D/C/F/TAF FDC. The drug-drug interaction potential of the D/C/F/TAF FDC has been evaluated on the basis of interactions observed with each of the single components and, in the case of DRV, also when co-administered with rtv. All these studies have been assessed as part of the previous dossiers.

The overview of drug interactions (based on observed data with single agents or predicted) and dosing recommendations has been directly combined for all (non-ARV) concomitant medications from the currently approved prescribing information for DRV/COBI and for FTC/TAF.

An overview of drug interactions (based on observed data with single agents or predicted) and dosing recommendations are summarised in SmPC Section 4.5.

2.4.3. Pharmacodynamics

Mechanism of action

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

Cobicistat has no antiviral activity in cell culture against HIV-1 and does not antagonize the antiviral activity of DRV. Cobicistat is a pharmacoenhancer that is used to boost DRV exposures.

Emtricitabine is a nucleoside analogue of 2'-deoxycytidine, which is phosphorylated by cellular enzymes to form FTC triphosphate. Emtricitabine triphosphate inhibits HIV-1 replication through incorporation into viral deoxyribonucleic acid (DNA) by the HIV-1 RT, which results in DNA chain termination. Emtricitabine is specific to HIV-1 and HIV-2 and HBV. Intracellularly, FTC is phosphorylated by cellular enzymes to form the active metabolite, FTC 5'-triphosphate, which competitively inhibits the HIV-1 RT, resulting in DNA chain termination. Emtricitabine 5'-triphosphate is a very weak inhibitor of mammalian DNA polymerase α, β, ε, and mitochondrial DNA polymerase γ, and there is no evidence of toxicity to mitochondria in vitro and in vivo.

Tenofovir alafenamide is a phosphonamidate prodrug of TFV (2'-deoxyadenosine monophosphate analogue). Tenofovir alafenamide is permeable to cells and due to increased plasma stability and intracellular activation through hydrolysis by CatA, TAF is more efficient than TDF in loading TFV into PBMCs (including lymphocytes and other HIV-1 target cells) and macrophages. Following its release from the TAF prodrug, intracellular TFV is subsequently phosphorylated to the pharmacologically active metabolite TFV diphosphate. Tenofovir diphosphate inhibits HIV-1 replication through incorporation into viral DNA by the HIV-1 RT, which results in DNA chain termination, thereby effectively blocking the replication and spread of infectious HIV-1.

Tenofovir is specific to HIV-1, HIV-2 and HBV. In vitro studies have shown that both FTC and TFV can be fully phosphorylated when combined in cells. Tenofovir diphosphate is a weak inhibitor of mammalian DNA polymerases that include mitochondrial DNA polymerase γ, and there is no evidence of toxicity to mitochondria in vitro.

Primary pharmacology

Integrated virology analyses

In the comparative Phase 2 study GS-US-299-0102 in HIV-1 infected treatment-naïve patients, no patient developed any DRV or primary PR mutations through Week 48. One patient, receiving D/C/F/TAF, had an NRTI-resistance mutation emerging after Week 48 (K65K/R and M184M/I). These mutations are associated with resistance to TDF/TAF and FTC, respectively. However, phenotypic susceptibilities to both FTC and TDF were in the sensitive range despite the presence of those mutations. These data are in line with the low level of development of resistance to DRV, FTC/TDF or TAF observed in earlier studies.

Based on data of DRV/r 600/100mg twice daily in highly treatment-experienced patients, 'development of drug resistance' was initially classified as an important potential risk and later classified as an identified risk based on the Week-48 data from the trial TMC114-C212, in treatment-experienced paediatric subjects (from 6 to < 18 years of age) evaluating the twice daily dosing regimen of DRV/rtv. Cumulative numbers on the development of drug resistance (including any genotype and/or phenotype data) were collected and discussed in the Periodic Safety Update Reports. It has been demonstrated that the risk of developing drug resistance is very low in treatment naïve and treatment-experienced patients with 0 DRV RAMs who take DRV/rtv 800/100 mg once daily. This evaluation is based on the TMC114-C211 (Week 48 up to Week 192 data) and the TMC114-C229 (Week 48 data) and post-marketing data presented in the PSUR; development of genotypic/phenotypic resistance to DRV or other PIs and to NRTIs in the backbone (including FTC/TDF) is rarely observed.

As expected, similar low level of resistance development was seen in virologic failures on DRV/COBI FDC (GS-US-216-0130 Week 48 up to Week 192 data). However, the risk of development of drug resistance was retained.

'Development of drug resistance' has not been classified as a risk for FTC/TDF. There is no evidence to suggest that the substitution of TDF with TAF in the FDC will increase the risk of resistance development.

Although there seems to be low levels of resistance development, the risk still exists and remains a safety concern.

Secondary pharmacology

No specific studies with D/C/F/TAF (as FDC or coadministered as single agents) have been conducted to investigate potential effects on the QT interval. In GS-US-299-0102 in ART-naïve subjects, there were no clinically relevant ECG findings that would suggest a potential effect of D/C/F/TAF on the QT interval. The

potential effects on QT interval, has been investigated for the separate components and no clinically relevant effects were observed.

Relationship between plasma concentration and effect

There was no apparent exposure-response relationship for virologic response and safety parameters.

2.4.4. Discussion on clinical pharmacology

The clinical development program for the D/C/F/TAF 800/150/200/10 mg FDC tablet is based on the clinical development programs for the DRV, COBI, FTC and TAF single agents and combinations thereof (darunavir/cobicistat [DRV/COBI, Rezolsta] and emtricitabine/tenofovir alafenamide [F/TAF, Descovy]). A PK bridging clinical development program formed the basis for the application of this FDC tablet combining the four components in one tablet (D/C/F/TAF FDC).

The objective of the pivotal bioequivalence study TMC114FD2HTX1001 was to evaluate the single-dose PK and pivotal bioequivalence of the D/C/F/TAF FDC relative to the separate agents (DRV 800 mg tablet formulation and F/TAF 200/10 mg FDC in the presence of 150 mg COBI), under fed conditions (standardized regular-fat breakfast, in 96 healthy subjects.

The study showed that the D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration of the separate agents DRV, the F/TAF FDC, and COBI, with respect to both rate and extent of absorption of the four components involved. The 90% CIs of the LS mean ratios of all main PK parameters for all four compounds (DRV, COBI, FTC, TAF) were within the 80.00% to 125.00% acceptance range.

The comparison of the D/C/F/TAF 800/150/200/10-mg FDC tablet to the separate agents DRV, the F/TAF FDC, and COBI is acceptable for assessment of bioequivalence. Of note, the fixed dose combinations of the components DRV/COBI and F/TAF are authorised as REZOLSTA and DESCOVY, respectively and can be used in combination to construct an antiretroviral regimen.

Furthermore, in study TMC114FD2HTX1002, the effect of concomitant food intake (standardized high calorie/high-fat breakfast, 56 g fat) on the oral bioavailability of DRV, COBI, FTC and TAF following oral administration of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet was investigated. The impact of food on the PK of COBI, FTC and TAF is not considered to be clinically relevant. Based on the improved absorption of DRV in fed condition and in line with other DRV containing formulations, it is recommended that the D/C/F/TAF FDC tablet be taken with food. This is adequately reflected in the SmPC.

In another panel of this study the relative oral bioavailability of DRV, COBI, FTC, and TAF after single-dose administration of D/C/F/TAF 800/150/200/10 mg FDC was compared to the separate agents (DRV as 1 x 800 mg tablet, F/TAF as 1 x 200/10 mg tablet and COBI as 1 x 150 mg tablet) under fed (regular-fat standard breakfast, 21 g fat) conditions. The study design was similar to the design of the pivotal bioequivalence study TMC114FD2HTX1001, but preceded the pivotal bioequivalence study and used a smaller sample size (24 subjects versus 96 subjects). It could be concluded that the results of this panel are in agreement with the results of the fully powered pivotal bioequivalence study.

An integrated virology analyses was provided which included the Phase 2 study (GS-US-299-0102 in HIV-1 infected treatment-naïve patients), as well as results reported from studies with the individual components. Although development of drug resistance mutations is rare, this safety concern is reflected in the RMP.

2.4.5. Conclusions on clinical pharmacology

The comparable exposure (i.e. AUC and Cmax) for DRV, COBI, FTC, and TAF when administered as single agents or as the D/C/F/TAF FDC in healthy subjects and HIV-1 infected ART-naïve subjects as compared with historical data, allows the extrapolation of safety and efficacy data from either darunavir/low-dose ritonavir (DRV/rtv) 800/100 mg once daily, DRV/COBI 800/150 mg once daily or F/TAF 200/10 mg once daily to D/C/F/TAF 800/150/200/10 mg once daily.

The pivotal bioequivalence study showed that the D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration of the separate agents DRV, the F/TAF FDC, and COBI.

2.5. Clinical efficacy

2.5.1. Dose response studies and main clinical studies

For D/C/F/TAF, the efficacy, resistance, and safety profile is derived from the DRV/COBI and F/TAF development programs, supported by the Phase 2 double-blind Study GS-US-299-0102 (N=153; 103 subjects on D/C/F/TAF). An overview of relevant Phase 2 and 3 clinical studies supporting the DRV/COBI, the F/TAF and hence the D/C/F/TAF efficacy, resistance, and safety profile is presented in Table 10.

Table 10. Overview of key clinical studies

Study	Study Design	Numbers[a] by Treatment Regimen	Data
DRV/COBI			
GS-US-216-0130 ART-naïve	Phase 3, open-label, multicenter study to evaluate the safety, efficacy, and tolerability of DRV/COBI administered as single agents	DRV/COBI (N=313)	Week 48 efficacy, Week 48 and roll-over phase safety
GS-US-236-0118 ART-naïve or virologically suppressed Renal impairment (mild/moderate)	Phase 3, open-label, multicenter study to evaluate the safety, of COBI-containing HAART in HIV-1 infected patients with mild to moderate renal impairment	DRV/COBI (N=22, Cohort 2 PI, DRV/COBI subgroup)	Week 96 efficacy and safety
F/TAF (as either E/C/F/TAF FDC or as F/TAF FDC + 3rd Agent			
GS-US-292-0104 ART-naïve	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + PBO-to-match STB (N = 435) STB + PBO-to-match E/C/F/TAF FDC (N = 432)	Week 48 efficacy, PK, and safety
GS-US-292-0111 ART-naïve	Phase 3, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB	E/C/F/TAF FDC + PBO-to-match STB (N = 431) STB + PBO-to-match E/C/F/TAF FDC (N = 435)	Week 48 efficacy, PK, and safety

GS-US-292-0102 ART-naïve	Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of E/C/F/TAF FDC vs STB Open-label extension phase allowed crossover from STB to E/C/F/TAF after the Week 48 visit and enrollment of virologically suppressed adult subjects who had received a DRV+COBI-containing regimen in Study GS-US-299-0102	Randomized phase: E/C/F/TAF FDC + placebo-to-match STB (N = 112) STB + placebo-to-match E/C/F/TAF FDC (N = 58) Open-label extension phase: Continued on E/C/F/TAF FDC (N = 105) Switch to E/C/F/TAF FDC (N = 161) from STB to E/C/F/TAF FDC (N = 53) from D/C/F/TAF to E/C/F/TAF FDC (N = 70) from DRV+COBI+TVD to E/C/F/TAF FDC (N = 38)	Week 48[b] efficacy, PK, and safety
GS-US-311-1089 Virologically suppressed	Phase 3, open-label study to evaluate the efficacy, safety, and tolerability of switching from a TDF-containing combination regimen to F/TAF FDC-containing combination regimen	Switch to F/TAF FDC (N=333) Stay on F/TDF +3rd Agent (N=330)	Week 48 efficacy and safety
GS-US-292-0112 ART-naïve or virologically suppressed Renal impairment (mild/moderate)	Phase 3, open-label, multicenter, multiple cohort study to evaluate the safety, efficacy, and tolerability of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 248)	Week 24 (and partial Week 48) efficacy and safety
GS-US-292-1249 ART-naïve or virologically suppressed HIV-1/HBV coinfected	Phase 3b, open-label study to evaluate the efficacy and safety of E/C/F/TAF FDC in HIV-1/hepatitis B coinfected adults	E/C/F/TAF FDC (N = 77) HIV-suppressed (N=74) HIV and HBV treatment-naive (N=3)	Week 48 efficacy, PK, and safety
GS-US-292-0106 ART-naïve Adolescents	Phase 2/3, open-label, multicenter, 2-part, single-arm study to evaluate the PK, safety, tolerability, and antiviral activity of E/C/F/TAF FDC	E/C/F/TAF FDC (N = 50) PK sub-study: N = 24	Week 48 efficacy, PK, and safety
D/C/F/TAF			
GS-US-299-0102 ART-naïve	Phase 2, randomized, double-blind, multicenter, active controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD	D/C/F/TAF FDC (N = 103) DRV+COBI+TVD (N = 50)	Week 48 efficacy, PK, and safety

Study GS-US-299-0102 is the only clinical study submitted that has evaluated the proposed FDC containing D/C/F/TAF.

Dose response studies

The to be marketed fixed dose combination tablet consists of DRV 800 mg, COBI 150 mg, FTC 200 mg and TAF 10 mg. The 800 mg dose of DRV is approved for treatment-naive subjects and treatment-experienced subjects with no DRV-resistance-associated mutations.

Cobicistat is a pharmacoenhancer that is used to boost DRV exposures, and the 150 mg dose was shown to boost DRV levels similarly to 100 mg ritonavir (Norvir®) in a Phase 1, multiple dose study to evaluate the relative bioavailability and pharmacokinetics of DRV once daily when coadministered with COBI or ritonavir once daily (GS-US-216-0115). Pharmacokinetic analyses demonstrated that DRV trough concentrations were consistently maintained above protein-adjusted EC50 for wild-type virus with COBI coadministration.

The 200 mg dose of FTC represents the marketed dose for this drug. This dose of FTC is also part of the approved FDC products Truvada® (emtricitabine/tenofovir DF), Atripla® (efavirenz/emtricitabine/ tenofovir DF), and Genvoya (E/C/F/TAF), Descovy (F/TAF) and Odefsey (F/R/TAF), all indicated for the treatment of HIV-1 infection.

The 10 mg dose of TAF was selected based on the results of 3 Phase 1 or 1/2 studies, including the proof-of-concept Study GS-120-0104 and the 2 drug combination Studies GS-US-299-0101 and GS-US-311-0101. The proof-of-concept study, GS-US-120-0104, demonstrated that 3 doses of TAF monotherapy had potent antiviral activity in HIV-1 patients compared with TDF, with mean (± SD) change from baseline in HIV-1 RNA of -0.95 ± 0.45, -1.53 ± 0.40, -1.7 ± 0.22 and -0.81± 0.66 log10 copies/mL at the 8, 25, and 40 mg doses of TAF, and 300 mg dose of TDF, respectively.

Preliminary results from Studies GS-US299-0101 and GS-US-311-0101 of TAF in various combination drug formulations, indicated that TAF exposure associated with potent antiviral activity were achieved with the D/C/F/TAF 10 mg (monolayer formulation) and TFV exposures with this formulation were in the range of historical data with TAF 25 mg dosed alone or with another combination product, elvitegravir (EVG)/C/F/TAF 10 mg. Moreover, administration of D/C/F/TAF 10 mg resulted in ~90% lower steady-state TFV exposure versus DRV/co plus F/TDF. Exposures of DRV/COBI and FTC were comparable when administered as an FDC or as individual components. Study GS-US-299-0101 also showed that the relative bioavailability of DRV, COBI, FTC, and TFV when administered as DRV/co plus F/TDF was similar relative to that when administered as individual components.

The proposed indication for the D/C/F/TAF FDC is for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg).

2.5.2. Main study

Study GS-US-299-0102

Study title: *A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Darunavir/Cobicistat/ Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/ Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults.*

Subjects were enrolled at a total of 38 study centers: 37 centers in the United States and 1 center in Puerto Rico.

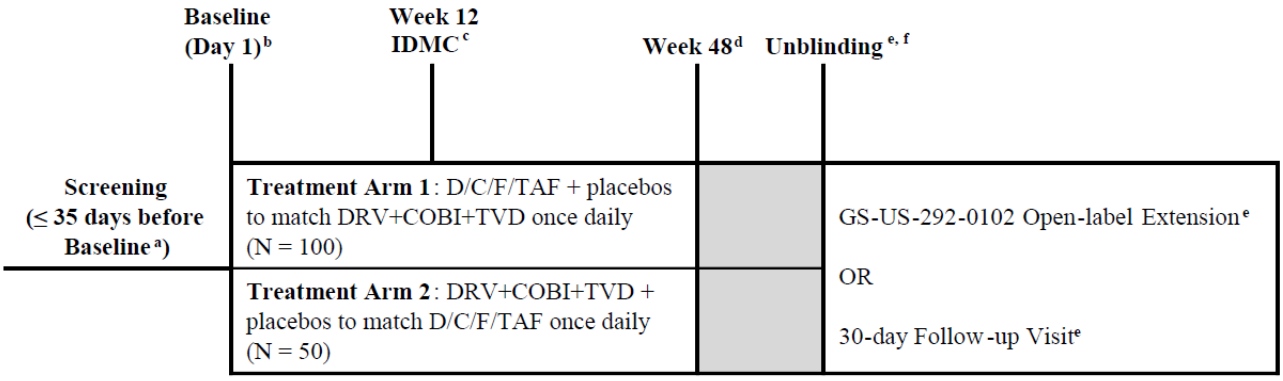
Methods

Subjects were randomized in a 2:1 ratio to one of the following 2 treatment arms:

- Treatment Arm 1: FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg + placebos to match DRV 800 mg (400mg tablet x 2) and COBI 150 mg tablet and FDC tablet FTC 200 mg/TDF 300 mg once daily (5 tablets in total)
- Treatment Arm 2: DRV 800 mg (400 mg tablet x 2) + COBI 150 mg tablet + FDC tablet FTC 200 mg/TDF 300 mg + placebos to match an FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg once daily (5 tablets in total)

Subjects were treated for 48 weeks. After Week 48, subjects continued to take blinded study drug and attend visits every 12 weeks until treatment assignments were unblinded, at which point all subjects returned for an Unblinding Visit, when the current study was terminated. If still receiving study drug at that point, subjects were

given the option to participate in the open-label rollover extension phase of Study GS-US-292-0102 and to receive the E/C/F/TAF FDC until it becomes commercially available, or until Gilead Sciences elects to terminate the development of the E/C/F/TAF FDC. Subjects who completed the study and did not wish to participate in or were ineligible for the Study GS-US-292-0102 open-label rollover extension were required to return to the clinic 30 days after the completion of study drugs for a 30-day Follow-up Visit.



a Screening window was extended to 42 days for subjects who required repeat testing of HIV-1 genotype.

b Following the Baseline visit, subjects returned for study visits at Weeks 2, 4, 8, 12, 16, and then every 8 weeks through Week 48.

c An external Independent Data Monitoring Committee (IDMC) reviewed the progress, efficacy, and safety profile of the study regimens while the study was ongoing. The committee convened after the last subjects enrolled completed Week 12 of the study.

d Subjects continued to attend visits every 12 weeks following Week 48 until treatment assignment was unblinded.

e Once Gilead Sciences provided unblinded treatment assignments to the Investigators, all subjects returned to the clinic within 30 days (+6 days) for an Unblinding Visit. At the Unblinding Visit all subjects discontinued blinded study drugs and were given an option to participate in the Study GS-US-292-0102 open-label rollover extension. Subjects who did not wish to participate in the open-label rollover extension discontinued blinded study drugs and returned for a 30-day Follow-up visit following the Unblinding Visit.

f Subjects who discontinued study drug prior to the Unblinding Visit were not eligible for the open label rollover extension; these subjects discontinued the study after the Unblinding Visit.

Figure 6. Study schema

Study Participants

Subjects enrolled were ART-naïve, HIV-1 infected adult subjects (>18 years of age) who had plasma HIV-1 RNA ≥5,000 copies/mL, a CD4+ cell count >50 cells/µL, an HIV-1 genotype showing sensitivity to DRV, TDF and FTC, and an eGFRCG of ≥70 mL/min. Subjects were excluded if they were hepatitis B or C co-infected, had a new AIDS-defining condition within 30 days of screening, or were pregnant.

Treatments

Subjects were randomized in a 2:1 ratio to one of the following 2 treatment arms:

- Treatment Arm 1: FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg + placebos to match DRV 800 mg (400mg tablet x 2) and COBI 150 mg tablet and FDC tablet FTC 200 mg/TDF 300 mg once daily (5 tablets in total)
- Treatment Arm 2: DRV 800 mg (400 mg tablet x 2) + COBI 150 mg tablet + FDC tablet FTC 200 mg/TDF 300 mg + placebos to match an FDC tablet of DRV 800 mg/COBI 150 mg/FTC 200 mg/TAF 10 mg once daily (5 tablets in total)

Randomization was stratified by HIV-1 RNA level (≤ 100,000 or > 100,000 copies/mL) and race (black or non-black) at screening.

Objectives

The primary objective of this study was:

- To evaluate the efficacy of a regimen containing D/C/F/TAF versus DRV+COBI+TVD in HIV-1 infected, ART-naive adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 24.

The secondary objectives of this study were as follows:

- To evaluate the efficacy of a regimen containing D/C/F/TAF versus DRV+COBI+TVD in HIV-1 infected, ART-naive adult subjects, as determined by the achievement of HIV-1 RNA < 50 copies/mL at Week 48.
- To evaluate the safety and tolerability of the 2 treatment regimens through 48 weeks of treatment.

Outcomes/endpoints

The primary efficacy endpoint is the percentage of subjects who achieved HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA snapshot analysis algorithm. Secondary efficacy endpoints included the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 48 as defined by the snapshot analysis algorithm, the change from baseline in log10 HIV-1 RNA and in CD4+ cell count at Weeks 24 and 48.

The pharmacokinetics (PK) of TAF, tenofovir (TFV), DRV, COBI, and FTC was assessed for all subjects who participated in an intensive PK substudy, which included a subset of subjects who were randomized in the double-blind phase, received at least 1 dose of study drug, and for whom steady-state PK parameters of any of the 5 analytes were evaluable. Additionally, at substudy sites that could perform peripheral blood mononuclear cell (PBMC) processing, the PK of tenofovir-diphosphate (TFV-DP) was assessed. Pharmacokinetic parameters estimated in the substudy included C_{max}, T_{max}, C_{tau}, AUC_{tau}, and t½. For all subjects, a single trough (pre-dose) PK blood sample was to be collected 20-24 hours following an observed (in-clinic) dose of DRV/COBI/FTC/GS-7340 STR or DRV+COBI+FTC/TDF at Weeks 8, 24, and 48. In addition, a single PK blood sample was collected at Weeks 2, 4, 12, 16, 32, and 40. Concentrations of study drugs were determined.

Safety endpoints were Adverse events (AEs) and clinical laboratory tests, including bone mineral density (BMD) using dual energy x-ray absorptiometry (DXA), bone biomarkers (C-type collagen sequence [CTx] and procollagen type 1 N-terminal propeptide [P1NP]), serum creatinine, eGFR by 3 formulae (eGFRCG, Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] creatinine [eGFRCKD-EPI, creatinine] and cystatin C [eGFRCKD-EPI, cysC]), and renal biomarkers (urine retinol-binding protein [RBP], beta-2-microglobulin, RBP to creatinine ratio, beta-2-microglobulin to creatinine ratio, urine protein to creatinine ratio [UPCR], and urine albumin to creatinine ratio [UACR]) were performed to evaluate the safety and tolerability of the treatment regimens.

Sample size

A sample size of 100 subjects in the single-tablet regimen (D/C/F/TAF) group was chosen to estimate the response rate of HIV-1 RNA < 50 copies/mL at Week 24 for the regimen to allow for the planning of Phase 3 studies. A total sample size of 150 subjects had 56% power to evaluate non-inferiority with respect to the response rate of HIV-1 RNA < 50 copies/mL at Week 24 if a response rate of 88% for both groups and a non-inferiority margin of 0.12 were assumed.

The total sample size of 150 subjects provided 43% power to observe a smaller decrease of 1% with a standard deviation (SD) of 3.2% in hip BMD in the D/C/F/TAF group relative to the DRV+COBI+TVD group.

Randomisation

Randomization was stratified by HIV 1 RNA level (≤ 100,000 or > 100,000 copies/mL) at screening and race (black or non-black) based on data submitted in the IVRS/IWRS by the Investigator.

Blinding

The IVRS/IWRS assigned blinded study drug bottle numbers at each study visit. Study drugs were dispensed to the subject in a blinded fashion. All baseline tests and procedures were completed prior to the administration of the first dose of study drug. Initiation of treatment with the study drugs took place within 24 hours after the baseline visit.

In the event of a medical emergency where breaking of the blind was being considered by the treating physician, the Investigator could request unblinding by contacting the Gilead Medical Monitor. The treatment assignment was not unblinded if unblinding would not have affected the way the subject would be treated. If the Gilead Medical Monitor granted the unblinding, then any broken blinding code was clearly justified and explained by a comment in the source documentation and on the electronic case report form, along with the date on which the code was broken and the identity of the person authorizing the unblinding.

Gilead Sciences Drug Safety Public Health (DSPH) could independently unblind cases for expedited reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs). In addition to the above stated prespecified situations requiring unblinding, an unplanned, inadvertent unblinding of all study sites occurred on 13 June 2013, after the Week 24 interim analyses and before the planned Week 48 analyses and the Unblinding Visit.

Statistical methods

The primary efficacy endpoint is the percentage of subjects who achieved HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA snapshot analysis algorithm. Virologic outcome was categorized as virologic success, virologic failure, or no virologic data in the Week 24 analysis window. The number and percentage of subjects having virologic success, virologic failure, and the reasons for no virologic data at Week 24 were summarized.

The analysis purpose of the primary efficacy endpoint was to assess the non-inferiority of the treatment with D/C/F/TAF relative to the treatment with DRV+COBI+TVD. Non-inferiority was assessed using a conventional 95% CI approach, with a non-inferiority margin of 12%. Non-inferiority was concluded if the lower bound of the 2-sided 95% CI of the difference (D/C/F/TAF - DRV+COBI+TVD) in the response rate was > -12%. The primary analysis used the FAS and a secondary analysis used the PP analysis set.

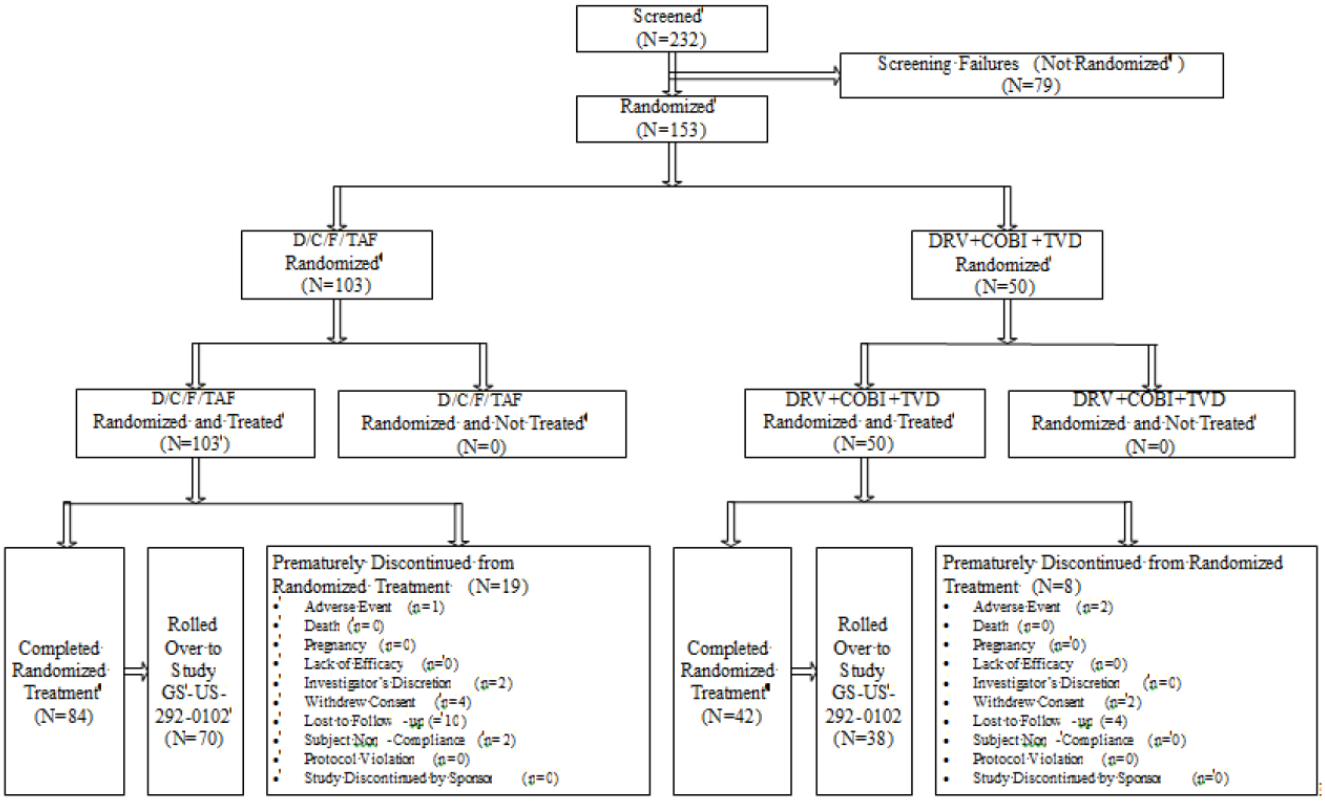
The baseline HIV-1 RNA stratum (≤ 100,000 or >100,000 copies/mL) - and race stratum (black or nonblack) - weighted difference in the response rate (P1 – P2) and its 95% CI was calculated based on stratum-adjusted Mantel-Haenszel proportion.

If non-inferiority of D/C/F/TAF versus DRV+COBI+TVD was established, the same 95% CI used in evaluating non-inferiority was to be used to evaluate superiority. If the lower bound of the 95% CI was greater than 0, then superiority of D/C/F/TAF over DRV+COBI+TVD would be established. The baseline HIV-1 RNA and race stratum stratified 2-sided CMH test would also be used to assess superiority as a secondary assessment. The FAS would be used for the superiority evaluation.

The analyses for all the secondary efficacy endpoints were conducted using the FAS and the endpoint related to the virologic response at Week 48 was also analysed using the PP analysis set. The same statistical method applied for the analysis of the primary efficacy endpoint was used for the analysis of all the secondary endpoints involving percentages. Alpha level of 0.05 was used to construct the 95% CIs.

Results

Participant flow



Subject 0991-3037 was reported with AE (substance abuse) leading to study drug discontinuation and Investigator's discretion as the reason for study drug discontinuation.

Figure 7. GS-US-299-0102: Disposition of Study Subjects

Recruitment

Table 11. GS-US-299-0102: Disposition of Subjects (All Screened Subjects)

Subject Disposition	D/C/F/TAF n (%)	DRV+COBI+TVD n (%)	Total n (%)
Screened			232
Screen Failures Not Randomized			79
Randomized	103	50	153
Treated	103	50	153
Completed Study Treatment	84 (81.6%)	42 (84.0%)	126 (82.4%)
Rolled Over to Study GS-US-292-0102	70 (68.0%)	38 (76.0%)	108 (70.6%)
Prematurely Discontinued Study Treatment	19 (18.4%)	8 (16.0%)	27 (17.6%)
Adverse Event	1 (1.0%)	2 (4.0%)	3 (2.0%)
Death	0	0	0
Lost to Follow-up	10 (9.7%)	4 (8.0%)	14 (9.2%)
Investigator's Discretion	2 (1.9%)	0	2 (1.3%)
Lack of Efficacy	0	0	0
Subject Non-compliance	2 (1.9%)	0	2 (1.3%)
Pregnancy	0	0	0
Protocol Violation	0	0	0
Study Discontinued by Sponsor	0	0	0
Withdrew Consent	4 (3.9%)	2 (4.0%)	6 (3.9%)
Completed Study	83 (80.6%)	42 (84.0%)	125 (81.7%)
Rolled Over to Study GS-US-292-0102	70 (68.0%)	38 (76.0%)	108 (70.6%)
Prematurely Discontinued Study[a]	20 (19.4%)	8 (16.0%)	28 (18.3%)
Adverse Event	0	1 (2.0%)	1 (0.7%)
Death	0	0	0
Lost to Follow-up	12 (11.7%)	4 (8.0%)	16 (10.5%)
Investigator's Discretion	2 (1.9%)	1 (2.0%)	3 (2.0%)
Lack of Efficacy	0	0	0
Subject Non-compliance	2 (1.9%)	0	2 (1.3%)
Pregnancy	0	0	0
Protocol Violation	0	0	0
Study Discontinued by Sponsor	0	0	0
Withdrew Consent	4 (3.9%)	2 (4.0%)	6 (3.9%)

The denominator for percentages is based on the number of subjects in the safety analysis set.

a Subjects prematurely discontinuing study drug could still be in the study (ie, not prematurely discontinued from the study).

Conduct of the study

The original study protocol (dated 27 February 2012) was amended once (dated 06 June 2012) and 6 administrative letters (dated between 29 February 2012 and 02 December 2013) were issued; all except the first 2 administrative letters were issued after subject screening was initiated.

In addition, an inadvertent study unblinding occurred on 13 June 2013, after the study had reached the Week 24 primary efficacy endpoint and analyses had already been conducted but before the planned Week 48 analyses and the Unblinding Visit. The unblinding event and subsequent actions are described in an accidental study site unblinding letter to investigators on 17 June 2013. Finally, the study was terminated following the Unblinding Visit (or 30-day Follow-up Visit, if applicable). Instead of participation in the current study's open-label rollover extension phase, subjects were given the option to participate in the open-label rollover extension phase of Study GS-US-292-0102 to receive the FDC tablet E/C/F/TAF. This change in study procedures was described in a study termination letter and accompanying documentation to investigators on 10 October 2013.

Important changes to the study design implemented in Amendment 1 were:

- Specific and additional information pertaining to the disallowed/discouraged medications was provided.

- Protocol and DXA visit windows at Weeks 24 and 48 were expanded.
- Adverse event/reaction reporting requirements were updated in accordance with the European Union CT3 regulation.

A total of 52 important protocol deviations occurred in 35 subjects during the study. Of those 35 subjects with important protocol deviations reported, 21 subjects were in the D/C/F/TAF group and 14 subjects were in the DRV+COBI+TVD group.

The most common important protocol deviations were associated with incorrect dispensing or dosing of study drug. None of these important deviations affected the overall interpretation of the study data.

Baseline data

Demographic and general baseline characteristics were similar between the 2 treatment groups (Table 12). The majority of subjects were male (92.8%), and the mean age was 35 years (range, 18 to 68 years). The most common races were white (60.1%) or black (34.6%) and the most common ethnicity was not Hispanic/Latino (79.1%). The mean (SD) value for BMI at baseline was 26.2 (4.81) kg/m2.

Table 12. GU-US-299-102 – Demographic and baseline characteristics (safety analysis set)

Characteristic	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)	D/C/F/TAF vs DRV+COBI+TVD (p-value)
Age (years)				
N	103	50	153	0.23
Mean (SD)	35 (11.3)	37 (10.9)	35 (11.2)	
Median	31	36	33	
Q1, Q3	25, 42	28, 44	26, 43	
Min, Max	20, 68	18, 57	18, 68	
Sex (n, %)				
Male	95 (92.2%)	47 (94.0%)	142 (92.8%)	0.69
Female	8 (7.8%)	3 (6.0%)	11 (7.2%)	
Race (n, %)				
White	62 (60.2%)	30 (60.0%)	92 (60.1%)	0.99
Black or African American	36 (35.0%)	17 (34.0%)	53 (34.6%)	
Asian	2 (1.9%)	1 (2.0%)	3 (2.0%)	
Native Hawaiian or Other Pacific Islander	1 (1.0%)	1 (2.0%)	2 (1.3%)	
Other	2 (1.9%)	1 (2.0%)	3 (2.0%)	
Ethnicity (n, %)				
Hispanic or Latino	23 (22.3%)	9 (18.0%)	32 (20.9%)	0.54
Not Hispanic or Latino	80 (77.7%)	41 (82.0%)	121 (79.1%)	
Baseline Body Mass index (kg/m^2)				
N	103	50	153	0.94
Mean (SD)	26.3 (4.97)	26.1 (4.53)	26.2 (4.81)	
Median	25.1	24.7	24.9	
Q1, Q3	22.4, 29.6	22.7, 29.0	22.7, 29.2	
Min, Max	18.2, 42.7	17.6, 37.9	17.6, 42.7	

Baseline disease characteristics were similar between the 2 treatment groups (Table 13). The mean (SD) baseline HIV-1 RNA value was 4.68 (0.515) log10 copies/mL, CD4 count was 417 (205.7) cells/µL, and CD4% was 23.7 (8.81). Overall, 80.4% of the subjects had baseline HIV 1 RNA ≤ 100,000 copies/mL, 14.4% had > 100,000 to ≤ 400,000 copies/mL, and 5.2% had > 400,000 copies/mL. The most common HIV risk factor category was homosexual sex (84.3% of subjects). The majority of subjects (89.5%) had asymptomatic HIV-1 infection; 7.2% of subjects had symptomatic HIV-1 infection, and 3.3% of subjects were diagnosed with AIDS.

Values for eGFR (as measured by CG) were similar between the 2 treatment groups. Most subjects (90.2%) had no or trace proteinuria (Grade 0 by dipstick) on urinalysis.

Table 13. GS-US-299-0102: Baseline Disease Characteristics (Safety Analysis Set)

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)	D/C/F/TAF vs DRV+COBI+TVD (p-value)
HIV-1 RNA (log10 copies/mL)				
N	103	50	153	0.39
Mean (SD)	4.70 (0.516)	4.65 (0.514)	4.68 (0.515)	
Median	4.67	4.58	4.66	
Q1, Q3	4.43, 4.93	4.28, 4.91	4.37, 4.91	
Min, Max	3.27, 6.12	3.59, 6.29	3.27, 6.29	
HIV-1 RNA Category (copies/mL)				
<= 100,000	80 (77.7%)	43 (86.0%)	123 (80.4%)	0.28
> 100,000 to <= 400,000	17 (16.5%)	5 (10.0%)	22 (14.4%)	
> 400,000	6 (5.8%)	2 (4.0%)	8 (5.2%)	
CD4 Cell Count (/uL)				
N	103	50	153	0.14
Mean (SD)	395 (169.3)	464 (261.6)	417 (205.7)	
Median	368	433	384	
Q1, Q3	270, 515	320, 606	283, 532	
Min, Max	7, 909	49, 1463	7, 1463	
CD4 Cell Count Category (/uL)				
< 50	1 (1.0%)	1 (2.0%)	2 (1.3%)	0.48
>=50 and <200	10 (9.7%)	9 (18.0%)	19 (12.4%)	
>=200 and <350	37 (35.9%)	8 (16.0%)	45 (29.4%)	
>=350 and <500	27 (26.2%)	12 (24.0%)	39 (25.5%)	
>= 500	28 (27.2%)	20 (40.0%)	48 (31.4%)	
CD4 Percentage (%)				
N	103	50	153	0.16
Mean (SD)	22.9 (8.14)	25.3 (9.95)	23.7 (8.81)	
Median	22.1	25.3	23.6	
Q1, Q3	17.4, 29.1	18.5, 31.1	17.6, 29.6	
Min, Max	1.0, 42.8	6.9, 49.7	1.0, 49.7	
HIV Risk Factors				
Heterosexual Sex	19 (18.4%)	8 (16.0%)	27 (17.6%)	
Homosexual Sex	86 (83.5%)	43 (86.0%)	129 (84.3%)	
IV Drug Use	0	2 (4.0%)	2 (1.3%)	
Unknown	3 (2.9%)	0	3 (2.0%)	
Other	2 (1.9%)	2 (4.0%)	4 (2.6%)	
HIV Disease Status				
Asymptomatic	93 (90.3%)	44 (88.0%)	137 (89.5%)	0.39
Symptomatic HIV Infections	8 (7.8%)	3 (6.0%)	11 (7.2%)	
AIDS	2 (1.9%)	3 (6.0%)	5 (3.3%)	
$eGFR_{CG}$ (mL/min)				
N	103	50	153	0.17
Mean (SD)	119.6 (26.89)	115.7 (31.41)	118.3 (28.40)	
Median	116.0	109.6	114.6	
Q1, Q3	97.0, 137.6	92.5, 131.4	96.5, 132.3	
Min, Max	77.3, 223.0	73.7, 259.2	73.7, 259.2	

	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)	Total (N = 153)	D/C/F/TAF vs DRV+COBI+TVD (p-value)
Proteinuria by Urinalysis (dipstick)				
Negative	69 (67.0%)	39 (78.0%)	108 (70.6%)	0.23
Trace	22 (21.4%)	8 (16.0%)	30 (19.6%)	
+1	9 (8.7%)	2 (4.0%)	11 (7.2%)	
+2	2 (1.9%)	0	2 (1.3%)	
+3	1 (1.0%)	1 (2.0%)	2 (1.3%)	

The denominator for percentages is based on the number of subjects in the safety analysis set.

For categorical data, p-value was from the CMH test (general association statistic was used for nominal data, row mean scores differ statistics was used for ordinal data).

For continuous data, p-value was from the 2-sided Wilcoxon rank sum test.

A subject may fit more than 1 HIV risk factor category; therefore, percentages may add to more than 100.

Numbers analysed

Overall, 153 subjects (D/C/F/TAF: 103 subjects; DRV+COBI+TVD: 50 subjects) who were randomized and received at least 1 dose of treatment were included in the safety analysis set and FAS. A total of 21 subjects (D/C/F/TAF: 17 subjects; DRV+COBI+TVD: 4 subjects) were excluded from the Week 48 PP analysis set for reasons other than lack of efficacy and 3 subjects were excluded from the Week 48 PP analysis set due to poor adherence (Table 14).

A total of 133 subjects (D/C/F/TAF: 85 subjects; DRV+COBI+TVD: 48 subjects) were included in the hip DXA analysis set and 134 subjects (D/C/F/TAF: 86 subjects; DRV+COBI+TVD: 48 subjects) were included in the spine DXA analysis set.

Overall, 32 subjects (D/C/F/TAF: 21 subjects; DRV+COBI+TVD: 11 subjects) were included in the analysis set for the intensive PK substudy.

Table 14. GS-US-299-0102: Analysis Sets

	D/C/F/TAF	DRV+COBI+TVD	Total
Subjects Randomized	103	50	153
Subjects in Safety Analysis Set	103 (100.0%)	50 (100.0%)	153 (100.0%)
Subjects in Full Analysis Set	103 (100.0%)	50 (100.0%)	153 (100.0%)
Subjects in Week 24 Per Protocol (PP) Analysis Set	91 (88.3%)	47 (94.0%)	138 (90.2%)
Reasons for Exclusion from Week 24 PP Analysis Set			
Discontinued Study Drug for Reason Other than Lack of Efficacy with No Week 24 HIV-1 RNA Data	12	2	14
Adherence Rate for Active Study Drug up to Week 24 Visit Below the 2.5th Percentile	2	1	3
Subjects in Week 48 Per Protocol (PP) Analysis Set	85 (82.5%)	46 (92.0%)	131 (85.6%)
Reasons for Exclusion from Week 48 PP Analysis Set			
Discontinued Study Drug for Reason Other than Lack of Efficacy with No Week 48 HIV-1 RNA Data	17	4	21
Adherence Rate for Active Study Drug up to Week 48 Visit Below the 2.5th Percentile	3	0	3
Subjects in PK Analysis Set	102 (99.0%)	48 (96.0%)	150 (98.0%)
Subjects in PK Substudy Analysis Set	21 (20.4%)	11 (22.0%)	32 (20.9%)
Subjects in PBMC PK Substudy Analysis Set	14 (13.6%)	8 (16.0%)	22 (14.4%)
Subjects in Spine DXA Analysis Set	86 (83.5%)	48 (96.0%)	134 (87.6%)
Subjects in Hip DXA Analysis Set	85 (82.5%)	48 (96.0%)	133 (86.9%)

Outcomes and estimation

The primary efficacy endpoint was the percentage of subjects with HIV-1 RNA < 50 copies/mL at Week 24 using the FDA-defined snapshot algorithm.

Virologic outcomes at Week 24 were similar between the 2 treatment groups for the primary endpoint analysis for the FAS (Table 15). Virologic success rates were as follows: D/C/F/TAF 74.8%, DRV+COBI+TVD 74.0%; difference in percentages: 3.3%, 95% CI -11.4% to 18.1%. Because the lower bound of the 2-sided 95% CI of the difference in the response rate (D/C/F/TAF – DRV+COBI+TVD) was greater than the pre-specified –12% non-inferiority margin, D/C/F/TAF was determined to be non-inferior to DRV+COBI+TVD.

Percentages of subjects with virologic failure at Week 24 (and reasons for failure) were similar for the 2 treatment groups (D/C/F/TAF 20.4%, DRV+COBI+TVD 24.0%).

Virologic success rates at Week 24 were similar between treatment groups using the Week 24 PP analysis set, as follows: D/C/F/TAF 84.6%, 77 of 91 subjects; DRV+COBI+TVD 78.7%, 37 of 47 subjects; difference in percentages: 8.3%, 95% CI: -5.3% to 22.0%.

Table 15. GS-US-299-0102: Virologic Outcome at Week 24 using Snapshot Analysis Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	D/C/F/TAF (N=103)	DRV+COBI +TVD (N=50)	D/C/F/TAF vs. DRV+COBI+TVD	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 24[c]				
HIV-1 RNA < 50 copies/mL	77 (74.8%)	37 (74.0%)	0.64	3.3% (-11.4% to 18.1%)
Virologic Failure at Week 24[c]	21 (20.4%)	12 (24.0%)		
HIV-1 RNA ≥ 50 copies/mL	14 (13.6%)	11 (22.0%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	7 (6.8%)	1 (2.0%)		
Added New ARV	0	0		
No Virologic Data in Week 24 Window[c]	5 (4.9%)	1 (2.0%)		
Discontinued Study Drug Due to AE/Death	1 (1.0%)	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	4 (3.9%)	1 (2.0%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 24 window was between Day 140 and 195 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

In contrast, the virologic success rates through Week 48 were lower for D/C/F/TAF vs. DRV+COBI+TVD (Table 16), which reflected numbers that discontinued study drug and had a last available HIV-1 RNA ≥ 50 copies/mL (D/C/F/TAF: 8.7%, 9 subjects; DRV+COBI+TVD: 4.0%, 2 subjects). Percentages with documented virologic failure at Week 48 were more comparable (6.8% vs. 8%).

Table 16. GS-US-299-0102: Virologic Outcome at Week 48 using Snapshot Analysis Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

	D/C/F/TAF (N=103)	DRV+COBI +TVD (N=50)	D/C/F/TAF vs. DRV+COBI+TVD	
			p-value[a]	Difference in Percentages (95% CI)[b]
Virologic Success at Week 48[c]				
HIV-1 RNA < 50 copies/mL	79 (76.7%)	42 (84.0%)	0.35	-6.2% (-19.9% to 7.4%)
Virologic Failure at Week 48[c]	16 (15.5%)	6 (12.0%)		
HIV-1 RNA ≥ 50 copies/mL	7 (6.8%)	4 (8.0%)		
Discontinued Study Drug Due to Lack of Efficacy	0	0		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥ 50 copies/mL[d]	9 (8.7%)	2 (4.0%)		
Added New ARV	0	0		
No Virologic Data in Week 48 Window[c]	8 (7.8%)	2 (4.0%)		
Discontinued Study Drug Due to AE/Death	1 (1.0%)	1 (2.0%)		
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA < 50 copies/mL	7 (6.8%)	1 (2.0%)		

a P-value for the superiority test comparing the percentages of virologic success was from the CMH test stratified by baseline HIV-1 RNA and race strata.
b Difference in percentages of virologic success and its 95% CI were calculated based on baseline HIV-1 RNA stratum-adjusted MH proportion.
c Week 48 window was between Day 308 and 337 (inclusive).
d Discontinuation due to other reasons included subjects who discontinued study drug due to investigator's discretion, withdrew consent, lost to follow-up, subject noncompliance, protocol violation, pregnancy, and study discontinued by sponsor.

In the Week 48 PP analysis set the virologic success rates were D/C/F/TAF 92.9% (79/85) vs. DRV+COBI+TVD 91.3% (42/46); difference 2.4%, 95% CI: -8.8% to 13.7%. Other approaches to analysis of the FAS gave generally similar results to the primary analysis and also applied to the PP sets.

A pure virologic response (HIV-1 RNA < 50 copies/mL on 2 consecutive visits) through Week 48 was observed for D/C/F/TAF 81.6% (84/103) vs. DRV+COBI+TVD 86.0% (43/50). Similar percentages in each treatment group did not achieve confirmed suppression (15% vs. 12%). At Week 48, the KM estimates for the percentages with pure virologic failure (PVF) were 18% in the D/C/F/TAF group and 14% in the DRV+COBI+TVD group (overall p-value = 0.89).

CD4 cell counts increased for each treatment group with mean increases through Week 24 (observed data) using the FAS of D/C/F/TAF 186 (137.9) cells/μL vs. DRV+COBI+TVD 139 (185.8) cells/μL.

CD4 cell counts increased for each treatment group with mean increases through Week 48 (observed data) using the FAS of D/C/F/TAF 231 (141.9) cells/μL vs. DRV+COBI+TVD 212 (151.5) cells/μL. The CD4% also increased in each treatment group with mean increases from baseline at Week 48 of D/C/F/TAF 8.2% vs. DRV+COBI+TVD 9.3%.

Ancillary analyses

At Week 24, the rate of virologic success by FDA-defined snapshot algorithm for subgroups according to age, sex, race, baseline HIV-1 RNA level, baseline CD4 cell count or study drug adherence rate was similar for the D/C/F/TAF and DRV+COBI+TVD. Data for Week 48 were consistent with Week 24 (Figure 8).

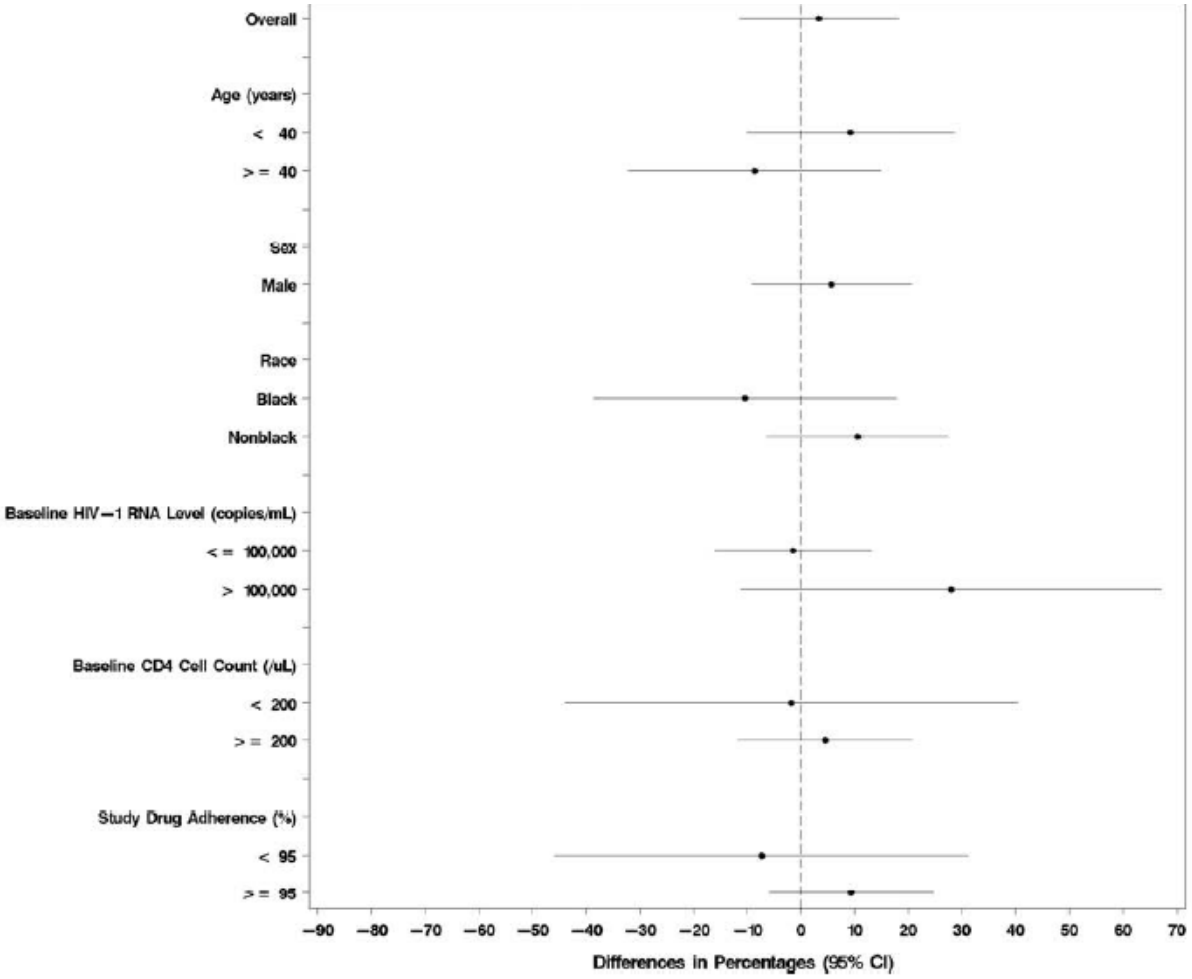


Figure 8. GS-US-299-0102: Forest Plot of Treatment Difference in Virologic Success by Subgroup at Week 24 using Snapshot Analysis Algorithm and HIV-1 RNA < 50 copies/mL (FAS)

Summary of main study

Summary of efficacy for Study GS-US-299-0102

Title: A Phase 2, Randomized, Double-Blinded Study of the Safety and Efficacy of Darunavir/Cobicistat/Emtricitabine/GS-7340 Single Tablet Regimen Versus Cobicistat-boosted Darunavir plus Emtricitabine/Tenofovir Disoproxil Fumarate Fixed Dose Combination in HIV-1 Infected, Antiretroviral Treatment-Naïve Adults				
Study identifier	GS-US-299-0102			
Design	Randomized, double-blinded, multicenter, active-controlled study			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		48 weeks not applicable After Week 48, subjects were to continue to take blinded study drug until treatment assignments were unblinded, at which point subjects were given the option to participate in the open-label rollover extension phase of Study GS-US-292-0102 and receive the FDC tablet of E/C/F/TAF (Genvoya)	
Hypothesis	Non-inferiority / Exploratory			
Treatments groups	D/C/F/TAF FDC		D/C/F/TAF (800/150/200/10 mg), 48 weeks, 103 subjects	
	DRV+COBI+TVD		DRV 800 mg (2 x 400 mg) + COBI 150 mg + TVD (FTC 200 mg/TDF 300 mg, 48 weeks, 50 subjects	
Endpoints and definitions	Primary endpoint	Virologic success, week 24	Percentage of subjects who achieved HIV-1 RNA <50 copies/mL at Week 24 as defined by the FDA snapshot analysis algorithm	
	Secondary endpoint	Virologic success, week 48	Percentage of subjects who achieved HIV-1 RNA < 50 copies/mL at Week 48 as defined by the FDA snapshot analysis algorithm	
	Secondary endpoint	HIV-1 RNA, CD4+ count	The change from baseline in $\log_{10}$ HIV-1 RNA and in CD4+ cell count at Weeks 24 and 48	
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	FAS Week 24			
Descriptive statistics and estimate variability	Treatment group		D/C/F/TAF	DRV+COBI+TVD
	Number of subject		103	50
	HIV-1 RNA <50 copies/mL, week 24 (n/N (%))		77/103 (74.8%)	37/50 (74.0%)
Effect estimate per comparison	Primary endpoint		Comparison groups	D/C/F/TAF vs DRV+COBI+TVD
			Virologic Success	3.3%
			95%CI	-11.4% to 18.1%
			P-value (for superiority test)	0.64
Analysis description	**Secondary Analyses**			
Analysis population and time point description	FAS Week 48			
Descriptive statistics and estimate variability	Treatment group		D/C/F/TAF	DRV+COBI+TVD
	Number of subject		103	50
	HIV-1 RNA <50 copies/mL, week 48 (n/N (%))		79/103 (76.7%)	42/50 (84.0%)
Effect estimate per comparison	Secondary endpoint		Comparison groups	D/C/F/TAF vs DRV+COBI+TVD

		Virologic Success	-6.2%
		95%CI	-19.9% to 7.4%
		P-value (for superiority test)	0.35
Descriptive statistics and estimate variability	Treatment group	D/C/F/TAF	DRV+COBI+TVD
	Number of subject	103	50
	Change in plasma HIV-1 RNA Log_{10} copies/mL, week 48 (mean (SD))	-3.27 (0.668)	-3.26 (0.521)
Descriptive statistics and estimate variability	Treatment group	D/C/F/TAF	DRV+COBI+TVD
	Number of subject	103	50
	Change in CD4 cell count cells/µL, week 48 (mean (SD))	231 (141.9)	212 (151.5)

Clinical studies in special populations

No specific clinical study was performed with the D/C/F/TAF FDC in special populations, all available data derives from data generated with the separate components.

Subjects with mild to moderate renal impairment

The use of D/C/F/TAF in subjects with renal impairment is similar to what is recommended for Genvoya, which is *No dose adjustment of […] is required in patients with estimated glomerular filtration rate according to the Cockcroft-Gault formula (eGFRCG) ≥ 30 mL/min,* and mainly relies on data from Studies GS-US-236-0118 and GS-US-292-0112. Data available from these studies indicate that the overall efficacy profile in subjects with mild to moderate renal impairment was similar to that observed in the adult population with normal renal function. Although the additional POPPK data in study GS-US-292-0112 demonstrated a difference in FTC AUCs for patients with $eGFR_{CG}$, >50 vs. < 50 mL/min, the available safety data supported the use of E/C/F/TAF down to CrCL 30 mL/min.

Subjects with hepatic impairment

The effect of hepatic impairment on the PK of DRV, COBI, FTC and TAF when coadministered as the D/C/F/TAF FDC has not been evaluated. The information provided in the current application is based on data derived during the development programs of the individual components. Based on the PK, efficacy and safety data for the individual components, no dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, D/C/F/TAF should be used with caution in these patients due to the increase in unbound DRV plasma concentrations. The D/C/F/TAF FDC or its components have not been studied in patients with severe hepatic impairment (Child-Pugh Class C), therefore, the D/C/F/TAF FDC must not be used in patients with severe hepatic impairment.

Adolescents

The proposed use of the D/C/F/TAF FDC in adolescents is based on the results of studies TMC114-C230 and GS-US-292-0106, in which the D/C/F/TAF components studied showed similar exposures in adolescents and adults, the boosting effect of COBI was shown to be the same in adolescents and adults, and regimens were shown to be safe and efficacious in adolescents. As such, doses of DRV 800 mg, COBI 150 mg, FTC 200 mg and TAF 10 mg are each approved for use in adolescents, in different combinations. Therefore, the D/C/F/TAF FDC, combining these components at their respective doses approved for use in adolescents, is considered to be appropriate for use in adolescents, aged ≥12 years and weighing at least 40 kg.

Elderly

Use in Elderly patients is listed as missing information in the RMP as there is hardly any data available in patients >65 years of age, and no data at all in patients >68 years of age.

HIV and HBV/HCV co-infection

No specific clinical study was performed with the D/C/F/TAF FDC in subjects co-infected with HIV and HBV and/or HCV and HIV/HBV-co-infected subjects were excluded from the Phase 2 study with the D/C/F/TAF FDC (GS-US-299-0102). The applicant submitted a Phase 3b open-label F/TAF study (GS-US-292-1249) investigating the efficacy and safety of Genvoya in HIV-1/HBV co-infected adult subjects. Virological outcome data from Cohort 2 (enrolling HIV/HBV co-infected adults who were HIV suppressed (with or without suppression of HBV DNA)) for both HIV and HBV, seem to be in line with previous results in mono-infected patients. As it is a non-comparative study, no firm conclusions can - be drawn. The SmPC states in section 4.4 that Tenofovir alafenamide is active against hepatitis B virus (HBV).

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

Based on PK bridging, clinical evidence to support the efficacy and resistance profile of D/C/F/TAF is provided by ten Phase 2 and 3 clinical studies with DRV/COBI, F/TAF (either as E/C/F/TAF FDC or as F/TAF FDC+3rd agent) or D/C/F/TAF and are presented in this summary. For DRV/COBI, the efficacy and resistance profile is bridged to DRV/rtv, based on the similar PK of DRV using rtv or COBI as pharmacoenhancer. For F/TAF, pooled data of the Phase 3 pivotal studies with E/C/F/TAF in ART-naïve subjects are discussed. Key efficacy results across studies are provided in Table 17.

Table 17. Main Efficacy Endpoints - Comparison across Studies

	GS-US-216-0130	Pooled GS-US-292-0104 and GS-US-292-0111		GS-US-311-1089		GS-US-292-0102		GS-US-299-0102		GS-US-292-0106
	DRV+ COBI N=313	E/C/F/ TAF N=866	E/C/F/ TDF N=867	F/TAF Switch N=333	F/TDF-based Regimen N=330	E/C/F/ TAF N=112	E/C/F/ TDF N=58	D/C/F/ TAF N=103	DRV+ COBI+ F/TDF N=50	E/C/F/TAF N=50
Virologic Response (Snapshot)										
Virologic Success at Week 48 (FAS)										
HIV-1 RNA <50 copies/mL	247 (80.8%)	800 (92.4%)	784 (90.4%)	314 (94.3%)	307 (93.0%)	99 (88.4%)	51 (87.9%)	79 (76.7%)	42 (84.0%)	46 (92.0%)
adjusted % difference (95% CI)	-	2·0%, (-0·7 to 4·7)		1.3% (-2.5 to 5.1)		-1.0% (-12.1 to 10.0)		-6.2% (-19.9 to 7.4)		-
Virologic Failure at Week 48 (FAS)	33 (10.5%)	31 (3.6%)	35 (4.0%)	1 (0.3%)	5 (1.5%)	7 (6.3%)	6 (10.3%)	16 (15.5%)	6 (12.0%)	3 (6.0%)
HIV-1 RNA ≥50 copies/mL	14 (4.5%)	20 (2.3%)	23 (2.7%)	0	5 (1.5%)	6 (5.4%)	4 (6.9%)	7 (6.8%)	4 (8.0%)	2 (4.0%)
Discontinued Study Drug Due to Lack of Efficacy	0	2 (0.2%)	3 (0.3%)	0	0	0	1 (1.7%)	0	0	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 copies/mL	19 (6.1%)	8 (0.9%)	8 (0.9%)	1 (0.3%)	0	1 (0.9%)	1 (1.7%)	9 (8.7%)	2 (4.0%)	1 (2.0%)
No Virologic Data in Week-48 Window	27 (8.6%)	35 (4.0%)	48 (5.5%)	18 (5.4%)	18 (5.5%)	6 (5.4%)	1 (1.7%)	8 (7.8%)	2 (4.0%)	1 (2.0%)
Discontinued Study Drug Due to AE/Death	15 (4.8%)	8 (0.9%)	14 (1.6%)	7 (2.1%)	3 (0.9%)	4 (3.6%)	0	1 (1.0%)	1 (2.0%)	0
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA <50 copies/mL	10 (3.2%)	21 (2.4%)	31 (3.6%)	10 (3.0%)	15 (4.5%)	2 (1.8%)	1 (1.7%)	7 (6.8%)	1 (2.0%)	1 (2.0%)
Virologic Success at Week 48 (PP)						101	54	85	46	
HIV-1 RNA <50 copies/mL	-	-	-	-	-	96 (95.0%)	49 (90.7%)	79 (92.9%)	42 (91.3%)	-
adjusted % difference (95% CI)	-	-		-		2.8% (-7.1% to 12.7%)		2.4% (-8.8 to 13.7)		-
Virologic Failure at Week 48 (PP)	-	-	-	-	-	5 (5.0%)	5 (9.3%)	6 (7.1%)	4 (8.7%)	-

Supportive studies

Efficacy of DRV/COBI

Information on the efficacy of DRV/COBI 800/150 mg once daily in combination with other ARVs in HIV-1 infected adults is provided by the results of **Study GS-US-216-0130**. This was a Phase 3b, open-label, single-arm, multicenter study to evaluate the safety and efficacy of a regimen of DRV 800 mg and COBI 150 mg once daily, together with 2 fully active NRTIs in HIV-1 infected (plasma HIV-1 RNA levels ≥1,000 copies/mL at screening), ART-naïve (no prior use of ARV drugs for any length of time) or ART-experienced (stable ARV treatment for at least 12 weeks prior to screening) adult subjects with no DRV RAMs.

Overall, virologic success at Week 24 and at Week 48 (HIV-1 RNA <50 copies/mL, FDA defined snapshot analysis algorithm) was achieved in 82.4% (258 of 313 subjects) and 80.8% (253 of 313 subjects), respectively, and virologic failure was reported in 11.5% (36 of 313 subjects) and 10.5% (33 of 313 subjects), respectively.

In the ART-naïve cohort, virologic success at Week 24 (HIV-1 RNA <50 copies/mL, FDA-defined snapshot analysis algorithm) was achieved in 83.7% (247 of 295 subjects), and virologic failure was reported in 9.8% (29 of 295 subjects). In the ART-experienced cohort, virologic success at Week 24 was achieved in 61.1% (11 of 18 subjects), and virologic failure was reported for 38.9% (7 of 18 subjects).

In the ART-naïve cohort, virologic success at Week 48 (HIV-1 RNA <50 copies/mL, FDA-defined snapshot analysis algorithm) was achieved in 82.7% (244 of 295 subjects), virologic failure was reported in 8.1% (24 of 295 subjects). In the ART-experienced cohort, virologic success at Week 48 was achieved in 50.0% (9 of 18 subjects), and virologic failure was reported for 50.0% (9 of 18 subjects).

No subgroup analysis, besides analysis of viral outcomes by baseline viral load, was performed in Study GS-US-216-0130. No differences in virologic success were observed by baseline viral load.

Table 18. Virologic Outcomes at Week 48 for HIV-1 RNA Cut-off at 50 Copies/mL (Snapshot Analysis; FAS; Week-48 dataset) - GS-US-216-0130

	ART-naïve (N=295)	ART-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%)

Overall, the response to DRV/cobi can be considered comparable to DRV/rtv, however such cross-study comparisons should always be viewed with caution.

Efficacy of F/TAF

In two Phase 3 studies in ART-naïve subjects (**GS-US-292-0104** and **GS-US-292-0111**), E/C/F/TAF was shown to be non-inferior to E/C/F/TDF (92% vs 90% for pooled data). At Week 48, the difference (95% CI) in virologic response (HIV-1 RNA <50 copies/mL) between E/C/F/TAF and the control group was 2.0% (-0.7 to 4.7) in a model adjusted for baseline factors. The PK/PD analysis of these pooled studies indicated that virologic response was uniformly high across TAF AUCtau quartiles (96.3%, 92.6%, 94.8% and 91.9% in Q1 through Q4) with no trends in exposure response relationship across the wide range of TAF exposures observed.

In virologically suppressed subjects who switched from an F/TDF-containing regimen to a regimen containing the F/TAF FDC plus a third agent (Study GS-US-311-1089), F/TAF was non-inferior to F/TDF. At Week 48, the difference (95% CI) in virologic response (HIV-1 RNA <50 copies/mL) between F/TAF and the control group was 1.3% (-2.5 to 5.1). Virologic response rates were similar across the range of third agents used and did not suggest any clinically relevant differences. The results of the PK/PD analysis for Study GS-US-311-1089 are in line with observations in the E/C/F/TAF studies and show that virologic response rates were similar across the AUCtau quartiles (93.2%, 95.9%, 97.3% and 95.9% in Q1 through Q4), with no trends in exposure-response relationship across the wide range of TAF exposures observed. This again indicates an absence of PK/PD relationship for TAF, as was demonstrated in the E/C/F/TAF Phase 3 studies.

The overall conclusion was that E/C/F/TAF has been shown to achieve high virologic suppression rates in ART-naïve patients and supports maintenance of suppression after switching from successful regimens.

2.5.3. Discussion on clinical efficacy

The development program for the D/C/F/TAF FDC is primarily based on a pharmacokinetic bridging program. This is acceptable for a dossier submitted in accordance with article 10 (b) of Directive 2001/83/EC. In addition, a single Phase 2 Study (GS-US-299-0102) that investigated efficacy and safety of the to be marketed formulation, was provided.

Design and conduct of clinical studies

The Phase 2 Study GS-US-299-0102 in ART naïve subjects was an exploratory study to estimate the relative efficacy and safety without the objective to demonstrate non-inferiority. According to the applicant, the sample size for study GS-US-299-0102 was initially chosen to estimate the response rate in order to subsequently plan for Phase 3 studies. This resulted in a low power to evaluate non-inferiority, which is unfortunate (but not considered an issue, due to the PK bridging) as it is the only clinical efficacy data provided. Of note, Phase 3 studies are ongoing and primary analyses of both studies, ie, when all subjects have been treated for 48 weeks (or discontinued earlier), were planned for Q2 2017. While these studies will provide additional information regarding the D/C/F/TAF regimen (including adherence information), the Applicant did not consider these studies to be pivotal for this application, given the approved indication for F/TAF, which includes use in combination with DRV/COBI. The CHMP considered this approach acceptable.

Efficacy data and additional analyses

A total of 153 subjects were enrolled in the study, 103 of which were treated with D/C/F/TAF. There were only few females included, and hardly any elderly patients. Elderly patients is considered missing information. Only limited numbers of subjects with baseline viral load >100.000 copies/mL were included (19.6%), with only few

subjects having baseline viral load >400.000 copies/mL (5.2%). The far majority of subjects (97.4 %, 149 of 153) had HIV-1 subtype B.

Based on the primary analysis it was concluded that D/C/F/TAF is non-inferior to DRV+COBI+TVD. However, the analysis of the Week 48 data seems to indicate a lower overall virologic success rate for D/C/F/TAF vs. DRV+COBI+TVD. This was already noted during the MAA procedure for F/TAF (Descovy) where Study GS-US-299-0102 was also part of the application. It was concluded that "this relatively small study was not powered for inferential testing […] and the findings of this study are currently unexplained."

The main reason is that the difference was due to an imbalance in the fraction of subjects that discontinued the study due to reasons other than lack of efficacy (who were excluded from the PP analysis set between the groups), with 20/103 (19.4%) subjects excluded in the D/C/F/TAF arm vs 4/50 (8%) in the DRV+COBI+TVD arm. The applicant claimed that, given the randomized and double-blinded study nature, there are no indications that there was a systematic non-safety drug-related reason for the higher discontinuation rate in the D/C/F/TAF group.

Special populations

No specific clinical study was performed with the D/C/F/TAF FDC in subjects with mild to moderate or severe renal impairment. However, data available for the components of D/C/F/TAF indicate that the overall efficacy profile in subjects with mild to moderate renal impairment was similar to that observed in the adult population with normal renal function. The SmPC states that no dose adjustment is required in patients with eGFRCG ≥ 30 mL/min.

The single agents are each approved for use in adolescents aged ≥12 years and weighing at least 40 kg. It is therefore accepted that the FDC is indicated for use in adolescents aged ≥12 years and weighing at least 40 kg and adults.

No specific clinical study was performed with the D/C/F/TAF FDC in subjects co-infected with HIV and HBV and/or HCV and HIV/HBV-co-infected subjects were excluded from the Phase 2 study with the D/C/F/TAF FDC (GS-US-299-0102). The applicant submitted a Phase 3b open-label F/TAF study (GS-US-292-1249) investigating the efficacy and safety of Genvoya in HIV-1/HBV co-infected adult subjects. Virological outcome data in this study, for both HIV and HBV, seems to be in line with previous results in mono-infected patients.

Integrated virology analyses

Development of resistance-associated mutations seems to occur quite rarely when treated with the combined use of the single agents. Although resistance is rare, the RMP adequately reflect this concern.

2.5.4. Conclusions on the clinical efficacy

There are no major objections based on the efficacy data. The separate components of the D/C/F/TAF fixed dose combination are already approved, also for use with specific combination. Bioequivalence of the FDC to the separate components has been established. A non-inferior efficacy of D/C/F/TAF vs DRV+COBI+TVD has been shown in the phase 2 study, although a higher than expected discontinuation rate was observed in the D/C/F/TAF group. Preliminary results from the ongoing phase 3 studies are reassuring in this respect.

2.6. Clinical safety

The main focus of this section will be on the description of the safety as reported in Study GS-US-299-0102, as this is the only study in the target population with the to be marketed formulation of the medicinal product and the main basis for section 4.8 of the SmPC.

The D/C/F/TAF Phase 1 studies involving 270 healthy subjects (of which 231 subjects received the D/C/F/TAF FDC; Studies TMC114FD2HTX1001, TMC114FD2HTX1002, and GS-US-299-0101) provide further supportive evidence of the safety profile of D/C/F/TAF. In addition, two Phase 3 studies with the D/C/F/TAF FDC in 725 ART-naïve (TMC114FD2HTX3001) and in 1,149 virologically suppressed (TMC114IFD3013) HIV-1 infected subjects are ongoing (primary analyses for both trials read, i.e., when all subjects have been treated for 48 weeks or discontinued earlier).

Patient exposure

Study GS-US-299-0102 was a Phase 2, randomized, double-blind, multicenter, active-controlled study to evaluate the safety and efficacy of the D/C/F/TAF FDC vs COBI-boosted DRV (DRV+COBI) +F/TDF FDC in 153 HIV-1 infected treatment-naïve adult subjects (103 subjects in the D/C/F/TAF FDC group; 50 subjects in the DRV+COBI+F/TDF group). The median duration of study drug exposure was 68.0 weeks.

The relevant clinical studies supporting the DRV/COBI, the F/TAF and hence the D/C/F/TAF efficacy, safety, and resistance profile in total enrolled or randomized 3,674 subjects, of whom:

- 335 adult subjects received at least 1 dose of DRV/COBI,
- 1,797 adult subjects and 50 adolescents received at least 1 dose of E/C/F/TAF.
- 103 adult subjects received at least 1 dose of D/C/F/TAF.

Adverse events

A summary of AEs observed in Study GS-US-299-0102 is provided in Table 19. No subjects died during the study. Similar percentages of subjects in each group had any AE (D/C/F/TAF: 92.2%, 95 subjects; DRV+COBI+TVD: 94.0%, 47 subjects) or any AE considered by the investigator to be related to study drug (D/C/F/TAF 41.7%, 43 subjects; DRV+COBI+TVD 38.0%, 19 subjects). Any Grade 3 or 4 AE was reported for 6.8% of subjects (n = 7) in the D/C/F/TAF group, and 8.0% of subjects (n = 4) in the DRV+COBI+TVD group. Any SAE was reported for 4.9% of subjects (n = 5) in the D/C/F/TAF group and 4.0% of subjects (n = 2) in the DRV+COBI+TVD group.

Any Grade 2, 3, or 4 AE was reported for 55.3% of subjects (n = 57) in the D/C/F/TAF group, and 48.0% of subjects (n = 24) in the DRV+COBI+TVD group. Any Grade 2, 3, or 4 AE considered by the investigator to be related to study drug was reported for 9.7% of subjects (n = 10) in the D/C/F/TAF group and 6.0% of subjects (n = 3) in the DRV+COBI+TVD group.

One subject in each treatment group had a Grade 3 or 4 AE considered by the investigator to be related to study drug. Two subjects (1.9%) in the D/C/F/TAF group and 2 subjects (4.0%) in the DRV+COBI+TVD group had any AE leading to premature study drug discontinuation. In the D/C/F/TAF group, 1 subject discontinued study drug due to an SAE of substance abuse, and the other discontinued study drug due to a study drug-related SAE of hypersensitivity and a study drug-related non-serious AE of rash. In the DRV+COBI+TVD group, 1 subject

discontinued study drug due to an SAE of renal tubular disorder (reported as proximal renal tubulopathy [PRT]), and the other subject discontinued study drug due to a study drug-related non-serious AE of worsening of diarrhoea. Two subjects in the D/C/F/TAF group had Centers for Disease Control (CDC) Class C AIDS-defining events; one non-serious Kaposi's sarcoma and one non-serious HIV wasting syndrome. One subject in the DRV+COBI+TVD group had a CDC Class C AIDS-defining event of non-serious Kaposi's sarcoma.

Table 19. GS-US-299-0102: Overall Summary of Adverse Events (Safety Analysis Set)

Subjects Experiencing Any	D/C/F/TAF (N = 103)	DRV+COBI+TVD (N = 50)
Treatment-Emergent AE	95 (92.2%)	47 (94.0%)
Any Grade 2, 3, or 4 Treatment-Emergent AE	57 (55.3%)	24 (48.0%)
Any Grade 3 or 4 Treatment-Emergent AE	7 (6.8%)	4 (8.0%)
Any Treatment-Emergent Study Drug–Related AE	43 (41.7%)	19 (38.0%)
Any Grade 2, 3, or 4 Treatment-Emergent Study Drug–Related AE	10 (9.7%)	3 (6.0%)
Any Grade 3 or 4 Treatment-Emergent Study Drug–Related AE	1 (1.0%)	1 (2.0%)
Any Treatment-Emergent SAE	5 (4.9%)	2 (4.0%)
Any Treatment-Emergent Study Drug–Related SAE	1 (1.0%)	0
Any Treatment-Emergent AE Leading to Premature Study Drug Discontinuation	2 (1.9%)	2 (4.0%)
Treatment-Emergent Death	0	0

Adverse events that occurred in ≥5% of subjects are presented in Table 20. Common AEs were consistent with those expected in the subject population and the known safety profiles of the study drugs. The AEs by PT reported for ≥10% of subjects in either treatment group were as follows:

- D/C/F/TAF group — diarrhoea (21.4%, 22 subjects); upper respiratory tract infection (15.5%, 16 subjects); fatigue (13.6%, 14 subjects); nausea (12.6%, 13 subjects); and rash (11.7%, 12 subjects)
- DRV+COBI+TVD group — diarrhoea (26.0%, 13 subjects); fatigue (18.0%, 9 subjects); upper respiratory tract infection (14.0%, 7 subjects); flatulence (12.0%, 6 subjects); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, 5 subjects)

Table 20. GS-US-299-0102: Adverse Events Reported for ≥5% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b]	D/C/F/TAF (N = 103) n (%)	DRV+COBI+TVD (N = 50) n (%)
Any Treatment-Emergent AE	95 (92.2)	47 (94.0)
Gastrointestinal Disorders	54 (52.4)	26 (52.0)
Diarrhoea	22 (21.4)	13 (26.0)
Nausea	13 (12.6)	5 (10.0)
Flatulence	5 (4.9)	6 (12.0)
Abdominal pain	6 (5.8)	3 (6.0)
Vomiting	4 (3.9)	5 (10.0)
Haemorrhoids	3 (2.9)	4 (8.0)
General Disorders and Administration Site Conditions	26 (25.2)	11 (22.0)
Fatigue	14 (13.6)	9 (18.0)
Pyrexia	7 (6.8)	2 (4.0)
Infections and Infestations	62 (60.2)	32 (64.0)
Upper respiratory tract infection	16 (15.5)	7 (14.0)
Bronchitis	9 (8.7)	2 (4.0)
Sinusitis	7 (6.8)	4 (8.0)
Nasopharyngitis	5 (4.9)	3 (6.0)
Folliculitis	3 (2.9)	4 (8.0)
Influenza	2 (1.9)	3 (6.0)
Pharyngitis	1 (1.0)	3 (6.0)
Tooth abscess	0	3 (6.0)
Metabolism and Nutrition Disorders	16 (15.5)	13 (26.0)
Decreased appetite	4 (3.9)	3 (6.0)
Vitamin D deficiency	2 (1.9)	5 (10.0)
Musculoskeletal and connective tissue disorders	28 (27.2)	18 (36.0)
Pain in extremity	8 (7.8)	5 (10.0)
Arthralgia	9 (8.7)	0
Back pain	1 (1.0)	3 (6.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	8 (7.8)	5 (10.0)
Anogenital warts	3 (2.9)	3 (6.0)
Nervous system disorders	16 (15.5)	11 (22.0)
Headache	7 (6.8)	4 (8.0)
Psychiatric disorders	19 (18.4)	6 (12.0)
Insomnia	6 (5.8)	2 (4.0)
Respiratory, thoracic and mediastinal disorders	20 (19.4)	9 (18.0)
Cough	7 (6.8)	3 (6.0)
Oropharyngeal pain	5 (4.9)	4 (8.0)
Sinus congestion	6 (5.8)	3 (6.0)
Skin and subcutaneous tissue disorders	29 (28.2)	13 (26.0)
Rash	12 (11.7)	4 (8.0)
Vascular disorders	4 (3.9)	3 (6.0)
Hypertension	2 (1.9)	3 (6.0)

a Adverse events were coded using MedDRA 17.0.

b Multiple AEs were counted only once per subject for each system organ class, high level term, and preferred term, respectively.

Adverse events by relationship to the study drug

Similar percentages of subjects in each group had any AE considered by the investigator to be related to study drug (D/C/F/TAF 41.7%, 43 subjects; DRV+COBI+TVD 38.0%, 19 subjects). The most commonly reported AEs considered related to the study drugs by the investigator by PT were as follows: diarrhoea (D/C/F/TAF 13.6%, 14 subjects; DRV+COBI+TVD 14.0%, 7 subjects), flatulence (D/C/F/TAF 3.9%, 4 subjects; DRV+COBI+TVD 10.0%, 5 subjects), nausea (D/C/F/TAF 9.7%, 10 subjects; DRV+COBI+TVD 6.0%, 3 subjects), and fatigue (D/C/F/TAF 8.7%, 9 subjects; DRV+COBI+TVD 8.0%, 4 subjects).

Table 21. GS-US-299-0102: Study drug related adverse events Reported for >2% of Subjects in Either Treatment Group (Safety Analysis Set)

Adverse Events by System Organ Class and Preferred Term[a,b]	D/C/F/TAF (N = 103) n (%)	DRV+COBI+TVD (N = 50) n (%)
Number of Subjects Experiencing Any Treatment-Emergent Study Drug–Related AE	43 (41.7)	19 (38.0)
Gastrointestinal Disorders	31 (30.1)	13 (26.0)
Diarrhoea	14 (13.6)	7 (14.0)
Flatulence	4 (3.9)	5 (10.0)
Abdominal pain	5 (4.9)	0
Nausea	10 (9.7)	3 (6.0)
General Disorders and Administration Site Conditions	10 (9.7)	4 (8.0)
Fatigue	9 (8.7)	4 (8.0)
Investigations	2 (1.9)	2 (4.0)
Bone density decreased	0	2 (4.0)
Metabolism and Nutrition Disorders	2 (1.9)	4 (8.0)
Decreased appetite	1 (1.0)	2 (4.0)
Nervous System Disorders	2 (1.9)	4 (8.0)
Headache	0	2 (4.0)
Psychiatric Disorders	1 (1.0)	2 (4.0)
Abnormal dreams	0	2 (4.0)
Skin and Subcutaneous Tissue Disorders	5 (4.9)	5 (10.0)
Night sweats	0	2 (4.0)
Rash	3 (2.9)	3 (6.0)

a Adverse events were coded using MedDRA 17.0.

b Multiple AEs were counted only once per subject for each system organ class, high level term, and preferred term, respectively.

Serious adverse event / deaths / other significant events

Events and parameters of special interest from Study GS-US-299-0102 are summarized in Table 22.

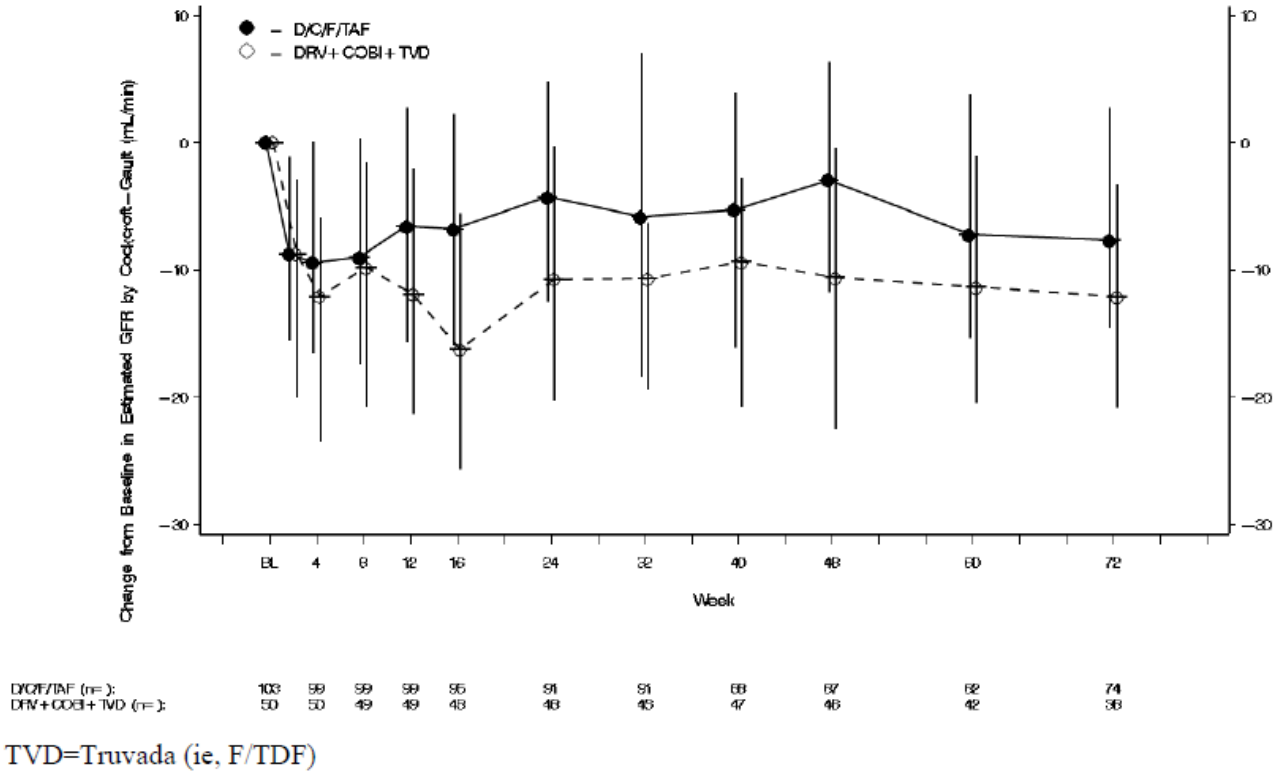
Table 22. Events and Parameters of Special Interest for D/C/F/TAF – Study GS-US-299-0102

	D/C/F/TAF (N=103)	DRV+COBI+F/TDF (N=50)
Exposure (weeks)		
Mean (SD)	61.7 (20.26)	66.1 (14.83)
Median	68.0	69.1
Q1, Q3	65.4, 72.7	66.0, 73.6
Renal Safety		
Median BL $eGFR_{CG}$ (mL/min)	116.0 (97.0, 137.6)	109.6 (92.5, 131.4)
Median (Q1, Q3) change from baseline at Week 48:		
Serum creatinine (mg/dL)	0.06 (-0.02, 0.11)	0.12 (0.01, 0.18)
$eGFR_{CG}$ (mL/min)	-2.9 (-11.8, 6.2)	-10.6 (-22.4, -0.5)
$eGFR_{CKD\text{-}EPI,creatinine}$ (mL/min/1.73 m^2)	-5.9 (-12.7, 0.8)	-11.6 (-20.1, -1.8)
$eGFR_{CKD\text{-}EPI,CysC}$ (mL/min/1.73 m^2)	6.7 (-1.6, 14.9)	0.3 (-9.6, 12.0)
n (%) of subjects experiencing any renal AE leading to discontinuation	0	1 (2.0%)
Bone Safety		
Mean (SD) change from baseline at Week 48:		
Hip BMD (%)	-0.84 (2.582)	-3.82 (2.651)
Spine BMD (%)	-1.57 (3.920)	-3.62 (3.128)
n (%) of subjects at W48 with:		
>3% decrease in hip BMD	15/82 (18.3%)	29/47 (61.7%)
>3% decrease in spine BMD	27/83 (32.5%)	26/47 (55.3%)
n (%) of subjects experiencing any bone fracture	0	0
Lipid Parameters		
Median BL value:		
Total cholesterol (mg/dL)	156 (137, 174)	158 (137, 190)
Direct LDL cholesterol (mg/dL)	93 (81, 108)	101 (79, 136)
HDL cholesterol (mg/dL)	42 (33, 50)	42 (37, 53)
Triglycerides (mg/dL)	99 (76, 156)	99 (69, 129)
	3.8 (3.1, 4.7)	3.8 (3.1, 4.8)
Median (Q1, Q3) change from baseline at Week 48:		
Total cholesterol (mg/dL)	40 (13, 58)	5 (-9, 26)
Direct LDL cholesterol (mg/dL)	26 (9,44)	4 (-9, 17)
HDL cholesterol (mg/dL)	7 (1, 14)	3 (-3, 7)
Triglycerides (mg/dL)	29 (-6, 72)	-5 (-23, 29)

Renal safety

D/C/F/TAF showed a better renal safety profile compared to subjects who received DRV+COBI+F/TDF, as evidenced by significantly less reduction in eGFR (Figure 9) and less tubular proteinuria was observed. There were no cases of PRT (including Fanconi syndrome) reported in HIV-1 infected subjects receiving D/C/F/TAF; 1 case was reported in the DRV+COBI+F/TDF group. Increases from baseline in mean values for serum creatinine were smaller in the D/C/F/TAF group compared with the DRV+COBI+F/TDF group. Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function as assessed, for instance, by using cystatin C as filtration marker. In the Phase 2 Study GS-US-299-0102 in treatment-naïve subjects, increases in serum creatinine and concomitant changes in eGFRC occurred by Week 2 of treatment and remained stable through 48 weeks. Changes from baseline with D/C/F/TAF were smaller than

with DRV+COBI+F/TDF. No statistically significant differences were observed between the 2 treatment groups in median percentage change from baseline in UPCR or UACR at Week 48. There were statistically significant differences between the treatment groups, favouring D/C/F/TAF, in change from baseline in RBP to creatinine and β2-microglobulin to creatinine ratios.

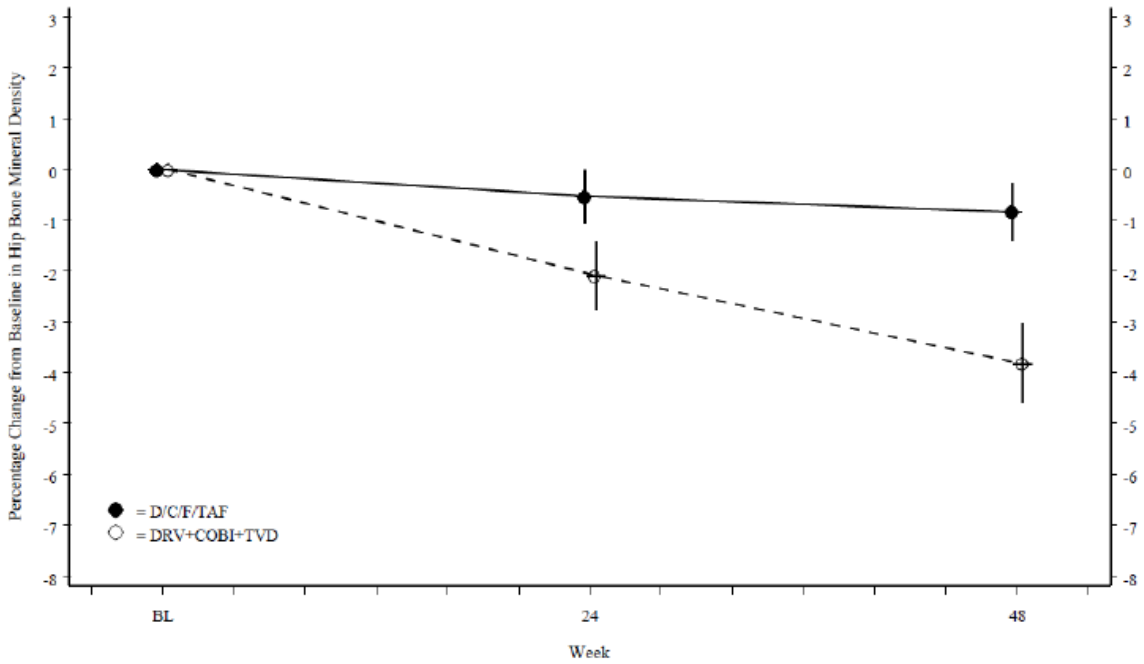


TVD=Truvada (ie, F/TDF)

Figure 9. Median (Q1, Q3) of Change from Baseline in Estimated GFR by Cockcroft-Gault (mL/min) by Visit (Safety Analysis Set) - GS-US-299-0102

Bone safety

At Week 48, subjects receiving D/C/F/TAF experienced less decline in BMD than those receiving DRV+COBI+F/TDF. A smaller proportion of subjects in the D/C/F/TAF group compared with those of the DRV+COBI+F/TDF group had a clinically significant (>3%) decrease from baseline in hip BMD (18.3% vs 61.7%) and in spine BMD (32.5% vs 55.3%). Increases from baseline in the bone turnover biomarkers type I collagen C-telopeptide (a bone resorption biomarker) and P1NP (a bone formation biomarker), as well as PTH (a hormone involved in bone metabolism) were smaller in the D/C/F/TAF group compared with the DRV+COBI+F/TDF group at both Weeks 24 and 48.



D/C/F/TAF (n=):	85	85	82
DRV+COBI+TVD (n=):	48	48	47

TVD=Truvada (ie, F/TDF)

Figure 10. Mean (95% CI) of Percentage Change from Baseline in Hip BMD by Visit (Hip DXA Analysis Set) - GS-US-299-0102

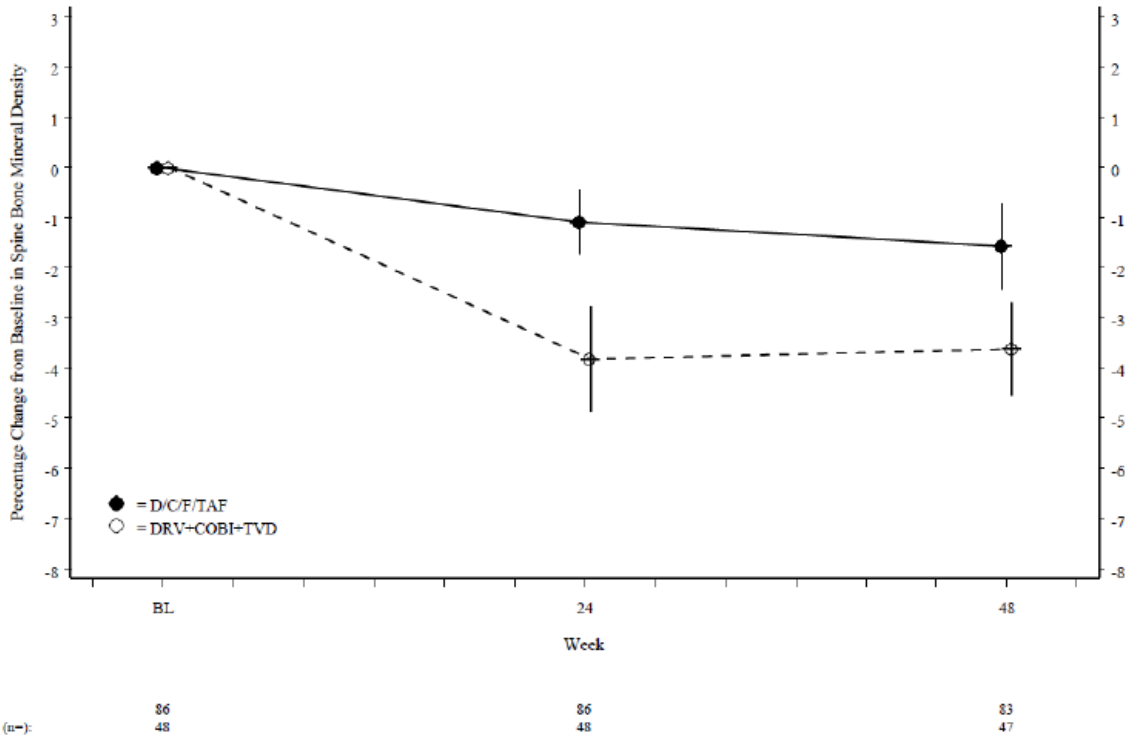


Figure 11. Mean (95% CI) of Percentage Change from Baseline in Spine BMD by Visit (Spine DXA Analysis Set) - GS-US-299-0102

Fasting lipid parameters

Increases (median) from baseline were observed in both the TAF- and TDF-containing treatment groups for the fasting lipid parameters total cholesterol, direct LDL and HDL cholesterol, and triglycerides at Weeks 24 and 48, with the exception of a decrease in fasting triglycerides at Week 48 for the DRV+COBI+F/TDF group. The median increase from baseline was greater in the D/C/F/TAF group compared with the DRV+COBI+F/TDF group at both Week 24 and Week 48. Statistically significant differences between the 2 groups in change from baseline were seen for fasting total cholesterol and fasting direct LDL cholesterol at Week 24 ($p=0.014$ for the difference between treatment groups for total cholesterol, $p=0.004$ for direct LDL cholesterol, $p=0.35$ for HDL cholesterol, and $p=0.13$ for triglycerides), and for all 4 lipid parameters at Week 48 ($p<0.001$ for the difference between treatment groups for total cholesterol and direct LDL cholesterol, $p=0.009$ for HDL cholesterol, and $p=0.007$ for triglycerides). There were no clinically relevant changes from baseline for either treatment group or statistically significant differences in changes from baseline between treatment groups for median fasting total cholesterol to HDL ratio. Lipid abnormalities is listed as an identified risk in the EU-RMP for D/C/F/TAF, which is supported. The company was requested to further discuss the impact of TAF vs TDF use may have on cardiovascular risk especially in adolescents, taking into account that receiving PI therapy in the age range of 10 to 15 years (the years of pubertal development) already seems to be significantly associated with the development of dyslipidaemia (Taylor et al., Pediatrics. 2004; 114: e235-242). The applicant argued that the TC/HDL ratio is providing the most relevant information and concluded, based on studies GS-US-292-0104, GS-US-292-0111, GS-US-292-0106, and TMC114-C230, that the changes in TC/HDL ratio are minimal in both adults and adolescents. The Applicant “expects that the changes in individual fasting lipid parameters and TC/HDL after

administration of D/C/F/TAF in adolescents will lie between the changes observed in study TMC114-C230 (as a proxy for the effects of DRV in the absence of the lipid-protective effects of TDF) and in study GS-US-292-0106 (as a proxy for the effects in the presence of TAF, having less lipid-protective effects than TDF)." This expectation is reasonable. The effect of D/C/F/TAF on lipids is reflected in section 4.8 of the SmPC to enable the prescriber to take this effect into consideration while considering the available treatment options, and the revised EU-RMP for D/C/F/TAF has been updated regarding current knowledge on this topic.

Other observations related to safety

Six subjects (5.8%) receiving D/C/F/TAF had non serious AEs in the Eye Disorders SOC compared with none of the subjects in the DRV+COBI+F/TDF group; preferred term (PT) included dry eye, ocular hyperaemia, eye irritation, lacrimation increased, eye pruritus, and photophobia. No AEs of uveitis were reported during the study. One (1.0%) subject in the D/C/F/TAF group presented a photophobia. The event, considered related to the study drug by the investigator, was non serious. No eye disorder resulted in discontinuation of study drugs.

There were no clinically significant ECG findings reported for any subjects during the study and there were no clinically relevant changes from baseline within groups or between treatment groups in median values for body weight in either group.

Special situations including medication error, misuse, overdose, and product complaints with associated AEs were collected during the study; no new safety concerns were identified from evaluation of reports of special situation events.

Subjects co-infected with hepatitis B or C were not allowed to participate in Study GS-US-299-0109, therefore no relevant safety information is available from this study on the HIV-1/HBV or HCV co-infected population.

Serious adverse events and deaths

Similar percentages of subjects in each treatment group had SAEs (D/C/F/TAF 4.9%, 5 subjects; DRV+COBI+TVD 4.0%, 2 subjects). The rate of SAEs is as can be expected in this patient population. No SAEs were reported for > 1 subject. There was 1 SAE that was considered related to study drug by the investigator. Subject 0302-3149 in the D/C/F/TAF group had an SAE of Grade 3 hypersensitivity (allergic reaction) starting on Study Day 1 and non-serious AE of Grade 3 rash (body rash) starting on Study Day 8, both of which were considered related to study drug. Study drug was discontinued due to the events; the last dose was administered on Study Day 8. Both events resolved on Study Day 16. Overall, no specific safety concern was identified. No subjects died during the study.

Laboratory findings

The majority of subjects had at least 1 laboratory abnormality reported (D/C/F/TAF 96.1%, 98 subjects; DRV+COBI+TVD 94.0%, 47 subjects). The majority of laboratory abnormalities were Grade 1 or Grade 2. Similar percentages of subjects in both treatment groups had Grade 3 or 4 laboratory abnormalities (D/C/F/TAF 27.5%, DRV+COBI+TVD 28.0%). The most commonly reported Grade 3 or 4 laboratory abnormality was creatine kinase (D/C/F/TAF 8.8%, 9 subjects; DRV+COBI+TVD 12.0%, 6 subjects).

As Pancreatitis is listed as an important identified risk for Rezolsta (DRV+COBI), the applicant was requested to provide further details for all subjects in study GS-US-299-0102 that reported either amylase and/or lipase ≥ 3 times the upper limit of normal in order to identify potential cases of pancreatitis. In study GS-US-299-0102, there was 1 transient isolated asymptomatic treatment-emergent increase of amylase levels ≥ 3xULN (1 in the D/C/F/TAF FDC group (1%), 0 in the DRV+COBI+F/TDF control group), and no subjects with lipase levels ≥3xULN (lipase testing was only performed if subjects had total amylase >1.5xULN). The increased amylase

levels were not associated with signs or symptoms suggestive of pancreatitis. There was no prior history of pancreatitis or alcohol use or abuse.

There was an increased rate of lipid abnormalities in the D/C/F/TAF group, which is known to occur and is considered related to the fact that subjects receiving D/C/F/TAF have lower plasma concentrations of TVF for which a lipid-lowering effect has effectively been reported in literature.

Safety in special populations

Designated studies with the D/C/F/TAF FDC in special populations have not been performed, and the effects of intrinsic/extrinsic factors or special situations on the safety of D/C/F/TAF cannot be determined from the phase 2 study GS-US-299-0102. As such, these effects are derived from data for the individual components.

Paediatric patients

The safety assessment of DRV once daily in paediatric subjects is based on the 48-week analysis of safety data from the Phase 2 Study TMC114-C230 in 12 ART-naïve HIV-1 infected paediatric subjects aged from 12 to 17 years and weighing at least 40 kg. These data supported the approval of DRV 800 mg once daily for use in adolescents weighing at least 40 kg.

The safety of COBI and F/TAF were evaluated in a single-arm clinical study (Study GS-US-292-0106) in which HIV-1 infected, treatment-naïve paediatric subjects aged 12 to <18 years received EVG, COBI, FTC and TAF as an FDC tablet. Results from this study show that the E/C/F/TAF FDC is well tolerated in adolescents, with a low incidence of study drug-related SAEs and the absence of AEs leading to discontinuation of study drug. There were no notable changes from baseline in height-age adjusted spine and TBLH BMD Z-scores after 48 weeks of treatment, indicating that subjects mineralized bone at rates consistent with those of the reference population. Few subjects experienced a clinically relevant decrease from baseline in BMD. These data supported the approval of E/C/F/TAF with a COBI dose of 150 mg and an F/TAF dose of 200/10 mg once daily for use in adolescents weighing at least 35 kg.

Although there are no clinical data available with the D/C/F/TAF FDC in paediatric patients, the single agents are approved for use in this population. No specific safety concerns are noted from the 2 studies described above. There is however a difference in the weight restriction approved for other TAF-containing products, which all are approved for use from 35 kg onwards, and the restriction in weight of at least 40 kg for use of Darunavir 800 mg tablet (Prezista). The indication for the D/C/F/TAF FDC covers adolescents weighing at least 40 kg.

Elderly

As the oldest subject included in Study GS-US-299-0102 was 68 years old, very limited information is available in this population. Therefore, the D/C/F/TAF FDC is to be used with caution in patients above 65 years of age, due to the greater frequency of decreased hepatic function, concomitant disease(s), and/or polypharmacy.

Renal impairment

There are no data regarding the use of the D/C/F/TAF FDC, or its components DRV and COBI in patients with severe renal insufficiency. There was 1 study with TAF in severe renal impairment (GS-US-120-0108) which showed that plasma TAF exposure was less than 2-fold higher in subjects with severe renal impairment, compared with healthy subjects. Available data for the components of D/C/F/TAF (derived from Study GS-US-236-0118 and Study GS-US-292-0112) indicate that the overall safety profile in subjects with mild to moderate renal impairment was similar to that observed in the adult population. The final (safety) results from Study GS-US-236-0118 were recently assessed (procedure EMEA/H/C/002819/II/0007). The main conclusion was that overall the findings of the study do not alter the known safety profile of cobicistat containing medicinal

products with regards to renal effects. In subjects with mild to moderate renal impairment treated with a cobicistat containing therapy for 96 weeks, the creatinine based eGFR endpoints showed a moderate decrease in eGFR values which remained stable from week 2 through week 96. This decrease seems not to be related to the occurrence of major renal events. Few discontinuations due to renal dysfunction were observed and few renal SAEs were described.

Hepatic impairment

Based on the PK, efficacy and safety data for the individual components, no dose adjustment is required in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. However, D/C/F/TAF should be used with caution in these patients due to the increase in unbound DRV plasma concentrations. The D/C/F/TAF FDC or its components have not been studied in patients with severe hepatic impairment (Child-Pugh Class C), therefore, the D/C/F/TAF FDC must not be used in patients with severe hepatic impairment.

Coinfection with HIV-1 and Hepatitis B/C

Patients with chronic hepatitis B or C treated with ART are at an increased risk for severe and potentially fatal hepatic adverse reactions. The safety and efficacy of D/C/F/TAF in patients co-infected with HIV-1 and HCV have not been established. No specific clinical study was performed with the D/C/F/TAF FDC in subjects co-infected with HIV and HBV and/or HCV. Subjects were excluded from the Phase 2 study with the D/C/F/TAF FDC (Study GS-US-99-0102) and from the F/TAF Phase 2 and 3 studies. There is limited experience with DRV (boosted with rtv) in subjects co-infected with HIV and HBV and/or HCV. Among the 1,986 treatment-experienced subjects receiving DRV/rtv 600/100 mg twice daily, 236 were co-infected with hepatitis B or C. Co-infected subjects were more likely to have baseline and treatment-emergent hepatic transaminase elevations than those without chronic viral hepatitis. The safety of F/TAF in combination with EVG and COBI as an FDC was evaluated in approximately 70 HIV/HBV co-infected subjects treated for HIV in an open-label clinical study (GS-US-292-1249). Based on this experience, the safety profile of F/TAF in subjects with HIV/HBV coinfection appears to be similar to that in subjects with HIV-1 mono-infection. It can reasonably be concluded that the safety profile will be similar for the D/C/F/TAF FDC. Tenofovir alafenamide is active against HBV. Discontinuation of D/C/F/TAF therapy in patients co-infected with HIV and HBV may be associated with severe acute exacerbations of hepatitis due to the F/TAF components of D/C/F/TAF. Patients co-infected with HIV and HBV who discontinue D/C/F/TAF should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping treatment. D/C/F/TAF should not be administered concomitantly with medicinal products containing tenofovir disoproxil (as fumarate), lamivudine, or adefovir dipivoxil used for the treatment of HBV infection.

Pregnancy, lactation and fertility

No adequate and well-controlled studies of D/C/F/TAF or its components have been conducted in pregnant women. The safety of the use of DRV, COBI, and FTC during pregnancy or breast-feeding is reflected in the respective approved drug labels. These products should only be used in pregnancy if the potential benefit justifies the potential risk. Because of both the potential for HIV transmission and the potential for adverse reactions in breast fed infants, mothers should be instructed not to breast feed while using D/C/F/TAF. No human data on the effect of darunavir, cobicistat, emtricitabine, or tenofovir alafenamide on fertility are available. There was no effect on mating or fertility in animals.

Overdose

Human experience of acute overdose with the administration of D/C/F/TAF is not available. No study with administration of supratherapeutic doses of D/C/F/TAF has been conducted. Limited clinical experience is available with the components of the D/C/F/TAF FDC at doses higher than the therapeutic doses. Increases in exposure when administering the D/C/F/TAF FDC with rtv or COBI are anticipated to be minimal as the inhibition of CYP3A is already near maximal for D/C/F/TAF.

Safety related to drug-drug interactions and other interactions

No drug-drug interaction studies with the D/C/F/TAF FDC have been conducted. The drug-drug interaction profile of the D/C/F/TAF FDC is based on the interactions observed with the single agents, and is mostly driven by DRV/COBI as FTC and TAF have a low potential for drug-drug interactions.

Based on the effect of DRV/COBI, co-administration of D/C/F/TAF is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

Discontinuation due to AEs

Two subjects in each treatment group (D/C/F/TAF 1.9%; DRV+COBI+TVD 4.0%) discontinued from the study due to the following AEs:

- One subject in the D/C/F/TAF group discontinued study drug due to an SAE of hypersensitivity and a non-serious AE of rash.
- One subject in the D/C/F/TAF group discontinued study drug due to an SAE of substance abuse, which started on Study Day 233. The subject had experienced a previous SAE of substance abuse from Study Days 140 to 164. The subject was hospitalized for both events. The last dose of study drug was administered on Study Day 234, and the event was resolved on Study Day 283. The investigator considered the SAE of substance abuse resulting in study drug discontinuation not to be related to study drug.
- One subject in the DRV+COBI+TVD group discontinued study drug due to an SAE of Grade 2 renal tubular disorder (reported as PRT).
- One subject in the DRV+COBI+TVD group discontinued study drug due to a non-serious AE of Grade 3 worsening of diarrhoea that was considered related to study drug. The event started on Study Day 373, and the last dose of study drug was administered on Study Day 382. Treatment included medication, and the event was reported as resolved on Study Day 389.

Post marketing experience

No data is available with the D/C/F/TAF fixed dose combination.

2.6.1. Discussion on clinical safety

Patient exposure

The safety of the D/C/F/TAF FDC is based on the well-established safety profile of the individual components DRV/COBI and F/TAF, further supported by the Phase 2 double-blind Study GS-US-299-0102. Actual exposure to the to be marketed FDC tablet is limited to 103 adult subjects who received at least 1 dose of D/C/F/TAF.

Based on the results of study GS-US-299-0102, treatment with the D/C/F/TAF FDC seems to have an acceptable tolerability. The percentage of subjects reporting adverse events (92.2%) was comparable to the comparator arm receiving DRV+COBI+TVD (94.0%). The proportion of subjects with drug related adverse events varied from 38% (DRV+COBI+TVD) to 41.7% (D/C/F/TAF), and discontinuations due to drug related adverse events were infrequent (2 subjects in each arm). SAEs were reported in <5% in both treatment arms.

Analysis of adverse events

The most frequently reported adverse events in the D/C/F/TAF arm in study GS-US-299-0102 were diarrhoea (21.4%, 22 subjects); upper respiratory tract infection (15.5%, 16 subjects); fatigue (13.6%, 14 subjects); nausea (12.6%, 13 subjects); and rash (11.7%, 12 subjects). In the DRV+COBI+TVD arm these were diarrhoea (26.0%, 13 subjects); fatigue (18.0%, 9 subjects); upper respiratory tract infection (14.0%, 7 subjects); flatulence (12.0%, 6 subjects); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, 5 subjects).

The most commonly reported AEs considered related to the study drugs by the investigator by PT were: diarrhoea (D/C/F/TAF 13.6%, 14 subjects; DRV+COBI+TVD 14.0%, 7 subjects), flatulence (D/C/F/TAF 3.9%, 4 subjects; DRV+COBI+TVD 10.0%, 5 subjects), nausea (D/C/F/TAF 9.7%, 10 subjects; DRV+COBI+TVD 6.0%, 3 subjects), and fatigue (D/C/F/TAF 8.7%, 9 subjects; DRV+COBI+TVD 8.0%, 4 subjects). Arthralgia was reported for at least 5% more subjects in the D/C/F/TAF group compared with the DRV+COBI+TVD group (D/C/F/TAF 8.7%, 9 subjects; DRV+COBI+TVD 0 subjects), however there was no evidence for a clear relationship.

There was 1 SAE (Grade 3 hypersensitivity (allergic reaction)) that was considered related to study drug by the investigator (D/C/F/TAF group). No subjects died. Two subjects in each treatment group discontinued from the study due to the following AEs: hypersensitivity (considered related to study drug by the investigator), and substance abuse (considered not related) in the D/C/F/TAF group; and Grade 2 renal tubular disorder (considered not related), and Grade 3 worsening of diarrhoea (considered related) in the DRV+COBI+TVD group.

AEs of special interest

D/C/F/TAF showed, as expected, a better renal and bone safety profile compared to the DRV+COBI+TVD combination. There was an increased rate of lipid abnormalities in the D/C/F/TAF arm, which was expected to occur and is considered due to the fact that subjects receiving D/C/F/TAF have lower plasma concentrations of TVF for which a lipid-lowering effect has been reported in literature. The applicant argued that the changes in individual fasting lipid parameters and TC/HDL after administration of D/C/F/TAF in adolescents will be limited as these are expected to lie between the changes observed in study TMC114-C230 (effects of DRV in the absence of the lipid-protective effects of TDF) and in study GS-US-292-0106 (effects of TAF, known to have less lipid-protective effects than TDF).

As Pancreatitis is listed as an important identified risk for Rezolsta (DRV+COBI), the applicant was requested to provide further details for all subjects in study GS-US-299-0102 that reported either amylase and/or lipase ≥ 3 times the upper limit of normal in order to identify potential cases of pancreatitis. The observation of one transient isolated asymptomatic treatment-emergent increase of amylase levels ≥3xULN with D/C/F/TAF FDC was reassuring.

Missing data

No specific clinical study was performed with the D/C/F/TAF FDC in the following special populations: paediatric subjects, elderly subjects, subjects with renal insufficiency, hepatic impairment, or in subjects co-infected with hepatitis B or C. No adequate and well-controlled studies of D/C/F/TAF or its components have been conducted in pregnant women. No human experience of acute overdose with the administration of D/C/F/TAF is available.

Safety related to drug-drug interactions

Co-administration of D/C/F/TAF is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events (narrow therapeutic index).

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

The safety profile of the D/C/F/TAF FDC is largely based on the well-established safety profile of the individual components. The safety profile of D/C/F/TAF FDC is supported by the results from the phase 2 study and as well by the preliminary results from the ongoing phase 3 studies. The observed safety profile is in line with expectations and did not raise additional concerns.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important identified risks	Severe skin reactions
	Hepatotoxicity
	Hyperglycaemia
	Lipid abnormalities
	Immune reconstitution inflammatory syndrome
	Drug-drug interactions
	Post-treatment hepatic flares in HIV/HBV coinfected patients
	Pancreatitis
	Development of drug resistance
Important potential risks	Coronary artery events
	Renal toxicity
	Bone events due to potential proximal renal tubulopathy/loss of BMD
	Ocular effects (posterior uveitis)
	Convulsions
Missing information	Use in elderly (65 years and above)

	Use in pregnant and breast-feeding women
	Use in children <12 years of age
	Long-term safety of Symtuza
	Use in patients with severe hepatic impairment (Child-Pugh C)
	Use in patients with moderate or severe renal impairment
	Use in patients coinfected with HIV and HBV and/or HCV
	Safety in patients with cardiac conduction disorders

Pharmacovigilance plan

Study ID/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)**
TMC114HIV3015 A single-arm, open-label trial to assess the pharmacokinetics of DRV/rtv, DRV/COBI, etravirine, and rilpivirine in HIV-1-infected pregnant women. Category 3	To assess the PK of DRV/COBI in HIV-1-infected pregnant women.	Missing information Use in pregnant and breast-feeding women	Started	Q4 2017 (Final report)
PANNA (Investigator Initiated Study) Study of Pharmacokinetics of newly developed Antiretroviral agents in HIV-infected pregnant women. Category 3	To assess the PK of DRV/COBI in HIV-1-infected pregnant women.	Missing information Use in pregnant and breast-feeding women	Started	Q4 2019 (DRV/COBI report)
GS-US-216-0128 A Phase 2/3, multicenter, open-label, multicohort, two-part study evaluating pharmacokinetics, safety, and efficacy of cobicistat-boosted atazanavir or cobicistat-boosted darunavir, administered with an optimized background regimen in HIV-1 infected, treatment-experienced, virologically suppressed pediatric subjects. Category 3	To evaluate the steady-state PK and confirm the dose of cobicistat-boosted atazanavir (ATV/COBI) or cobicistat-boosted darunavir (DRV/COBI). To evaluate the safety, tolerability, and efficacy of ATV/COBI and DRV/COBI.	Missing information Use in children <12 years of age	Started	Q1 2022 (Final report)

Study ID/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-311-1269 A Phase 2/3, Open-Label, Multi-Cohort Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV-1 Infected Children and Adolescents Virologically Suppressed on a 2-NRTI-Containing Regimen. Category 3	To evaluate the PK and confirm the dose of TAF. To evaluate the safety, tolerability and efficacy of F/TAF.	Missing information Use in children <12 years of age	Started	Q1 2019 (Final report)
TMC114IFD3013 A Phase 3, randomized, active-controlled, open-label study to evaluate switching to a D/C/F/TAF once-daily single-tablet regimen versus continuing the current regimen consisting of a boosted protease inhibitor combined with FTC/TDF in virologically-suppressed, HIV-1 infected subjects. Category 3	To demonstrate noninferiority in efficacy of switching to a D/C/F/TAF once-daily single-tablet regimen relative to continuing the current boosted protease inhibitor combined with FTC/TDF in virologically-suppressed (HIV-1 RNA <50 copies/mL) HIV-1 infected subjects, until Week 48.	Missing information Long-term safety of Symtuza	Started	Q2 2018 (Week 48 report)
TMC114FD2HTX3001 A Phase 3, randomized, active-controlled, double-blind study to evaluate efficacy and safety of D/C/F/TAF once daily fixed-dose combination regimen versus a regimen consisting of DRV/COBI FDC coadministered with FTC/TDF FDC in ARV treatment-naïve HIV-1 infected subjects. Category 3	To demonstrate noninferiority in efficacy of D/C/F/TAF FDC versus DRV/COBI FDC coadministered with FTC/TDF FDC in HIV-1 infected subjects. To evaluate long-term efficacy, resistance, and safety of the D/C/F/TAF FDC regimen (Week 96 and beyond).	Missing information Long-term safety of Symtuza	Started	Q2 2018 (Week 48 report)
GS-US-292-0106 A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment-Naive Adolescents and Virologically Suppressed Children. Category 3	To evaluate the pharmacokinetics, safety, tolerability, and antiviral activity of elvitegravir cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) in HIV-infected, antiretroviral treatment (ART)-naive adolescents and virologically suppressed HIV-infected children.	Missing information Long-term safety of Symtuza. Use in children <12 years of age.	Started	Q2 2022 (Final report)

Study ID / 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-292-0109 A Phase 3, Open-Label Study to Evaluate Switching from a TDF-Containing Combination Regimen to a TAF-Containing Combination Single Tablet Regimen (STR) in Virologically-Suppressed, HIV-1 Positive Subjects. Category 3	To evaluate switching from a TDF-containing combination regimen to a TAF-containing combination single tablet regimen (STR) in virologically-suppressed, HIV-1 positive subjects.	Missing information Long-term safety of Symtuza.	Started	Q1 2018 (Final report)
GS-US-311-1089 A Phase 3, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV 1 Positive Subjects who are Virologically Suppressed on Regimens containing FTC/TDF. Category 3	A switch study to evaluate F/TAF in HIV-1 positive subjects who are virologically suppressed on regimens containing FTC/TDF.	Missing information Long-term safety of Symtuza.	Started	Q3 2017 (Week 96 report)
GS-US-311-1717 A Phase 3b, Randomized, Double-Blind, Switch Study to Evaluate F/TAF in HIV-1 Positive Subjects who are Virologically Suppressed on Regimens containing ABC/3TC. Category 3	To collect information on the efficacy of switching ABC/3TC to F/TAF versus maintaining ABC/3TC in HIV-1 infected subjects who are virologically suppressed on regimens containing ABC/3TC as determined by the proportion of subjects with HIV-1 RNA < 50 copies/mL at Week 48.	Long-term safety of Symtuza.	Started	Q1 2019 (Week 96 report)

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	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), 4.4 (Special warnings and precautions for use), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) of the SmPC.	
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 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
Drug-drug interactions	Adequate information and guidance to help the prescriber is provided in Sections 4.3 (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.	None
Post-treatment hepatic flares in HIV/HBV coinfected patients	Adequate information and guidance to help the prescriber is provided in Section 4.4 (Special warnings and precautions for use) of the SmPC.	None
Pancreatitis	Adequate information is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Development of drug resistance	Adequate information is provided in Sections 4.1 (Therapeutic indications), 4.4 (Special warnings and precautions for use), and 5.1 (Pharmacodynamic properties) of the SmPC.	None
Important potential risks:		
Coronary artery events	None proposed.	None
Renal toxicity	Adequate information and guidance to help the prescriber is provided in Section 4.4 of the SmPC.	None
Bone events due to potential proximal renal tubulopathy/loss of BMD	None proposed.	None
Ocular effects (posterior uveitis)	None proposed.	None
Convulsions	None proposed.	None
Missing information:		
Use in eldery (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	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
	SmPC.	
Use in pregnant and breast-feeding women	Adequate information and guidance to help the prescriber is provided in Section 4.6 (Fertility, pregnancy and lactation) of the SmPC.	None
Use in children <12 years of age	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
Long-term safety of Symtuza	Adequate information and guidance to help the prescriber is provided in Section 4.8 (Undesirable effects) of the SmPC.	None
Use in patients with severe hepatic impairment (Child-Pugh C)	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), and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Use in patients with moderate or severe renal impairment	Adequate information and guidance to help the prescriber is provided in Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects) and 5.2 (Pharmacokinetic properties) of the SmPC.	None
Use in patients 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
Safety in patients with cardiac conduction disorders	None proposed.	None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion.

2.9. New Active Substance

The CHMP, based on the available data, considers that darunavir / cobicistat / emtricitabine / tenofovir alafenamide are not new active substances, as they are constituent of medicinal products previously authorised within the European Union. Darunavir/ cobicistat are contained in the marketing authorisation Rezolsta which was authorised in the Union on 19 November 2014 and emtricitabine/ tenofovir alafenamide are contained in the marketing authorisation Descovy which was authorised in the Union on 21 April 2016.

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.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Symtuza (darunavir / cobicistat / emtricitabine / tenofovir alafenamide) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The fixed dose combination (FDC) of Darunavir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (D/C/F/TAF) has been developed for the treatment of HIV infected individuals.

The following indication is claimed for D/C/F/TAF:

TRADENAME is indicated for the treatment of human immunodeficiency virus type 1 (HIV 1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg) (see sections 4.2, 4.4 and 5.1).

HIV-1 infection results in chronic immune activation and a subsequent gradual loss of CD4+ T cells eventually leading to a state of acquired immunodeficiency (AIDS). One of the predictors for HIV-1 disease progression is the level of HIV-1 RNA in the blood (i.e. viral load). The aim of treatment of HIV-1 infection is therefore to suppress the HIV-1 viral load to levels that are at least below 50 copies/mL of blood. It is a life-long treatment, as the viral load will rebound as soon as an individual stops taking effective antiretroviral therapy.

3.1.2. Available therapies and unmet medical need

The available treatment options for HIV-1 infected individuals have greatly improved in the last two decades. Current treatment options are generally considered to be potent, with an overall acceptable safety profile. Although rare, resistance can occur potentially leading to resistance to antiretroviral drugs or classes. Therefore, there is a continuous need for development of new antiretroviral treatment options as well as simple antiretroviral regimen to enhance adherence which is paramount for HIV treatment.

The current application for the D/C/F/TAF FDC is a combination of 3 known active substances with antiviral activity, combined with a PK enhancer. As such, it is not considered a new treatment option, but has rather been developed to further simplify HIV-1 treatment with a reduced pill-burden. The D/C/F/TAF FDC is the first complete protease inhibitor (PI)-based HIV-1 regimen in a single tablet to be taken once daily.

The co-formulation with TAF, a prodrug of the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir (TFV), instead of tenofovir disoproxil fumarate (TDF), offers an improved renal and bone safety profile compared to TDF, with similar efficacy.

3.1.3. Main clinical studies

This application is based on Phase 1 studies bridging to the clinical development programs for DRV, COBI, FTC, and TAF as single agents (DRV and COBI) and combinations thereof (DRV/COBI and F/TAF). The pivotal bioequivalence study is Study TMC114FD2HTX1001, further supported by the relative bioavailability studies TMC114FD2HTX1002 and GS-US-299-0101.

The clinical efficacy, resistance, and safety data are mainly extrapolated from previous studies with DRV/rtv and E/C/F/TAF and further supported by clinical data from one Phase 2 study with D/C/F/TAF (Study GS-US-299-0102).

Study **TMC114FD2HTX1001** was a randomized, two-way, cross-over study to evaluate the single-dose PK and pivotal bioequivalence of the D/C/F/TAF FDC compared to the separate agents (DRV 800 mg tablet formulation and F/TAF 200/10 mg FDC in the presence of 150 mg COBI), under fed conditions (standardized regular-fat breakfast, in healthy subjects.

Study **TMC114FD2HTX1002** investigated the effect of concomitant food intake (standardized high calorie/high-fat breakfast, 56 g fat) on the oral bioavailability of DRV, COBI, FTC and TAF following oral administration of D/C/F/TAF 800/150/200/10 mg as 1 x FDC tablet was investigated in a Phase 1, randomized, 3-panel, open-label, 2-way crossover study in healthy subjects.

Study **GS-US-299-0101** was a Phase 1, adaptive-design, randomized, open-label, multiple-dose, 3-part, multiple-cohort, single-center study and compared three candidate D/C/F/TAF FDC tablet formulations after repeated dosing in order to select a formulation for Phase 2; and subsequently the PK and bioavailability of DRV, COBI, FTC, TAF, and TFV when administered as the selected Phase 2 D/C/F/TAF FDC relative to the administration of the individual components: DRV plus COBI or FTC plus TAF.

Study **GS-US-299-0102** was a phase 2, randomized, double-blind, multicenter, active controlled study to evaluate the safety and efficacy of D/C/F/TAF FDC vs DRV+COBI+TVD in 153 subjects (N=103 and N=50, respectively).

3.2. Favourable effects

Studies TMC114FD2HTX1001, TMC114FD2HTX1002 and GS-US-299-0101 demonstrated comparable exposure (i.e. AUC and Cmax) for DRV, COBI, FTC, and TAF when administered as single agents or as the D/C/F/TAF FDC in healthy subjects and HIV-1 infected ART-naïve subjects as compared with historical data, allowing the extrapolation of safety and efficacy data from either darunavir/low-dose ritonavir (DRV/rtv) 800/100 mg once daily, DRV/COBI 800/150 mg once daily or F/TAF 200/10 mg once daily to D/C/F/TAF 800/150/200/10 mg once daily.

The pivotal bioequivalence study TMC114FD2HTX1001 showed that the D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration of the separate agents DRV, the F/TAF FDC, and COBI.

Study GS-US-299-0102 showed that the D/C/F/TAF FDC was non-inferior to DRV+COBI+TVD. Virologic success rates in the FAS at Week 24 were 77/103 (74.8%) for D/C/F/TAF, and 37/50 (74.0%) for DRV+COBI+TVD (difference in percentages (adjusted for baseline HIV RNA stratum and race stratum): 3.3%, 95% CI -11.4% to 18.1%). At week 48, virologic success rates were 79/103 (76.7%) and 42/50 (84.0%) for D/C/F/TAF FDC and DRV+COBI+TVD, respectively (difference in percentages: -6.2%, 95% CI -19.9% to 7.4%).

Virologic success rates in the PP analysis set were 77/91 (84.6%) for D/C/F/TAF and 37/47 (78.7%) for DRV+COBI+TVD (difference in percentages: 8.3%, 95% CI: -5.3% to 22.0%), at week 24, and 79/85 (92.9%) D/C/F/TAF vs. 42/46 (91.3%) DRV+COBI+TVD (difference 2.4%, 95% CI: -8.8% to 13.7%) at week 48.

CD4 cell counts increased for each treatment group with mean increases (SD) through Week 48 of 231 (141.9) cells/μL for D/C/F/TAF vs. 212 (151.5) cells/μL for DRV+COBI+TVD. The CD4% also increased in each treatment group with mean increases from baseline at Week 48 of 8.2% vs. 9.3% for D/C/F/TAF and DRV+COBI+TVD, respectively.

Subgroups analyses did not identify a subgroup clearly yielding more or less treatment benefit.

Mean (SD) percentage changes from baseline to week 48 in hip bone mineral density (BMD) were -0.84% (2.582) for D/C/F/TAF, and -3.82% (2.651) for DRV+COBI+TVD. Mean (SD) percentage changes from baseline to week 48 in spine BMD were -1.57% (3.920) for D/C/F/TAF, and -3.62% (3.128) DRV+COBI+TVD. Mean (SD) increases from baseline at Week 48 in serum creatinine were 0.06 (0.101) mg/dL for D/C/F/TAF, and 0.09 (0.161) mg/dL for DRV+COBI+TVD. Mean (SD) changes from baseline at Week 48 in estimated GFR were -2.9 (13.43) mL/min for D/C/F/TAF, and -9.2 (15.81) mL/min for DRV+COBI+TVD.

3.3. Uncertainties and limitations about favourable effects

External validity of trial results

The Phase 2 study GS-US-299-0102 enrolled patients aged 18-68 years, who were mainly male. The lack of data in patients older than 68 years does not allow characterizing the efficacy and safety of D/C/F/TAF in this population. Screening failures occurred in 34% of subjects screened (79/232). The trial population however does seem to be fully representative of the broad patient population with HIV-1 infection.

Assay sensitivity observations

Efficacy and safety of the to be marketed FDC has been tested in a single, exploratory, phase 2 study (GS-US-299-0102), set up with the aim to estimate the relative efficacy and safety. With the planned sample size of 150 subjects, the power to evaluate non-inferiority was 56% (with an assumed response rate of 88% for both groups and a non-inferiority margin of 0.12).

Internal consistency

Based on the primary analysis conducted at week 24 non-inferiority of D/C/F/TAF FDC vs. DRV+COBI+TVD could be concluded (albeit marginally). However, week 48 data showed a lower virological success rate in the D/C/F/TAF group vs. the DRV+COBI+TVD group. This was due to an imbalance in subjects who discontinued study drug for reason other than lack of efficacy. In conclusions, there were no indications for a systematic non-safety drug-related reason for the higher discontinuation rate in the D/C/F/TAF group.

Quality observations

As different formulations were used in the main clinical studies, additional justifications were provided stating the used formulations were representative for the commercial product.

Pharmacokinetic observations

The pivotal bioequivalence study showed that the D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration of the separate agents DRV, the F/TAF FDC, and COBI. The acceptability of the outcome of this study was dependent on the resolution of objections related to the bioanalysis (lack of proper QC coverage of the calibration curves of the clinical study samples). Extra revalidation experiments using an additional QC sample were carried out, which results met the usual bioanalysis acceptance criteria.

3.4. Unfavourable effects

The main adverse events reported in study GS-US-299-0102 were diarrhoea (21.4%, 22 subjects); upper respiratory tract infection (15.5%, 16 subjects); fatigue (13.6%, 14 subjects); nausea (12.6%, 13 subjects); and rash (11.7%, 12 subjects) in the D/C/F/TAF group, and diarrhoea (26.0%, 13 subjects); fatigue (18.0%, 9 subjects); upper respiratory tract infection (14.0%, 7 subjects); flatulence (12.0%, 6 subjects); and nausea, pain in extremity, vitamin D deficiency, and vomiting (each in 10.0%, 5 subjects) in the DRV+COBI+TVD group.

The percentages of subjects in each group with any AE considered by the investigator to be related to study drug were 41.7%, 43 subjects in the D/C/F/TAF group, and 38.0%, 19 subjects in the DRV+COBI+TVD group. The most commonly reported AEs considered related to the study drugs by the investigator by PT which formed the basis for identification of adverse drug reactions were as follows: diarrhoea (D/C/F/TAF 13.6%, 14 subjects; DRV+COBI+TVD 14.0%, 7 subjects), flatulence (D/C/F/TAF 3.9%, 4 subjects; DRV+COBI+TVD 10.0%, 5 subjects), nausea (D/C/F/TAF 9.7%, 10 subjects; DRV+COBI+TVD 6.0%, 3 subjects), and fatigue (D/C/F/TAF 8.7%, 9 subjects; DRV+COBI+TVD 8.0%, 4 subjects).

Changes from baseline at week 48 were observed in total cholesterol (40 mg/dL with D/C/F/TAF and 5 mg/dL with D/C/F/TDF, $p<0.001$), direct LDL cholesterol (26 mg/dL with D/C/F/TAF vs 4 mg/dL with DRV+COBI+F/TDF, $p<0.001$) HDL cholesterol (7 mg/dL with D/C/F/TAF vs 3 mg/dL with DRV+COBI+F/TDF, $p=0.009$), and triglycerides (29 mg/dL with D/C/F/TAF vs -5 mg/dL with DRV+COBI+F/TDF, $p=0.007$).

SAEs were reported in <5% of subjects with similar percentages in each treatment group. There was 1 SAE (Grade 3 hypersensitivity (allergic reaction)) that was considered related to study drug by the investigator (D/C/F/TAF group). No subjects died.

Two subjects in each treatment group (D/C/F/TAF 1.9%; DRV+COBI+TVD 4.0%) discontinued from the study due to the following AEs: hypersensitivity (considered related to study drug by the investigator), and substance abuse (considered not related) in the D/C/F/TAF group; and Grade 2 renal tubular disorder (considered not related), and Grade 3 worsening of diarrhoea (considered related) in the DRV+COBI+TVD group.

3.5. Uncertainties and limitations about unfavourable effects

D/C/F/TAF FDC has been evaluated in a limited data set of 103 HIV-1 infected subjects (Phase 2 study GS-US-299-0102) with a median duration of study drug exposure of 68.0 weeks. Additional 231 healthy subjects received the D/C/F/TAF FDC in Phase 1 studies. Long-term data is missing, however phase 3 studies are ongoing and will provide additional and longer-term data.

No specific clinical study was performed with the D/C/F/TAF FDC in adolescent subjects, elderly subjects, and subjects with renal insufficiency or hepatic impairment, or subjects co-infected with HIV-1 and hepatitis B or C. No adequate and well-controlled studies of D/C/F/TAF or its components have been conducted in pregnant women. No human experience of acute overdose with the administration of D/C/F/TAF is available.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

The pivotal bioequivalence study showed that the D/C/F/TAF 800/150/200/10-mg FDC tablet is bioequivalent to combined administration of the separate agents DRV, the F/TAF FDC, and COBI.

The D/C/F/TAF FDC is the first complete protease inhibitor (PI)-based HIV-1 regimen in a single tablet to be taken once daily, and thereby adds to further simplify HIV-1 treatment with a reduced pill-burden.

The viral success rates observed in the phase 2 study GS-US-299-0102 are somewhat lower than those previously observed in studies of similar design. Non-inferiority of the D/C/F/TAF FDC vs. DRV+COBI+TVD could be established based on the week 24 efficacy data of study GS-US-299-0102. Results after 48 weeks of treatment suggested lower virologic response for D/C/F/TAF vs. the single components. This seems to be caused by a disproportionally greater frequency of subjects in the D/C/F/TAF group who discontinued for other reasons than lack of efficacy. There were no indications for a systematic non-safety drug-related reason for the higher discontinuation rate in the D/C/F/TAF group. Efficacy results from the PP analysis at week 48 (excluding those subjects who discontinued the study prematurely) is more in line with expected virologic response and similar to what observed with other FDC (e.g: Genvoya phase 2 study with 95% and 90.7%, for E/C/F/TAF and Stribild, respectively).

The safety of the D/C/F/TAF FDC is based on the well-established safety profile of the single components and further supported by the phase 2 study results and preliminary Phase 3 study results with D/C/F/TAF. In conclusion, the safety profile however is in line with expectations and did not raise additional concerns.

3.6.2. Balance of benefits and risks

Bioequivalence of the FDC to the separate components has been established. Non-inferiority of D/C/F/TAF vs DRV+COBI+TVD has been shown in the phase 2 study. The safety of D/C/F/TAF FDC is in line with the one known for the single components.

3.7. Conclusions

The overall B/R of Symtuza is positive.

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 Symtuza is favourable in the following indication:

Symtuza is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents (aged 12 years and older with body weight at least 40 kg).
Genotypic testing should guide the use of Symtuza (see sections 4.2 and 5.1).

The CHMP 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).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.